Modelling the impact of varicella vaccination in Hong Kong

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Declaration of authorship

I, Yung-Wai Chan, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Date: 19 Jun 2025

Abstract

Universal varicella vaccination (UVV) was introduced in Hong Kong in July 2014 with no catch-up vaccination programme (CUP), following private vaccination since late 1990s. This PhD aims at understanding the impact of private and public varicella vaccination on the epidemiology of varicella, and to evaluate the varicella vaccination strategies in Hong Kong.

First, I conducted analyses on the epidemiology of varicella and zoster. Vaccine uptake in preschool children reached 50% before UVV introduction, and first dose uptake quickly rose to 98% after UVV. Under private vaccination, varicella notifications reduced significantly in children aged 4 years or below, and the reduction became more substantial five years after UVV. On the other hand, there was a shift in the burden of varicella to slightly older age groups with a corresponding increase in incidence before UVV, which persisted after UVV. Serological data also showed age shifts in infections before UVV, albeit starting before vaccine licensure. By 2020, seroprevalence in UVV ineligible individuals aged 5 to 25 years reduced, leaving a larger pool of adolescents and young adults susceptible to varicella infections.

Next, I estimated that one-dose varicella vaccination was moderately effective, and two dose vaccination was highly effective in preventing notified varicella with no evidence of waning protection in the first four years since vaccination.

Finally, I modelled the impact of varicella vaccination in Hong Kong on varicella epidemiology. The model predicted an upsurge of infections among adolescents and young adults after the lifting of non-pharmaceutical interventions against COVID-19. This upsurge could be reverted if a timely CUP was offered to non-UVV cohorts. In summary, this PhD

demonstrated the direct and indirect effect of vaccination on varicella transmission and disease burden, which illustrated the complexities around varicella vaccine use and the usefulness of closely monitored epidemiology.

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Acronyms and abbreviations

ACIP	Advisory Committee on Immunization Practices (of the U.S.)
AED	Accident & Emergency Department
CMI	Cell-mediated immunity
CTL	Cytotoxic T lymphocytes
CUP	Catch-up vaccination programme
DH	Department of Health (of Hong Kong Special Administrative Region)
DIC	Deviance information criterion
EIA	Enzyme immune-assays
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-linked immunosorbent spot-forming cell
FVS	Fetal varicella syndrome
FAMA	Fluorescent antibody to membrane antigen
FOI	Force-of-infection
HA	Hospital Authority (of Hong Kong Special Administrative Region)
HKCIP	Hong Kong Childhood Immunisation Programme
HZ	Herpes zoster
ICS	Intracellular cytokine staining
IFN	Interferon
IgG	Immuno-globulin G
IL	Interleukin
IVIG	Intravenous immune globulin
JCVI	Joint Committee on Vaccination and Immunisation
LPA	Lymphocyte proliferation assay
MCHC	Maternal and Child Health Centres
MCMC	Markov-Chain Monte Carlo
MMRV	Combined measles, mumps, rubella and varicella vaccine
mVV	Monovalent varicella vaccine
NPI	Non-pharmaceutical interventions
ODE	Ordinary differential equation
PCR	Polymerase chain reaction
PCV	Proportion of cases vaccinated

PDE	Partial differential equation
PHN	Postherpetic neuralgia
PPV	Population of population vaccinated
R	Reproduction number
RCF	Responder cell frequency
SCVPD	Scientific Committee of Vaccine Preventable Diseases
SIT	School Immunisation Teams
UVV	Universal varicella vaccination
VCV	Varicella-containing vaccines
VE	Vaccine efficacy/ effectiveness
VZIG	Varicella-zoster immunoglobulin
VZV	Varicella-zoster virus
WHO	World Health Organization

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Chapter 1. General introduction

1.1 Varicella and its epidemiology

Varicella-zoster virus and its diseases

Varicella-zoster virus (VZV) is a DNA virus under the family of Herpesviridae. VZV affects humans exclusively. Primary infection leads to varicella, commonly known as chickenpox. Varicella is characterised by a maculopapular, vesicular rash. Other symptoms may include fever, muscle aches, and malaise (1). In healthy, unvaccinated children, the average number of vesicles ranges from 250 to 500 (2). Fever and rash typically subsides in five to seven days (2). Whilst most childhood varicella is mild and self-limiting, some children develop complications, including secondary bacterial infections of skin lesions and in rare cases, encephalitis, pneumonitis, and stroke. These complications can result in hospitalisation and even death. Varicella complications are more common in adults, pregnant women, infants and immunocompromised individuals (2-4).

In developed countries, varicella leads to 2 to 6 hospital admissions per 100,000 person-year, with children accounting for 56 to 67% of these admissions (3). The most common complications of varicella are secondary bacterial infections, with Group A β-haemolytic streptococci or *Staphylococcus aureus* as the common causative agents (5). Skin infection is the most common manifestations, occurring in 15% to 25% of children hospitalised with varicella (6). These secondary bacterial infections can also present as more severe invasive infections such as pneumonia, necrotising fasciitis, and sepsis (5). Neurological complications involving the central nervous system can present as acute

cerebellar ataxia (occurring in about 1 in 4,000 clinically-attended varicella cases among children aged under 15 years) and encephalitis (occurring in 1 in 33,000 to 50,000 cases) (7).

The case fatality ratios for varicella were estimated to be 2 to 4 per 100,000 cases (8). Globally, there were an estimated 11,200 and 6,800 varicella deaths in 1990 and 2010, corresponding to an age-standardised mortality rates of 2 and 1 per 1,000,000 population (9). Before vaccine introduction in the U.S., the average age-adjusted mortality rate of varicella as underlying cause of death was 0.41 per 1,000,000 population between 1990 and 1994, with a higher rate in children and adolescents aged under 20 years (0.65 per 1,000,000) than adults aged 20 to 49 years (0.30 per 1,000,000) (10). In England and Wales, varicella case fatality was estimated to be 9.2 per 100,000 primary care consultations between 1995 and 1997 (corresponding to 0.5 per 1,000,000 population) (11). Estimates of burden of varicella and its complications vary across different countries, likely due to difference in quality of surveillance systems and study methodologies (12).

Varicella during pregnancy

Notably, varicella infections in pregnancy can lead to serious complications in both the mothers and fetuses (13-15). Fetal varicella syndrome (FVS) refers to varicella infections of the fetuses due to maternal varicella during pregnancy and is believed to be a result of the herpes zoster reactivation in utero (16-18). Clinical presentation and the severity of the fetus depends on the stage of pregnancy when maternal varicella occurs (14). In the first two trimesters, intrauterine infections may result in congenital defects, including neurological defects, eye diseases, skin scarring, or skeletal malformations in 0.4 to 2% of fetuses (13-15). Infections at any stage of pregnancy can cause intrauterine death or premature birth. Maternal infections in the 4 to 5

days before to 2 days after delivery can result in severe varicella in neonates. Mortality of neonatal varicella can be as high as 20% (14). In temperate areas, seroprevalence of VZV generally reaches 90% or above by age of ten, indicating children usually acquire varicella infections at young age (1, 19). Therefore, chickenpox in pregnancy and adulthood is rare when varicella is endemic.

Seronegative women can be offered active immunisation with varicella vaccine before pregnancy or postpartum (14, 18). Pregnant women who are seronegative should avoid contact with varicella and shingles cases during pregnancy (18). Since varicella vaccine is a live-attenuated vaccine and is contra-indicated in pregnancy, susceptible pregnant women with significant exposure to VZV should be offered post-exposure prophylaxis to prevent severe maternal varicella and infections of the fetuses or neonates (14, 15). Antivirals aciclovir (or valaciclovir) is recommended for pregnant contacts, with varicella-zoster immunoglobulin (VZIG) as an alternative if there is contraindication or adverse events to anti-virals (20). If the pregnant woman develops varicella, maternal complications and fetal development should be monitored (18, 21). If maternal varicella occurs within 1 week of delivery, neonates should be given intravenous VZIG or intravenous immune globulin (IVIG), and aciclovir (20). Delaying planned delivery can be considered to allow maternal antibodies to transfer to the child (14, 18). These newborns should also be under surveillance for potential signs of developing neonatal varicella (14, 22).

Varicella and herpes zoster

Varicella is highly infectious and is mainly transmitted through droplet or air-borne spread of respiratory tract secretions or vesicle fluid of infectious individuals (2, 23). Primary infection

of VZV is believed to lead to life-long immunity against varicella. Reports on second episodes of clinical varicella in immunocompetent individuals are infrequent (23). After primary infection of varicella, VZV establishes latency in the dorsal root ganglia (1). These latent viruses may reactivate and replicate sub-clinically, which stimulate immunity against development of secondary disease (endogenous boosting) (1, 2). When cell-mediated immunity (CMI) falls under a certain protective level, the latent viruses can successfully reactivate and lead to the development of secondary VZV disease, herpes zoster (HZ), also known as shingles (1, 24). Herpes zoster is presented with prodromal pain and localised vesicular rash that usually involves a single dermatome in immunocompetent persons. The pain and eruptions typically start to resolve in 3 to 5 days but may prolong to months and even years in some individuals (24). Extensive dissemination of the lesions (disseminated zoster) can occur in about 2 to 10% of patients and is more frequent among those with immunocompromised conditions (24, 25). About 7 to 25% of zoster cases develop prolonged pain in the previously affected area, known as post-herpetic neuralgia (PHN), which can last for a year or in some cases even longer (24). Herpes zoster and PHN occur more frequently with advanced age and among those with immuno-compromising conditions. Other less common complications of zoster include involvement of the central nervous system (such as encephalitis and meningitis), auricular and ophthalmic involvements. As varicella is generally ubiquitous, almost all older adults in the pre-vaccine era harbour VZV through primary varicella infections and are at risk of developing zoster. The life-time risk of zoster for unvaccinated persons who reach 80 years of age is estimated to be about 50% (24).

As varicella in immunocompetent children is usually mild and self-limiting, uncomplicated varicella is usually managed with symptomatic relief. Antivirals such as aciclovir, valaciclovir and famciclovir, are reserved for those at higher risk of severe outcomes, such as adolescents,

adults, pregnant women and immunocompromised persons (1). On the other hand, antiviral therapy is generally recommended for immunocompetent persons with zoster, in particular those who are older, immunocompromised, or at higher risk of complications (1).

Immunity to varicella and herpes zoster

Humoral immunity and cell mediated immunity (CMI) play different roles in the protection against varicella and herpes zoster. Humoral immunity is important in suppressing cell-free viruses and prevention of primary infection of VZV (2, 23). On the other hand, CMI controls the intracellular activities of VZV during the acute phase of primary varicella infection and clearance of primary infection, as well as prevents the occurrence of zoster by suppressing the reversion of latent VZV (2, 5, 23). After natural varicella and varicella vaccination, CMI is detected earlier than humoral antibody and peaks within 1 to 2 weeks (2, 26). VZV CMI against primary varicella involves the innate immune system, including the natural killer cells and dendritic cells that initiate the subsequent adaptive immune responses (27). VZV-specific CD4+ and CD8+ T lymphocytes proliferated after primary viremia. The effector CD4+ and CD8+ T lymphocytes and memory T lymphocytes are crucial in VZV T-cell mediated immunity (27). CD4+ T helper lymphocytes stimulate B lymphocytes to produce VZV-specific circulating antibodies and release cytokines such as interferon (IFN)-y and interleukin (IL)-2 to support CD8+ cytotoxic T lymphocytes (CTL) and macrophages. The CD8+ CTL recognise and kill VZV-infected cells, limiting the intracellular viral spread and clearance of primary infection . Individuals with impaired cellular immunity (e.g. those with low CMI due to cancer or transplantation) are at higher risk of disseminated or even fatal varicella, which is relatively rare in children with impaired humoral immunity (e.g. isolated agammaglobulinemia) (2, 23). After primary infection, memory T lymphocytes developed during primary infection persist

long-term and respond to VZV re-exposure, including within host VZV re-activation (endogenous) and contacts of infectious persons with varicella or shingles (exogenous) (27).

Both endogenous and exogenous exposure boosts VZV CMI, which is important in preventing varicella re-infection and development of shingles. The role of VZV CMI in containing the re-activation of latent VZV and preventing the development of zoster is evident from observations of increasing occurrence of HZ with age, which is often associated with waning CMI, as well as severity of HZ in immunocompromised persons with impaired cellular immunity, for instance those with HIV or under immunosuppressive therapy (5, 23). In addition to endogenous boosting, there is evidence suggesting that CMI can be boosted for those with latent VZV by contacting infectious individuals (exogeneous boosting) (28). For instance, clinical studies among teachers and healthcare workers with more frequent contact of children (hence higher chance of contacting chickenpox cases) had a lower risk of HZ (1). However, the exact duration and strength of such boosting remains uncertain (29, 30). Therefore, reduction of VZV circulation in the community, such as after large-scale use of varicella vaccination in children, may reduce exogenous boosting in adults, potentially leading to an increase in shingles incidence (1, 31).

Laboratory diagnosis of varicella and zoster

Both varicella and herpes zoster are usually diagnosed clinically. A study by Leung *et al*. found that clinical diagnosis of varicella was 100% and 85% sensitive for unvaccinated and vaccinated cases, and was 70% specific (32). Laboratory testing is usually limited to severe or atypical cases, especially in vaccinees. Detection of DNA by polymerase chain reaction (PCR), antigen detection, and less commonly viral culture on specimens including vesicles or body

fluid are laboratory confirmation methods for VZV (2, 23).

Serological testing for varicella humoral immunity is usually done on VZV Immuno-globulin G (IgG) antibodies (23). VZV antibodies induced by natural infection generally persists for decades (33). Those induced by vaccination appear to be persistent in vaccinees, as immunised children were found to be sero-positive in various studies for up to 20 years post-vaccination (2, 23). Fluorescent antibody to membrane antigen (FAMA) is regarded as the most sensitive laboratory method in detecting VZV IgG induced by both natural infection and vaccination, but it is relatively laborious and difficult to standardise (23). Commercially available enzyme-linked immunosorbent assays (ELISA) / enzyme immunoassays (EIA) are often used to assess population immunity against VZV, though differences in sensitivity prelude direct comparisons between studies (19, 34). As the IgG level for vaccinees are generally 10 to 30 times lower than the level attained after natural infection (2), these ELISA assays are often less sensitive to vaccine-induced immunity (35).

There are various laboratory methods to measure CMI, most involve stimulation of VZV antigens and measurement of T lymphocyte activity and/ or levels of cytokines (24). Intradermal skin test for VZV-antigen is one of the earlier tests for VZV CMI (36). Erythema induced after intra-dermal injection of VZV test antigen was measured and scored to reflect the T lymphocytes function in vivo (36). VZV skin test is relatively easy to conduct but difficult to standardise. Measuring T lymphocytes proliferation after stimulation by VZV antigen in vitro, such as the limiting dilution responder cell frequency (RCF) assay (37) and the lymphocyte proliferation assays (LPA) (27), is another technique to evaluate CMI. The level of cytokines production such as IFN-γ, IL-2 and IL-10 by T lymphocytes after VZV antigens stimulation also reflects the CMI level (24, 38). This is performed using the IFN-γ release

assays (measuring the total level of IFN-γ produced) or the IFN-γ enzyme-linked immunosorbent spot-forming cell (ELISPOT) assay (measuring the number of IFN-γ producing T lymphocytes) (37, 39, 40). Flow cytometry with intracellular cytokine staining (ICS) is the more modern technique used to detect VZV-specific CD4+ and CD8+ T lymphocytes expressing cytokines such as IFN-γ or IL-2 (41, 42). In addition, the cytotoxic T lymphocyte assay measures the lysis of histocompatible target cells (such as autologous lymphoblastoid cell) by cytotoxic T lymphocytes after VZV antigen stimulation (43).

1.2 Varicella vaccination

Vaccines against varicella and shingles

A live-attenuated varicella vaccine (Oka strain) was first developed and registered in Japan in the 1970s (2). Oka VZV vaccines were proven to be immunogenic and effective in protecting vaccinated children from varicella in clinical studies (44, 45). Varicella-containing vaccines (VCV) are available as monovalent varicella vaccine (mVV) or as combined measles, mumps, rubella and varicella vaccine (MMRV). All mVV and MMRV registered in Hong Kong consists of the Oka strain VZV and have a potency of at least 1,350 plaque forming units (PFUs) [Table 1.1]. The measles, mumps, and rubella viruses in MMRV vaccine are identical and of equal potency to those in the MMR vaccine. For the MMRV manufactured by MSD (ProQuad), the potency of the VZV component is at least 10,000 PFU, seven times higher than that of mVV Varivax produced by the same manufacturer. There is no difference in potency of the varicella component between the mVV and MMRV manufactured by GSK. In addition to the Oka strain varicella vaccines, other live varicella vaccines based on the MAV/06 viruses have been developed and used in South Korea, but they are not commonly used in other countries (46).

The first prophylactic vaccine registered for the prevention of herpes zoster, Zostavax, consists of a higher concentration of the Oka strain VZV (at least 19,400 PFU). In recent years, a recombinant glycoprotein E (gE) herpes zoster vaccine, Shingrix, has been registered globally and has replaced Zostavax in the vaccination programme to prevent zoster in countries such as the US (47) and UK (48).

Table 1.1. Characteristics of varicella and zoster vaccines available in Hong Kong (2, 24, 49)

	Varicella vaccine[1]		Zoster vaccine
Composition	Live attenuated VZV (Oka strain)		Recombinant glycoprotein E
	≥1,350 PFU	≥19,400 PFU	
Brand name/ Manufacturer	• Monovalent Varilix/GSK Varivax/ MSD • MMRV ProQuad/ GSK Priorix-Tetra/ MSD	• Zostavax/MSD	• Shingrix/ GSK
First registration (global)	1970s (Japan) 1995 (USA)	2006 (USA)	2017 (USA)
First registration (Hong Kong)	1996	2007	2020
Inclusion in Hong Kong's funded vaccination programme	July 2014	No funded zoster vaccination programme (as at December 2024)	

Note:

1. *Okavax (Sanofi) is an Oka-VZV containing varicella but is no longer registered in Hong Kong.*

Use of varicella vaccines in national immunisation programme and post-licensure observational studies

By 2021, at least 44 countries/ areas have included varicella vaccine in their routine childhood immunisation programme (46). Differences in the schedule and dosage of universal varicella vaccination (UVV) exists. 15 of these 44 countries (34%) adopted a one-dose programme (46). Except for two countries, the first dose is usually scheduled between 12 and 18 months of age. The timing of the second dose varies between 18 months to 12 years of age, with more than half (52%) being scheduled between 4 to 6 years of age.

There has been an increasing number of observational studies reflecting real-world evidence of the impact and direct effect of varicella vaccine (23, 24). The U.S. was the first country to introduce UVV in 1995, initially as a one-dose programme that successfully reduced both varicella notifications and hospitalisations by 80% (50, 51). Despite its success in reducing the varicella burden at the population level, breakthrough varicella was frequent among 1-dose vaccinee, leading to outbreaks in schools and childcare centres (52, 53). Primary and secondary vaccine failure may contribute to the high rate of breakthrough infections after 1-dose varicella vaccination (54), prompting the Advisory Committee on Immunization Practices (ACIP) to recommend 2-dose varicella vaccination in 2007 (55). Both humoral antibody level and CMI increased significantly after second dose of varicella vaccine (23). Seroconversion improved from 87% to 100% from 1- to 2-dose in a clinical trial of the monovalent Varivax (56). The switch to a 2-dose programme in 2007 led to further reduction in varicella burden and reduced breakthrough infections in the U.S. (50, 51). The incremental impact of 2-dose varicella vaccine appears to be consistent with vaccine effectiveness (VE) studies, which showed that both 1- and 2-dose vaccination was highly effective against severe varicella, albeit 1-dose VE

against varicella was slightly lower (pooled VE: 81% [95%CI: 78%-94%]) (57). UVV has also been shown to substantially reduce the burden of varicella in other countries such as Canada (58, 59), as well as Germany and Italy (60).

Concerns of introducing universal varicella vaccination

The global introduction of varicella vaccine in routine immunisation remains slow in spite of the availability of varicella vaccines since the 1990s. Some of the reasons behind the slow introduction include: competing public health priorities; abundance of breakthrough infections with a one-dose schedule; potential increase in varicella in adulthood, including women of childbearing age and hence potentially increased risk of infections during pregnancy, leading to neonatal complications; and increase in herpes zoster incidence following the launch of UVV due to reduction in exogenous boosting (31, 61-64). Mathematical models predicted a significant number of breakthrough infections with a one-dose schedule (61, 65), which was reflected by outbreaks occurred in children receiving one-dose vaccine in the U.S. before the adoption of a two-dose schedule. The World Health Organization (WHO) recommends countries that introduce routine varicella vaccination maintaining vaccine uptake at ≥ 80% to avoid shifting infection to older ages (8). Modelling studies also suggested widespread use of varicella vaccine, in particular if offered as a one-dose programme and/ or with sub-optimal uptake, would result in an increase of chickenpox among adolescents and young adults (61, 65). Children who experienced vaccine failure and those who missed out on routine vaccination will be less likely to acquire natural infection at young age with reduced circulation of VZV. Catch-up vaccination programme (CUP) for older children offered by countries including the U.S. (55) and Canada (59) might have reduced the susceptibility to varicella in those not eligible for UVV, avoiding an upsurge in these cohorts after vaccination. For countries with a

1-dose UVV programme like Australia (with an adolescent catch-up programme implemented (22)) and South Korea (no CUP but the private vaccine uptake was as high as 73% before UVV (66)), varicella notifications in older children and adolescents remained substantial within 10 years after programme implementation (66, 67).

Limitations of observational VE studies

Some of these concerns remain unresolved as evidence from post-licensure observational studies remain inconsistent. Difference in dosing schedules of the routine programme, the scope of catch-up vaccination (if offered), and surveillance systems within or between countries, etc., could contribute to apparent difference in the impact of UVV. For instance, a meta-analysis on the global impact of varicella vaccination programmes showed that varicella incidence shifting to older ages was reported in Canada and Taiwan, but not in the U.S (68). Reports from Spain showed divergent regional trends in varicella incidence among adolescents, as a reduction was seen in Madrid but an increase was reported in Navarra (68). In addition, while there is some evidence that supports the exogenous boosting of circulating VZV to herpes zoster, the duration and strength of this boosting effect at the population level remains unclear (29-31).

Effectiveness against varicella infections is rarely evaluated in these studies, as most of the endpoints of these observational studies were based on clinical outcomes of various severity captured in surveillance systems. It is difficult to ascertain infections in routine surveillance, as not all infections lead to medical consultations. In addition, the full mechanism of vaccine protection is difficult to determine by vaccine efficacy/ effectiveness studies alone, which quantifies the relative risks/ odds of disease between the vaccinated and unvaccinated. The

effect of vaccine in preventing infection and disease consists of different elements such as acquisition of infection, development of symptomatic and severe diseases once infected, as well as onward transmission of the infections. These attributes are difficult to be delineated in observational and experimental studies unless further studies of human challenge and outbreak transmission are conducted.

1.3 Varicella surveillance and vaccination in Hong Kong

Provision of vaccination in Hong Kong

In Hong Kong, publicly-funded vaccines included in the Hong Kong Childhood Immunisation Programme (HKCIP), are provided by different public healthcare providers according to the recommended schedule (69, 70). Different services/ departments of the Hospital Authority (HA, the governing body of Hong Kong's public hospitals) and the Department of Health (DH) are responsible for delivering the HKCIP vaccines to children of different ages (70). Public hospitals provide Hepatitis B and BCG vaccines to new-borns. The Maternal and Child Health Centres (MCHC) of the DH vaccinate children up to five years of age. The School Immunisation Teams (SITs) visit all primary schools in Hong Kong to provide vaccinations scheduled for primary one, five and six students (about six, ten and eleven years of age, respectively). Parents can opt for their children to receive vaccines from private medical practitioners at a cost. These may include vaccines of different formulations than those provided in the HKCIP (such as combined Hepatitis A – Hepatitis B vaccine instead of the monovalent Hepatitis B vaccine in HKCIP) or other non-HKCIP vaccines (such as varicella vaccine before the incorporation in 2014 and rotavirus vaccine).

Monitoring vaccine uptake in Hong Kong

There is substantial difference in the contribution from public and private medical sectors to the healthcare system in Hong Kong for outpatient and inpatient settings, which affects the reliability of using administrative statistics to monitor vaccine uptake. Private medical sectors account for about 70% of the outpatient services but only about 10% of the inpatient services (71). In a study conducted between 2014 and 2015, 70% or more children presenting with respiratory and/ or gastro-intestinal symptoms sought consultations from general practitioners in the private sector (72). Although the administrative statistics on vaccination are available from public healthcare providers of HA and DH, the consultation data shared by the private medical providers in outpatient settings is incomplete, despite of the effort in developing a public-private electronic health record system (73). Therefore, the administrative statistics of the MCHC under the DH, who provide vaccination to new-borns and preschool children, only reflects vaccines administered in the public sector, or for those children using their services. To better capture the vaccination statistics for preschool children, the DH conducts surveys to monitor vaccine uptake of preschool children every three years since 2001. The administrative statistics captured by SITs include vaccination provided by the team and vaccination elsewhere. This data is representative of the vaccination status of the primary school children as nearly all children aged 6 to 11 years in Hong Kong attended primary schools (74).

Recommendation and implementation of universal varicella vaccination from the advisory committee

Immunisation policy in Hong Kong is advised by the Scientific Committee on Vaccine-

Preventable Diseases (SCVPD) (formerly Advisory Committee on Immunisation between 1992 and 2003), the advisory committee on immunisation in Hong Kong. A government-provisioned economic analysis on vaccines under consideration for inclusion to HKCIP, including varicella vaccines, was completed in 2006 (75). This study applied an age-structured dynamic mathematical model of one-dose varicella vaccination on the age-specific incidence of varicella and zoster to understand the cost-benefit ratio of mass varicella vaccination in Hong Kong (75). The mathematical model and economic analysis for varicella were adapted from the Canada's varicella vaccination model (75, 76). The model population was adapted based on Hong Kong's demographics. However, all biological and vaccination parameters, including the force of varicella infection and vaccine efficacy, were referenced from the model developed for Canada (75). No local data on varicella and zoster disease was adopted in the calibration of the mathematical model (75). Assuming there is no varicella vaccination in the community, UVV was not considered cost-beneficial and the model projected reduced exogenous boosting by UVV would lead to increased incidence of zoster (75). Considering all evidence including this economic analysis, the SCVPD did not recommend UVV introduction (70).

The DH of Hong Kong conducts cross-sectional surveys for preschool children every three years to monitor uptake of funded and private vaccines (immunisation coverage surveys). Since first available in the private market in 1996, varicella vaccine uptake among preschool children increased gradually to about 50% for those born between 2009 and 2011 even without funded vaccination (77). Due to the concern of this increasing vaccine uptake affecting varicella epidemiology, in particular shifting the disease burden to older children and adolescents, the SCVPD reconsidered introducing UVV in Hong Kong in 2012. The economic analysis was updated in 2012 to inform the SCVPD on the latest cost-benefit ratio of UVV. Instead of assuming no varicella vaccination in the community, an uptake of 30% was used as the baseline

to reflect the change in incidence of varicella and zoster under private vaccination [Personal communication with the Department of Health Hong Kong]. The assumption of target UVV uptake was also increased from 90% to 95% to reflect high uptake of measles, mumps and rubella (MMR) vaccine. In the cost-benefit model, more recent population demographics and costs (including salary, transportation and outbreak investigations) were also incorporated. Similar to the earlier study, local data on varicella serology and varicella incidence was not incorporated in the calibration of the transmission model. The updated economic analysis showed that UVV would be cost-beneficial in Hong Kong given the change in baseline epidemiology under private varicella vaccination. Along with evidence including local epidemiology and acceptability, SCVPD recommended a 2-dose UVV to be included in HKCIP. The recommended schedule included the first dose for children aged 12 months using mVV and a second dose at primary one (approximately six years of age) using MMRV (78). The programme was launched in July 2014 for children born in 2013 and after (78). Children born before 2013 were not eligible for UVV and there was no CUP for these children during the UVV roll-out.

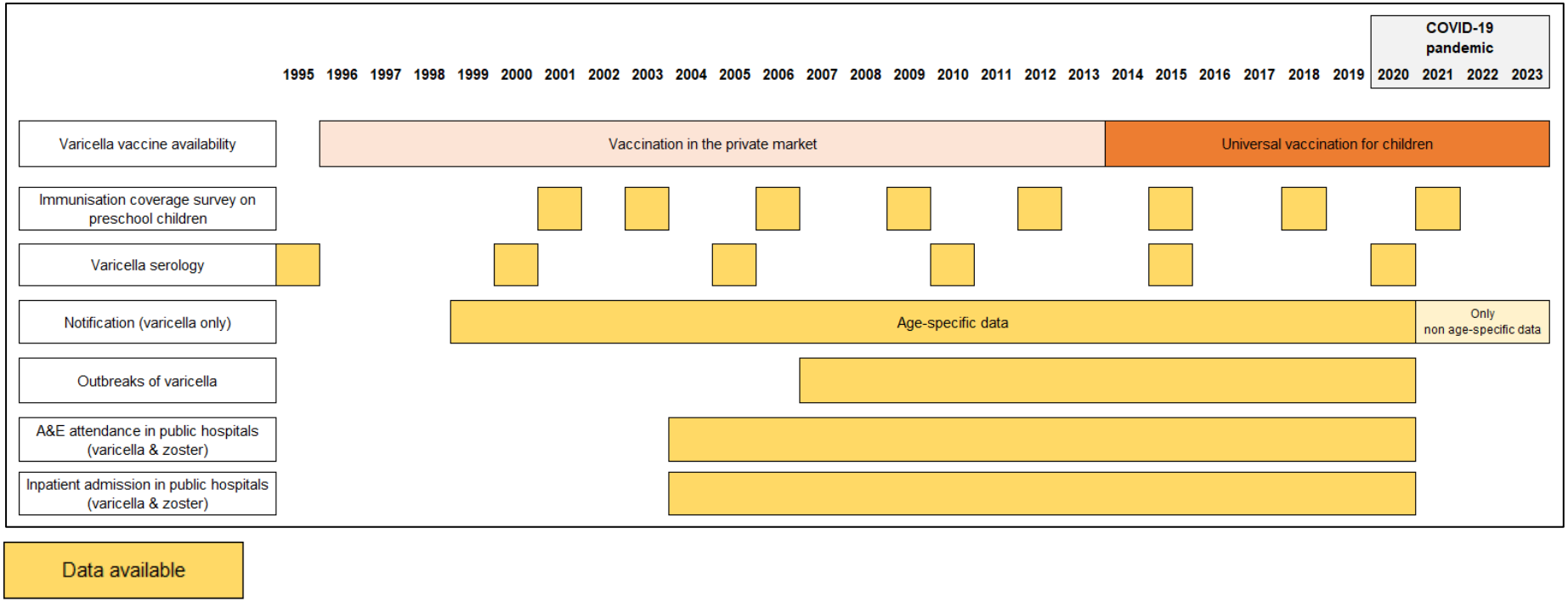
In 2018, the SCVPD recommended bringing forward the second dose of MMRV from primary one to 18 months of age to provide earlier boosting against measles (79). This change in schedule affected children born in July 2018 or after, whose second dose varicella vaccination started in January 2020 (80). On the other hand, those born between January 2013 and June 2018 started to receive their second dose varicella vaccine as they reach primary one according to the original recommendation in 2012 (80). As the SIT visits schools for the MMRV vaccination campaign for primary one school children in the second school term (usually starts in January), these children started to receive their second dose of varicella vaccine in 2020 (school year of 2019/20). Hence, second dose varicella vaccination started in 2020 for children

following both the original and updated schedule.

Surveillance of varicella and herpes zoster in Hong Kong

In addition to monitoring vaccine uptake, there are other surveillance activities being conducted by the DH that enables understanding of varicella epidemiology [Figure 1.1]. Serosurveys of varicella IgG has been conducted every five years since 1995. In anticipation of potential UVV and the need to understand local epidemiology, varicella was made notifiable since 1999 in Hong Kong (81). Case-based surveillance has been carried out on notified cases and outbreaks (defined as three or more persons in the same schools) are investigated as part of the public health protection. Starting in 2004, data on Accident & Emergency Department (AED) attendance and hospitalisations in public hospitals related to varicella and herpes zoster have become available. Collectively, these long-standing data allow population-level analyses of varicella sero-immunity and disease incidence.

Figure 1.1. Availability of varicella vaccines and data related to varicella and herpes zoster in Hong Kong, 1995 to 2023.



Note: age-specific varicella notification is still being collected by the DH after 2020, but they are not included in this PhD.

Table 1.2. Summary of published mathematical models on varicella vaccination[1].

Study	Country	Model type	Dose	Zoster[2]	Zoster vac	Model calibration using varicella seroprevalence data	Model calibration using varicella incidence data[3]	Parameterisation of vaccine efficacy related parameters during model calibration
Kim 2024 (82)	South Korea	Deterministic	2	Y	Y	Post-vaccine (up to 3 years after UVV)	N	Not fitted. Referenced from literatures and previous model estimate (83).
Lang 2024 (84)	Italy	Deterministic	2	Y	Y	Pre-vaccine era	Pre-vaccine era (hospitalisation)	Only duration of maternal immunity fitted. Other parameters referenced from literatures.
Ahern 2024 (85)	Ireland	Deterministic	2	Y	N	Pre-vaccine era	N	Not fitted, referenced from literatures.
Burgess 2023 (86)	Denmark	Deterministic	2	Y	N	Pre-vaccine era	N	Not fitted, referenced from other studies or estimations from clinical trials.
Feng 2022 (87)	China	Deterministic	2	N	N	N	N	Not fitted, referenced from literatures.
Sun 2022 (88)	China	Deterministic	2	N	N	N	Pre-vaccine era (voluntarily reported cases)	Not fitted, referenced from literatures.
Kujawski 2022 (89)	Israel	Deterministic	2	Y	Y	Pre-vaccine era	N	Not fitted. Reference from other studies or estimations from clinical trials.
Suh 2022 (83)	South Korea	Deterministic	1	Y	N	N	Post-vaccine varicella medically-attended incidence data (10 years)	Calibrated vaccine take and vaccine failure by fitting model to post-vaccine varicella incidence data from national database.
Bakker 2022 (90)	Thailand	Deterministic	2	Y	N	Pre-vaccine era	N	Not fitted, referenced from literatures.
Burgess 2022 (91)	Slovenia	Deterministic	2	Y	N	Pre-vaccine era	N	Not fitted, referenced from literatures.

Study	Country	Model type	Dose	Zoster[2]	Zoster vac	Model calibration using varicella seroprevalence data	Model calibration using varicella incidence data[3]	Parameterisation of vaccine efficacy related parameters during model calibration
Sharomi 2022 (92)	UK (England & Wales)	Deterministic	2	Y	N	Pre-vaccine era	N	Not fitted, referenced from literatures.
Pillsbury 2022 (93)	non-country specific (clinical trials data)	Deterministic	2	N	N	N	Clinical trials (follow-up observation)	Calibrated VE by fitting model to clinical trials data.
Suzuki 2022 (94)	Japan	Deterministic	2	N	N	N	Pre- and post-vaccine era (paediatric notification data, including 5 years post-UVV)	Not fitted (case reporting sensitivity estimated using time-series SIR in previous related study; Estimated parameters are related to trigonometric function that capture within-year variations but not vaccine efficacy).
Widgren 2022 (95)	Sweden	Deterministic	2	Y	Y	N	N	Not fitted, referenced from literatures.
Suzuki 2022 (96)	Japan	Deterministic	2	N	N	N	Pre- and post-vaccine era (paediatric notification data, including 5 years post-UVV)	Not fitted (case reporting sensitivity estimated using time-series SIR)
Akpo 2021 (97)	UK	Deterministic	2	Y	N	Pre-vaccine era	N	Not fitted, referenced from literatures (MSD and GSK varicella vaccine trials, other published modelling and CEA).
Pawaskar 2021 (98)	Norway	Deterministic	2	Y	N	Pre-vaccine era	N	Not fitted, referenced from literatures or fit to clinical trials data.
Heininger 2021 (99)	Switzerland	Deterministic	2	Y	N	Pre-vaccine era	N	Not fitted, referenced from literatures.

Study	Country	Model type	Dose	Zoster[2]	Zoster vac	Model calibration using varicella seroprevalence data	Model calibration using varicella incidence data[3]	Parameterisation of vaccine efficacy related parameters during model calibration
Wolff 2021 (100)	Sweden	Deterministic	2	Y	Y	Pre-vaccine era	N	Not fitted, referenced from literatures.
Suh 2021 (101)	South Korea	Deterministic	2	Y	N	Post-vaccine (up to 4 years post-UVV)	N	Not fitted, referenced from literatures (including local South Korea seroprevalence studies).
Azzari 2020 (102)	Italy	Deterministic	2	Y	N	Pre-vaccine era	N	Not fitted, referenced from literatures.
Zha 2020 (103)	China	Deterministic	1	N	N	N	Outbreak (single school)	Not fitted, referenced from literatures.
Rafferty 2020 (104)	Canada	Stochastic	2	Y	Y	N	Post-vaccine era medical attendance data	Probability of vaccination previously calibrated in previous related study [Rafferty 2018 (105)], other VE parameters referenced from literatures.
Wolfson 2019 (106)	Turkey	Deterministic	2	Y	N	Pre-vaccine era	N	Not fitted, referenced from literatures.
Betta 2019 (107)	Italy	Deterministic	1	Y	Y	Pre-vaccine era	N	Not fitted, referenced from literatures.
Sauboin 2019 (108)	France	Deterministic	2	Y	N	Pre-vaccine era	N	Not fitted, referenced from literatures or expert opinion.
Melegaro 2018 (109)	Italy	Stochastic	2	Y	Y	Pre-vaccine era	N	Not fitted, referenced from literatures.
Rafferty 2018 (105)	Canada	Stochastic	2	Y	Y	N	Pre-vaccine era (age-specific incidence of varicella data)	Probability of vaccination previously calibrated, other VE parameters referenced from literatures.
Marchetti 2018 (110)	Norway	Deterministic	2	Y	Y	Pre-vaccine era	N	Not fitted, referenced from literatures.
Horn 2018 (111)	Germany	Deterministic	2	Y	Y	Pre-vaccine era	N	Not fitted during model calibration, VE estimated separately from clinical trials and observational studies.
Tang 2017 (112)	China	Stochastic	1	N	N	N	Pre-vaccine era (notification)	Not fitted, referenced from literatures.

Study	Country	Model type	Dose	Zoster[2]	Zoster vac	Model calibration using varicella seroprevalence data	Model calibration using varicella incidence data[3]	Parameterisation of vaccine efficacy related parameters during model calibration
Holl 2016 (113)	Italy	Deterministic	2	Y	N	Pre-vaccine era	N	Not fitted, referenced from literatures.
Horn 2016 (114)	Germany	Deterministic	2	Y	N	Pre-vaccine era	Pre- and early post-vaccine era (hospitalisation)	Not fitted, referenced from literatures.
Betta 2016 (115)	Italy	Deterministic	1	Y	Y	Pre-vaccine era	N	Not fitted, referenced from literatures.
van Lier 2015 (116)	Netherlands	Deterministic	2	Y	N	Pre-vaccine era	N	Not fitted, referenced from literatures.
Zibolenová 2015 (117)	Slovakia	Deterministic	1	N	N	Pre-vaccine era	N	Not fitted, referenced from literatures.
Gao 2015 (118)	Australia	Deterministic	2	Y	Y	Pre-vaccine era	Pre-vaccine era (hospitalisation)	Not fitted, referenced from literatures.
Ouwens 2015 (119)	France	Deterministic	2	Y	N	N	Pre-vaccine era (sentinel surveillance)	Not fitted, referenced from literatures and clinical trials data.
Bilcke 2013 (120)	Belgium	Deterministic	2	Y	Y	Pre-vaccine era	N	Not fitted, referenced from literatures.
van Hoek 2011 (61)	England	Deterministic	2	Y	Y	Pre-vaccine era	Pre-vaccine era (primary care consultation)	VE (vaccine take and waning) estimated separately by fitting a simpler model to clinical trial data.
Brisson 2010 (65)	Canada	Deterministic	2	Y	N	Pre-vaccine era	N	VE estimated separately by fitting a simpler model to post-vaccine era active surveillance data in US during one-dose era [Chaves 2007 (121)] and clinical trial of 2-dose data.
Karhunen 2010 (122)	Finland	Deterministic	2	Y	N	Pre-vaccine era	N	Not fitted, referenced from literatures.
Gao 2010 (123)	Australia	Deterministic	2	Y	N	Pre-vaccine era	N	VE estimated separately by fitting a simpler model to post-vaccine era active surveillance data in US during one-dose era [Chaves 2007 (121)] and clinical trial of 2-dose data.

Study	Country	Model type	Dose	Zoster[2]	Zoster vac	Model calibration using varicella seroprevalence data	Model calibration using varicella incidence data[3]	Parameterisation of vaccine efficacy related parameters during model calibration
Valentim 2008 (124)	Brazil	Deterministic	2	N	N	Pre-vaccine era	N	Not fitted, referenced from literatures.
Lenne 2006 (125)	Spain	Deterministic	1	N	N	Pre-vaccine era	N	Not fitted, referenced from literatures.
Gidding 2005 (126)	Australia	Deterministic	1	Y	N	Pre-vaccine era	N	Not fitted, referenced from literatures.
Coudeville 2005 (127)	France and Germany	Deterministic	1	N	N	Pre-vaccine era	N	Not fitted, referenced from literatures.
Coudeville 2004 (128)	Italy	Deterministic	1	N	N	Pre-vaccine era	N	Not fitted, referenced from literatures.
Brisson 2003 (129)	UK (England & Wales)	Deterministic	1	Y	N	N	Pre-vaccine era (primary care consultation)	VE estimated separately by fitting a simpler model to clinical trial data and household transmission study.
Brisson 2000 (76)	Canada	Deterministic	1	Y	N	Pre-vaccine era	N	VE estimated separately by fitting a simpler model to clinical trial data and household transmission study.
Brisson 2000 (130)	Not country specific	Deterministic	1	N	N	N	Clinical trials data	VE estimated separately by fitting a simpler model to clinical trial data.
Deguen 2000 (131)	Not country specific	Deterministic	1	N	N	N	N	Not fitted, referenced from literatures.
Schuette 1999 (132)	US	Deterministic	1	Y	Y	N (FOI referenced from Halloran 1994 (133))	N	Not fitted, referenced from literatures.
Coudeville 1999 (134)	French	Deterministic	1	N	N	N	N	Not fitted, referenced from literatures.
Ferguson 1996 (135)	Not country specific (hypothetical)	Stochastic	1	Y	N	Pre-vaccine era	N (model output compared to primary care consultation data)	Not fitted, referenced from literatures.

Study	Country	Model type	Dose	Zoster[2]	Zoster vac	Model calibration using varicella seroprevalence data	Model calibration using varicella incidence data[3]	Parameterisation of vaccine efficacy related parameters during model calibration
Halloran 1994 (133)	US	Deterministic	1	N	N	Pre-vaccine era	N	Not fitted, VE estimates by panel of experts.

Note:

1. A PubMed search was conducted to retrieve articles related to varicella vaccination mathematical models written in English on 20 November 2024. The key words of the search were *("chickenpox vaccine"[MeSH Terms] OR ("chickenpox"[All Fields] AND "vaccine"[All Fields]) OR "chickenpox vaccine"[All Fields] OR ("varicella"[All Fields] AND "vaccine"[All Fields]) OR "varicella vaccine"[All Fields]) AND ("model"[All Fields] OR "model s"[All Fields] OR "modeled"[All Fields] OR "modeling"[All Fields] OR "modelings"[All Fields] OR "modelled"[All Fields] OR "modelling"[All Fields] OR "modellings"[All Fields] OR "models"[All Fields])*. I screened the titles and abstracts of the search results for articles that use dynamic mathematical models to study varicella vaccination. I excluded studies that used static models (e.g. decision analysis, Markov models, etc.) and those that modelled only shingles vaccination.
2. Inclusion of zoster in the models.
3. Incidence data include notification, outbreak, medical consultation and/ or hospitalisation.

1.4 Mathematical models for varicella vaccination

Dynamic nature of infectious disease transmission

The risk of acquiring an infection for a susceptible (non-immune) individual depends on the probability to come into effective contact with an infectious individual. On a population level, the proportion of individuals susceptible and infectious determines the number of new infections, which affects the infection risk/ pressure (often referred as force-of-infection (FOI)) at any given time (136, 137). These proportions and infection risk changes over time and this dynamic nature of infections should be considered when studying infectious disease and the effectiveness of intervention measures. For instance, an effective intervention that can reduce the risk of developing a non-communicable disease would only directly protect those receiving such intervention. On the other hand, an effective intervention measure against an infectious disease, such as vaccination, will reduce the risk of those receiving such intervention (direct effect among vaccinees) and those who do not (indirect effect). The reduction of proportion susceptible through vaccination leads to lower number of new infections, which in turn reduce the infection pressure in the population (136). As a result, those unvaccinated will be indirectly benefited from the vaccination due to a lower risk of infection in the community. This indirect effect of vaccination is often referred to as herd protection/ immunity (138). It should be noted that indirect effect may also result in undesired public health effects. For instance, the indirect effect of reduction in FOI will lead to a reduced risk of infection for those unvaccinated at young age, leading to a higher age of infection. Infections at adolescents and adulthood are associated with higher risk of complications for some infections, such as varicella (1). Another example of the dynamic nature of infectious diseases is the changing distribution of distinctive strains of a pathogen, in particular if the effectiveness of intervention differs by strains (136).

The emergence of non-vaccine serotype after widespread use of serotype-specific pneumococcal conjugate vaccines is an example of the indirect effect of vaccination (139, 140).

Mathematical models of infectious diseases

Mathematical models of infectious diseases are representations of these complex and interactive systems using mathematical equations. They have long been used to study transmission of infectious diseases and played an important role in guiding public health policy (137, 141). As a result of the dynamic nature of infections, infectious disease cannot be adequately studied by static models, which assume a constant infection risk. Instead, dynamic (transmission) model, which links the number of new infections to the proportion of infectious and susceptible individuals, should be used to study infectious disease transmission and the impact of interventions (136).

Both stochastic and deterministic models have been used to study infectious disease dynamics. Deterministic compartmental models, which describe the trajectory of different states of disease 'on average', have been extensively applied to diseases like varicella (61, 76, 123), measles (142), rubella (143), influenza (144) and Ebola (145). In contrast, stochastic models incorporate randomness in the models which are relatively computationally demanding, but can address more variable scenarios such as outbreaks or disease occurrence in smaller populations (137). To study infectious disease transmission, deterministic compartmental models are often developed to mimic the key infection/ disease status. The complex mechanism of an infection is simplified to retain the essential components, such that the most influential features can be represented by the model. An example of a basic compartmental model is the 'Susceptible-Infectious-Recovered' (SIR) model, which represents the state of being

susceptible (non-immune) to an infection, infected by a pathogen and become infectious (infectious), and eventually recovered and develop immunity against the infection (137). This basic SIR framework can be modified based on the characteristics of the infection and intervention of interest. Variations in model structure representing different mechanisms of protection can be used to test hypothesis using the available data (141). Important characteristics affecting the transmission of the pathogen, such as demographics, frequency of contact among different age groups, should be integrated into the model.

Ordinary differential equations (ODE) or partial differential equations (PDE) are used to describe the flow of individuals between compartments, for which the rates are controlled by different parameters corresponding to risk and/ or duration of the population at different disease status. These parameters are influential in producing a realistic model. They can either be referenced from the literature, separately estimated from existing data, or they can be estimated during the model calibration when included as 'free' parameters. These parameters are highly influential to the model output, and models should preferably be fitted to data to ensure they align with the observations. Fitting of infectious disease models are now commonly conducted using Monte Carlo Markov Chain (MCMC), a type of Bayesian inference (146). For each MCMC iteration, a new set of free candidate parameters is sampled, and the model will be simulated based on these parameters. According to the Bayes' theorem, the posterior distribution of the parameters given the data is a product of the likelihood of the observed data from the modelled outputs based on the (proposed) parameters and the prior belief of the parameters (147). In order to maximise the likelihood of the parameters given the data, the likelihood of the data given the modelled outputs and parameters is computed and compared to the previous iteration to decide on acceptance or rejection of the proposed parameters. Sufficient exploration of parameter space will yield a posterior distribution of these parameters,

given the data and the model. This posterior distribution represents the most likely parameter values and the associated uncertainties. Adaptive MCMC can be used to ensure efficient sampling of multiple parameters (148).

Using mathematical models to study varicella vaccination

The impact of varicella vaccination has been studied using mathematical models since the 1990s, with a growing number in the 2000s to facilitate immunisation policy (149). These mathematical models, combined with economic analyses, are used to predict the cost-effectiveness of vaccination programme and are central to the formulation of a number of varicella vaccination strategies world-wide (61, 149-152). A PubMed search revealed 56 studies that used dynamic mathematical models to study the effect of varicella vaccination [Table 1.2]. All except five (91%) were deterministic models. With the increasing evidence of vaccine failures following single dose of varicella vaccine, most of the recently published studies modelled two dose vaccination scenarios, and more have included compartments representing herpes zoster disease and immunity status to assess the combined strategy of varicella and herpes zoster vaccines. Although 50 (89%) of these models were calibrated with varicella seroprevalence and/ or incidence data to inform the transmission intensity, only ten incorporated data collected in the post-vaccine era in the model calibration, and none included both seroprevalence and incidence data collected after varicella vaccination programme started [Table 1.2]. Furthermore, only two of these studies parameterised vaccine efficacy related parameters during model calibration, with the rest adopting VE estimates from the existing literature. In summary, most of the existing varicella vaccine mathematical models used pre-vaccine era data to determine the endemic varicella transmission intensity and utilised vaccine efficacy parameters from the literature to predict the post-UVV impact. Only a few studies

attempted to study the population effect of varicella vaccination using surveillance data collected in the post-vaccine era. As described in earlier section, the mathematical models used to inform economic analysis of UVV in Hong Kong was also not fitted to data of local varicella epidemiology. Catch-up vaccination was not included in the previous Hong Kong model.

1.5 Overall aims and objectives of the PhD

Overall aims

The overall aim of this PhD is to understand the impact of varicella vaccination on the epidemiology of varicella and herpes zoster in Hong Kong and to evaluate the varicella vaccination strategy using mathematical modelling. Epidemiological analyses will be conducted to understand the epidemiology of varicella in Hong Kong. A mathematical model will be developed and calibrated with the rich pre- and post-vaccine era data collected in Hong Kong to understand the effect of varicella vaccine on varicella epidemiology. This model will also provide an opportunity to study the mode of varicella vaccine action by estimating the vaccine effect against infection, disease development and transmission (153). The calibrated model will reflect changes in transmission dynamics of varicella under the private and public-funded vaccination, predict the course of future epidemics and evaluate alternative vaccination strategies (154).

Objectives

1. To describe the burden and the epidemiology of varicella in Hong Kong before universal varicella vaccination [Chapter 2].
2. To estimate the dose-specific varicella vaccine effectiveness in Hong Kong [Chapter 3].
3. To understand the impact of universal varicella vaccination on the epidemiology of varicella and zoster [Chapter 4].
4. To model the impact of varicella vaccination in Hong Kong, evaluate alternative vaccination strategies, and understand the mode of varicella vaccine action [Chapter 5].

Chapter 2. Changing epidemiology of varicella in Hong Kong

Before UVV started in July 2014, vaccines against varicella had been available in Hong Kong through the private market since 1996. This Chapter includes my analyses on serosurveys and surveillance data to understand the change in varicella vaccination uptake in the private sector before UVV and its impact on the epidemiology of varicella and zoster. I first analysed varicella vaccine uptake from the immunisation coverage surveys between 2001 and 2015, of which I led three of these surveys (2009, 2012 and 2015) as the surveillance officer in DH. For the surveillance data, I included varicella notification to the DH, as well as AED attendance and hospitalisation in the public hospitals related to varicella and zoster. I led varicella surveillance at DH between 2006 and 2020 and overlooked the collection of these surveillance data. I cleaned, validated and analysed all surveillance data, including the statistical model in estimating the annual changes in rates of notification, AED attendance and hospitalisation. Together with co-author Dr H.L. Chan, we identified ICD-9-CM codes related to underlying medical conditions and complications of varicella and zoster (included in Supplementary Table S1). Lastly, I analysed varicella seroprevalence data between 1995 and 2010. I developed the catalytic model that fitted to these data under the guidance of my supervisor Dr Stefan Flasche.

I found that the vaccine uptake for preschool children increased from under 10% for children born before 2000, to 50% for those born in 2012. In the same period of this low to medium level of varicella vaccination in the private market, there was a shift in the burden of notified varicella, AED attendance and hospitalisations from very young children to slightly older age groups. The proportion seropositive for those aged between five and 19 years decreased between 1995 and 2010. Using the catalytic model that fitted to the seroprevalence data, I found that the varicella force-of-infection (FOI) decreased while the average age of infection

increased during this period. This observation in reduction in varicella transmission was later confirmed by the mathematical model developed in Chapter 5 of this thesis. For herpes zoster, I found an increase in AED attendance and hospital admissions among those aged 10 to 59 years.

I used the immunisation coverage surveys in 2009, 2012 and 2015, as well as varicella notification data in the corresponding years to estimate varicella vaccine effectiveness [Chapter 3]. The analyses of these surveillance data were extended in Chapter 4 to include data collected six years after the implementation of universal vaccination (2015 to 2020). These analyses were published in Epidemiology and Infection (2018) (155).

2.1 Research paper cover sheet

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Student ID Number	414373	**Title**	Mr
First Name(s)	Yung Wai		
Surname/Family Name	Chan		
Thesis Title	Modelling the impact of varicella vaccination in Hong Kong		
Primary Supervisor	Stefan Flasche		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Epidemiology & Infection		
When was the work published?	12 March 2018		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	The study involved four main data sources from the Department of Health (DH) Hong Kong, the immunisation surveys, varicella notification, AED attendance and hospitalisation, as well as varicella seroprevalence. I was the Scientific Officer of DH and I oversaw varicella and herpes zoster surveillance when the study was conducted. I led the immunisation surveys conducted by Department of Health Hong Kong in 2009, 2012 and 2015. This involved planning, training of field staff, data collection, validation and analyses. The second data source was varicella notification in Hong Kong, of which I oversaw as the lead scientist on varicella. I collated the data from different health protection teams, carried out data quality check and cleaning. For the third data source of AED attendance and hospitalisation, I liaised with the Hospital Authority, who manages all public hospitals in Hong Kong, on the specification and acquistion of these electronic data. I planned and conducted the analyses, including descriptive analyses, regression analysis and co-develop the catalytic model to fit the seroprevalence data. I drafted the manuscript and managed the article submission.

SECTION E

Student Signature	Yung-Wai Chan
Date	1 December 2024

Supervisor Signature	
Date	2/12/2024

Epidemiology and Infection

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The changing epidemiology of varicella and herpes zoster in Hong Kong before universal varicella vaccination in 2014

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Abstract

In Hong Kong, universal varicella vaccination started in July 2014. Before this, children could receive varicella vaccine via the private market. We analysed the epidemiology of varicella and zoster before universal vaccination. We estimated varicella vaccination coverage through surveys in preschool children. We estimated the burden of varicella and zoster with varicella notifications from 1999/00 to 2013/14, Accident and Emergency Department (A&E) attendance and inpatient admissions to public hospitals from 2004/05 to 2013/14. We fitted a catalytic model to serological data on antibodies against varicella-zoster virus to estimate the force of infection. We found that varicella vaccination coverage gradually increased to about 50% before programme inception. In children younger than 5 years, the annual rate of varicella notifications, varicella admission and zoster A&E attendance generally declined. The annual notification, A&E attendance and hospitalisation rate of varicella and zoster generally increased for individuals between 10 and 59 years old. Varicella serology indicated an age shift during the study period towards a higher proportion of infections in slightly older individuals, but the change was most notable before vaccine licensure. In conclusion, we observed a shift in the burden of varicella to slightly older age groups with a corresponding increase in incidence but it cannot necessarily be attributed to private market vaccine coverage alone. Increasing varicella vaccination uptake in the private market might affect varicella transmission and epidemiology, but not to the level of interrupting transmission.

Introduction

Varicella is an endemic disease in most parts of the world and it is the most commonly reported notifiable infectious disease in Hong Kong [1]. Varicella vaccination has been effective in reducing the disease burden of varicella wherein routine use [2–5]. However, vaccination at low coverage may not lead to an interruption of transmission, and it may even contribute to a shift of the varicella burden in unprotected individuals towards older ages who are typically at higher risk for severe outcomes [6]. Vaccines against varicella and herpes zoster have been available in Hong Kong through the private market since 1996 and 2006, respectively. Varicella vaccine was included in the Hong Kong Childhood Immunisation Programme (HKCIP) in July 2014 for children born on or after 1 January 2013 [7]. Under the HKCIP, eligible children receive monovalent varicella vaccine (mVV) at 12 months of age and combined MMRV (measles, mumps, rubella and varicella vaccine) during their first year at primary school (about 6 years of age) as a second dose.

We document the varicella vaccination uptake before universal childhood vaccination alongside serological population profiles and the disease burden of varicella and zoster. We describe the burden of varicella and zoster in Hong Kong in the pre-universal varicella vaccination era and its changing epidemiology as a result of varicella vaccination through the private market.

Methods

Varicella vaccination coverage in pre-school children

The Department of Health (DH) conducted six rounds of territory-wide immunisation surveys to assess the uptake of different vaccines in preschool children in 2001 [8], 2003 [9], 2006 [10], 2009 [11], 2012 [12] and 2015 [13]. In summary, pre-schools in Hong Kong were selected using stratified cluster sampling. About 5% of preschools were selected in each survey (range: 24–71). All parents of the selected preschools were invited to join the survey. Consented parents completed a self-administered questionnaire to collect demographic

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information on children (including place of birth and residence) and provide all relevant immunisation records to us through the pre-primary institutions. During field visits, trained field workers collected the questionnaires and extracted information from the immunisation records to a standardised data-recording form. When the immunisation record was incomplete, parents were asked to provide other immunisation documents, if any. The response rate of these six surveys was at least 73% [8–13]. There is a high rate of pre-school attendance amongst children aged 3–5 years in Hong Kong [14]. Thus, we included children aged 3–5 years in each survey for analysis and excluded younger children. Before 2015 only information for the first dose was recorded for vaccines not included in the routine immunisation schedule, including varicella vaccines. Date of vaccination was only collected in the 2015 survey. We defined varicella vaccination uptake as the proportion of respondents who received at least one dose of varicella vaccine.

Disease burden of varicella and zoster

We used data of varicella notifications to the DH from 1999 until 2014 which included reports from public and private health sector physicians and schools. The clinical case definition for such notifications is the acute onset of diffuse (generalised) papulovesicular rash without other apparent cause or alternatively atypical (milder) clinical presentation with previous varicella vaccination. We defined probable cases as those fulfilling the clinical case definition and confirmed cases as probable cases with either laboratory confirmation or with known epidemiological links to a confirmed case [15]. We included all confirmed and probable cases in our analyses.

Furthermore, we used data on Accident and Emergency Department (A&E) attendance and inpatient admissions to public hospitals routinely collected via the Communicable Disease Information System (CDIS) of the DH. In Hong Kong, public hospitals account for around 80% of all hospitalisations [16]. Doctors assign ICD-9-CM diagnosis codes for A&E attendance and inpatient admissions as part of the clinical record. The main condition contributing to the disease episode is assigned as the primary (principal) diagnosis code, whereas other contributing condition(s) are assigned as secondary diagnosis codes. We included all A&E and inpatient admission records with an ICD-9-CM code of varicella (052) and/ or zoster (053) in the primary or secondary diagnosis code. Data from 2004 to 2015 were available for analyses. In addition, we analysed principal and secondary diagnosis codes to record the frequency of other common complications related to varicella and zoster, presence of immune-compromising conditions and pregnancy, according to a predefined list of ICD-9-CM codes (Table S1). All varicella and zoster attendance and admissions after the initial diagnosis were assumed to be part of the same illness episode. We defined the length of stay for inpatients with multiple varicella or zoster admissions during one illness episode as the cumulative number of days in the hospital. Fatal cases were defined based on discharge information in the last admission episodes.

In the fiscal year of 2009/10, the Hospital Authority (HA) introduced a pay-for-performance funding model to tie budget allocations with services provided by different hospitals [17]. In this system, the diagnoses codes are used to measure workloads [17]. We observed changes in coding practice during our study period as coding was more complete after 2009/10 (Fig. S1). Therefore, changes in the rate of varicella and zoster A&E attendance and admission might be affected by the improvement in coding completeness. To account for this change, we adjusted the annual number of A&E attendances (hospital admissions) that were coded as varicella according to the principal diagnosis by the proportion of attendances (admissions) not coded in the corresponding year and age group relative to the last study year (2013/14) (Fig. S1). Similarly, we adjusted the annual number of attendances (admissions) that were coded as varicella according to the secondary diagnoses by the average number of codes assigned per attendance (admission) in the corresponding year and age group relative to the last study year. We similarly adjusted for a change in coding for zoster.

We defined an epidemiological year as the 12 months from September to August to account for the seasonality of varicella disease burden in Hong Kong. We obtained annual age-stratified population estimates from the Census and Statistics Department [18] to compute the annual rate of varicella notification, A&E attendance and hospitalisation. We conducted Poisson (log-linear) regression to evaluate trends in age-specific annual incidence rates for different surveillance data:

$$\text{Log(cases)/Log(population)} = \text{incidence} + \text{trend} \times \text{year} + \text{error},$$

where the population was included as an offset, year indicated the number of years before 2013/14 and coefficient (trend) indicated the annual change in rate with a value of 1 equivalent to no trend.

Varicella serology and force of infection

The Public Health Laboratory Services Branch (PHLSB) of the DH conducted serological surveillance on antibodies against varicella-zoster virus (VZV) in 1995, 2000, 2005 and 2010 [19]. Convenience samples were selected from sera submitted for laboratory tests other than virology. These residual sera were collected until a predefined number was attained for different age groups. To assess whether increasing vaccine uptake in the private market had impacted varicella transmission over the study period, we fitted a single catalytic model [20] to the seroprevalence data of all 4 years in order to estimate potential changes in the force of infection (FOI – the annual rate at which susceptible individuals become infected). We assumed that infants younger than six months are protected by maternal antibodies. We found that similar to other studies, more than 90% of adults in our study had seroconverted at the time of testing [21]. Hence, we assumed individuals aged 20 years or older contribute little to transmission and restricted the fitting of our model to data from children. Since only data for four broad age strata were available for individuals under 20 years old [19], we estimated and compared the overall FOI for these individuals in different periods. We further assumed that the FOI was constant before 1995, and we estimated potential changes in the force of infection between later surveys. We jointly estimated those FOIs using a Metropolis–Hastings Markov Chain Monte Carlo algorithm with a binomial likelihood. The model equation reads:

$$z_{1995}(a) = 1 - e^{-\lambda_{\text{pre}} \cdot a_m},$$

$$z_{2000}(a) = \begin{cases} 1 - e^{-\lambda_{1995} \cdot a_m}, & a \leq 5 \\ 1 - e^{-\lambda_{pre} \cdot (a_m - 5)} \cdot e^{-\lambda_{1995} \cdot 5}, & a > 5, \end{cases}$$

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$$z_{2005}(a) = \begin{cases} 1 - e^{-\lambda_{2000} \cdot a_m}, & a \leq 5 \\ 1 - e^{-\lambda_{1995} \cdot (a_m - 5)} \cdot e^{-\lambda_{2000} \cdot 5}, & 5 < a \leq 10 \\ 1 - e^{-\lambda_{pre} \cdot (a_m - 10)} \cdot e^{-\lambda_{1995} \cdot 5} \cdot e^{-\lambda_{2000} \cdot 5}, & a > 10, \end{cases}$$

$$z_{2010}(a) = \begin{cases} 1 - e^{-\lambda_{2005} \cdot a_m}, & a \leq 5 \\ 1 - e^{-\lambda_{2000} \cdot (a_m - 5)} \cdot e^{-\lambda_{2005} \cdot 5}, & 5 < a \leq 10 \\ 1 - e^{-\lambda_{1995} \cdot (a_m - 10)} \cdot e^{-\lambda_{2000} \cdot 5} \cdot e^{-\lambda_{2005} \cdot 5}, & 10 < a \leq 15 \\ 1 - e^{-\lambda_{pre} \cdot (a_m - 15)} \cdot e^{-\lambda_{1995} \cdot 5} \cdot e^{-\lambda_{2000} \cdot 5} \cdot e^{-\lambda_{2005} \cdot 5}, & a > 15, \end{cases}$$

where $z_Y(a)$ is the proportion of seropositive individuals in year Y and at age a and $a_m = a - 0.5$. Further, λ_{pre}, λ_{1995}, λ_{2000}, λ_{2005} are the FOI before 1995, from 1995 to 1999, from 2000 to 2004 and from 2005 onwards, respectively.

As varicella vaccine was available in the private market since 1996 and the vaccine uptake increased over the years, some individuals tested seropositive might have seroconverted through vaccination irrespective of natural infection. To adjust for that we calculated the age-specific proportion of vaccinees in respective survey years by interpolating results from the coverage surveys, assuming 65% of them seroconverted [22] (Table S2) and the remaining proportion of the population could seroconvert due to natural infection:

$$\hat{z}_Y(a) = z_Y(a) \cdot (1 - v_Y(a)) + v_Y(a),$$

where $\hat{z}_Y(a)$is the adjusted proportion of seropositive individuals in year Y and at age a, after taking into account the proportion of seroconversion arising from vaccination ($v_Y(a)$) and $z_Y(a)$ as defined above.

We conducted a sensitivity analysis on the model fitting by using data estimated from the 95% confidence bounds of the proportion of vaccinees seroconverted (Fig. S3). Based on the FOI estimated, we computed the reproduction number corresponding to each estimated FOI by assuming random mixing and a rectangular age distribution as $R_0 = L \cdot \lambda$ [23], where L is the average life-expectancy in Hong Kong in 1995 [24].

We further estimated the number of new infections $I_Y(a)$ as the product of the proportion of seronegative (and hence susceptible), the annual FOI and the respective population size ($P_Y(a)$):

$$I_Y(a) = (1 - z_Y(a)) \cdot \lambda_Y \cdot P_Y(a).$$

To assess underreporting of varicella notification, we computed the ratio between the number of notifications and the estimated number of new infections. As age-specific notification data are not available for 1995, this analysis was limited to 2000, 2005 and 2010 only.

All statistical tests and the catalytic model were programmed in R [25].

Results

Varicella vaccination uptake in preschool children

Uptake of at least one dose of varicella vaccine among preschool children gradually increased to about 50% during the decade before the introduction of the universal varicella vaccination programme in Hong Kong (Fig. 1a). For children born in 2009, 2010 and 2011, <10% had received a second dose of varicella vaccine before the age of 6, 5 and 4 years, respectively. Most children in these cohorts received the first dose of varicella vaccine before 20 months of age (Fig. 1b).

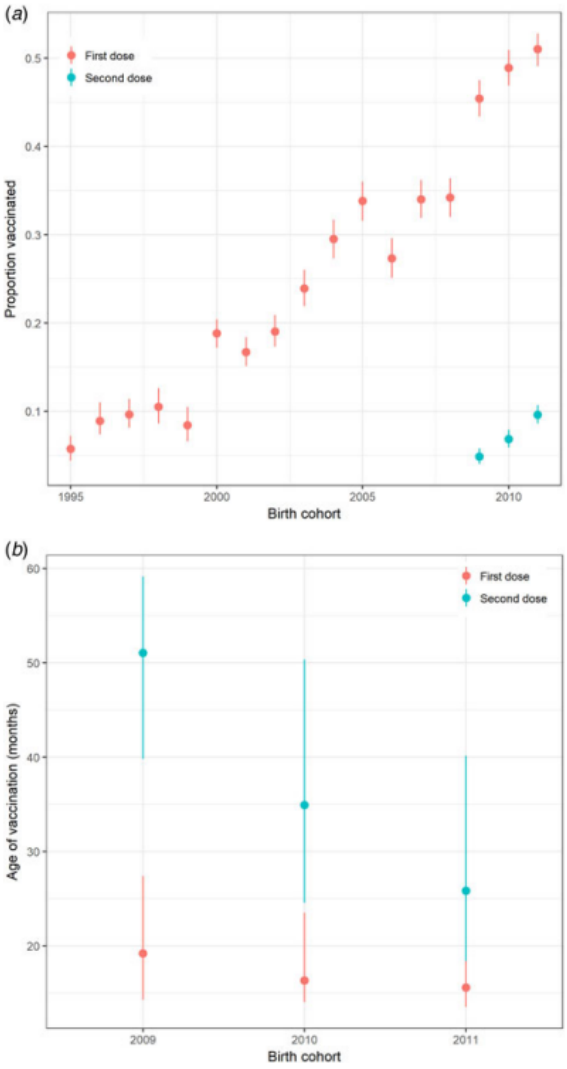

Fig. 1. Varicella vaccination in preschool children in Hong Kong. (a) Proportion of preschool children in Hong Kong receiving varicella vaccine by birth cohort, 1995–2011 and (b) Interquartile range of age at receipt of varicella vaccination (months) for preschool children born from 2009 to 2011 by birth cohort and a dose of vaccine calculated from the survey in 2015. Note: Uptake on the second dose of vaccine was only recorded for children born in 2009–2011.

Disease burden, temporal trends and seasonality of varicella and zoster

From September 1999 to August 2014, over 173 000 varicella cases were reported to the DH, corresponding to an average annual incidence of 156 per 100 000 population. There were 14 144 varicella episodes recorded under A&E attendance and 2860 under inpatient admissions during the same period (Table 1). Varicella primarily affected young children aged

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Table 1. Baseline characteristics of varicella and zoster cases in Hong Kong

		Varicella			Zoster	
		Statutory notification	A&E attendance	Inpatient admission	A&E attendance	Inpatient admission
Study period		September 1999–August 2014	September 2004–August 2014			
No. of cases		173 748	14 144	2860	23 456	12 885
No. of cases with multiple attendance/admission (%)		NA	1470 (10)	164 (6)	4423 (19)	2600 (20)
No. of attendance/admission	Median (range)	NA	1 (1–6)	1 (1–11)	1 (1–48)	1 (1–37)
Gender (%)	Male	90 355 (52)	7626 (54)	1546 (54)	11 721 (50)	6066 (47)
	Female	80 391 (47)	6518 (46)	1314 (46)	11 735 (50)	6819 (53)
	Unknown	2002 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Age in years	Median (range)	6 (0–99)	7 (0–92)	6 (0–98)	59 (0–104)	73 (0–110)
CFR (per 1000 cases)		0	0	3	0	38

under 10 years. The average annual notification, A&E attendance and inpatient admission rate decreased with age (Fig. 2a). The average annual notification rate per 100 000 for those aged 5–9 years and those aged under 5 years were similar (1620 and 1555, respectively). On the other hand, the A&E attendance and inpatient admission were highest for those aged under 5 years (202 and 51 per 100 000, respectively).

Four per cent of cases admitted due to varicella were immunodeficient (Table 2). Nineteen per cent of female admissions aged 20 years or above were pregnant. Less than 1% of varicella A&E attendance was associated with complications, compared with 20% in varicella admission (Tables 2).

The number of zoster A&E attendance and inpatient admissions was higher than that for varicella. Nineteen per cent had multiple A&E attendance or admissions (Table 1). The median age of zoster A&E attendance and admissions were 59 and 73 years, respectively. In contrast to varicella, the average annual A&E attendance and inpatient admission rate for zoster increased with age (Fig. 2a) and was highest for those aged 60 years and above (both 117 per 100 000). The rate of zoster admission for those aged 80 years and above was nearly four times higher than that for those aged 60–79 (Fig. 2a). Complications occurred in 23% of zoster admissions, with post-herpetic neuralgia (PHN) (13%) and ophthalmic complications (5%) being the most common (Table 3).

There were no deaths recorded for varicella and zoster A&E attendance. The crude case-fatality rate of varicella notification, varicella and zoster admissions were 0.005, 3.1 and 37.6 deaths per 1000 cases, respectively.

Varicella notifications, A&E attendance and hospitalisations exhibited strong seasonal patterns with additional inter-season variation (Figs 2b & c). In contrast, zoster-related A&E attendance and admission did not show much intra- or inter-season variance (Figs 2b & c). Both the rate of zoster A&E attendance and admission increased with age.

Changing epidemiology over time

The estimated coefficients for time trend in the annual rate of varicella notification, varicella and zoster A&E attendance and hospitalisations in Hong Kong is presented in Figure 3. In children younger than 5 years, the annual rate of varicella notification (−2.5% (95% CI −2.4 to −2.7%)), varicella admissions (−5.6% (95% CI −3.7 to −7.5%)) and zoster A&E attendance (−13.3% (95% CI −5.3 to −21.3%)) generally decreased during the study period (Fig. 3). The annual notification, A&E attendance and hospitalisation rate of varicella and zoster generally increased for individuals between 10 and 59 years old, although no significant changes were observed for some age groups (those aged 10–14 years in zoster A&E attendance, those aged 40–59 years in varicella admission and those aged 10–19 years in zoster admission). The annual rate of increase was 3.0% (95% CI 1.1–5.0%) to 11.2% (95% CI 9.5–12.9%) for varicella and 0.2% (95% CI −5.7 to 6.3%) to 6.8% (95% CI 5.3–8.3%) for zoster. For children aged 5–9 years and adults of at least 60 years, we found no consistent trend in either direction.

In addition to varicella notification, varicella serology also indicated an age shift towards a higher proportion of infections in slightly older individuals. These changes were most notable from the period before vaccine licensure to vaccine introduction in the private market and when the vaccine uptake further increased in the private market from 2005 onwards (Fig. 4a & b). The annual FOI before vaccine introduction in the private market was estimated to be 0.22 (95% CI 0.19–0.25) and it decreased to 0.13 (95% CI 0.10–0.17) from 1995 to 1999. After vaccine licensure, the FOI from 2000 to 2004 was stable at 0.12 (95% CI 0.10–0.15), but it further reduced to 0.08 (95% CI 0.06–0.11) from 2005 onwards (Fig. 4b). This corresponds to a reduction in reproduction number from 17.2 (95% CI 15.2–19.4) to 10.4 (95% CI 7.8–13.5), 9.8 (95% CI 7.8–12.1) and 6.6 (95% CI 4.7–8.7) (Fig. 4b). The estimated average age of infection increased from 4.6 (95% CI 4.1–5.2) in 1995 to 7.7 (95% CI 5.9–10.2) in 2000, and 8.3 (95% CI 6.7–10.4) in 2005 and 12.4 (95% CI 9.4–17.6) in 2010.

Underreporting of varicella notification

When compared with the number of varicella notifications, 13%, 22% and 29% of the estimated varicella infections in 2000, 2005

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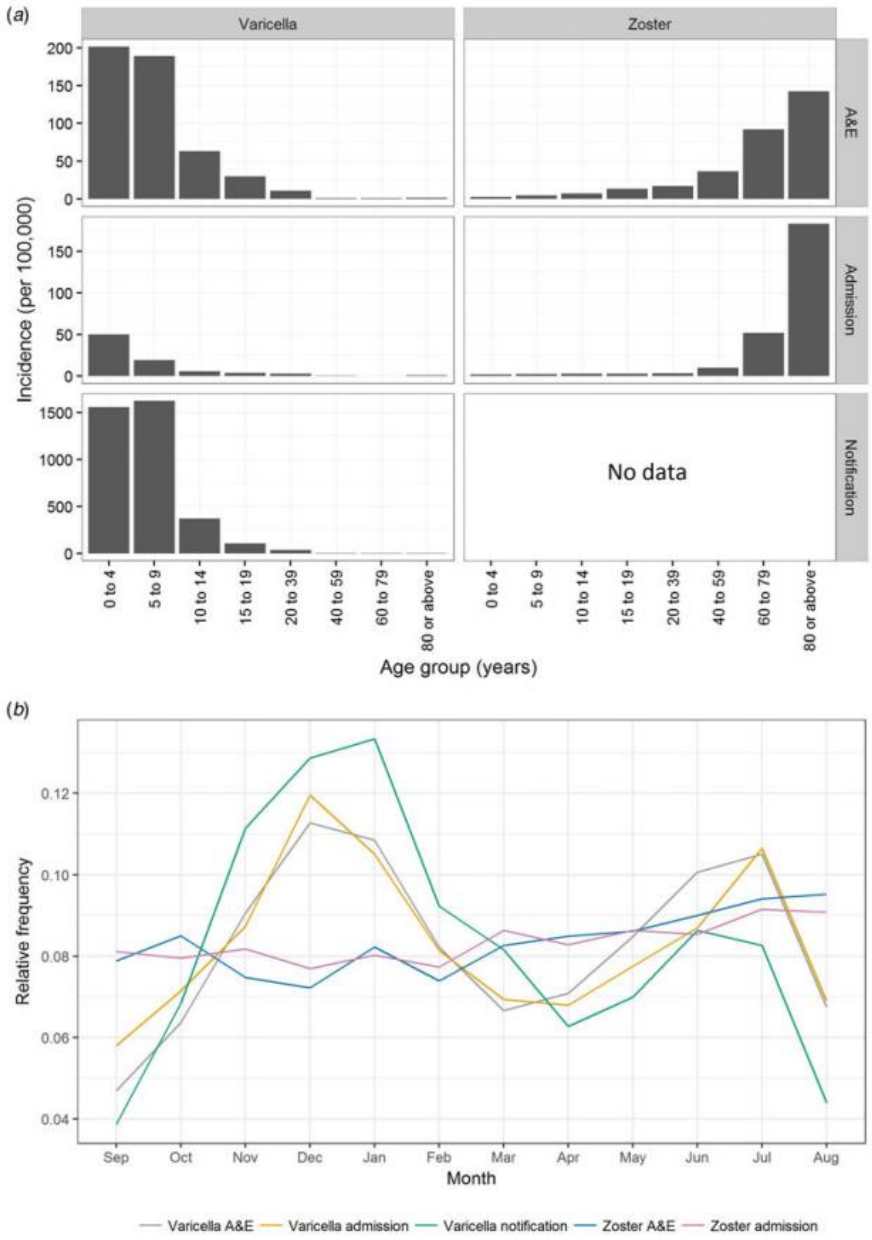

Fig. 2. Varicella notification, varicella and zoster A&E attendance and hospitalisation in Hong Kong. (a) The average annual rate of varicella and zoster in Hong Kong during the study period, (b) relative frequency distribution for cases of all ages by month throughout the study period and (c) rate of varicella and zoster by epidemiological year. Notification is available only for varicella. Epidemiological year was defined as 12 months from September to August.

and 2010 were reported. The reporting ratio differed by age and year (Fig. 4c). Reporting was most complete for those aged 3–10 years.

Discussion

Before the introduction of universal varicella vaccination in Hong Kong, vaccine uptake through the private market increased gradually to about 50%. We showed that varicella and zoster are common diseases in Hong Kong. We observed a shift in the burden of varicella to slightly older age groups with a corresponding increase in A&E attendance and hospitalisations in these age groups. We also showed from cross-sectional serological surveys that the transmission intensity of varicella decreased while the average age of varicella infection increased shortly after vaccine licensure. Therefore, the shift in disease burden

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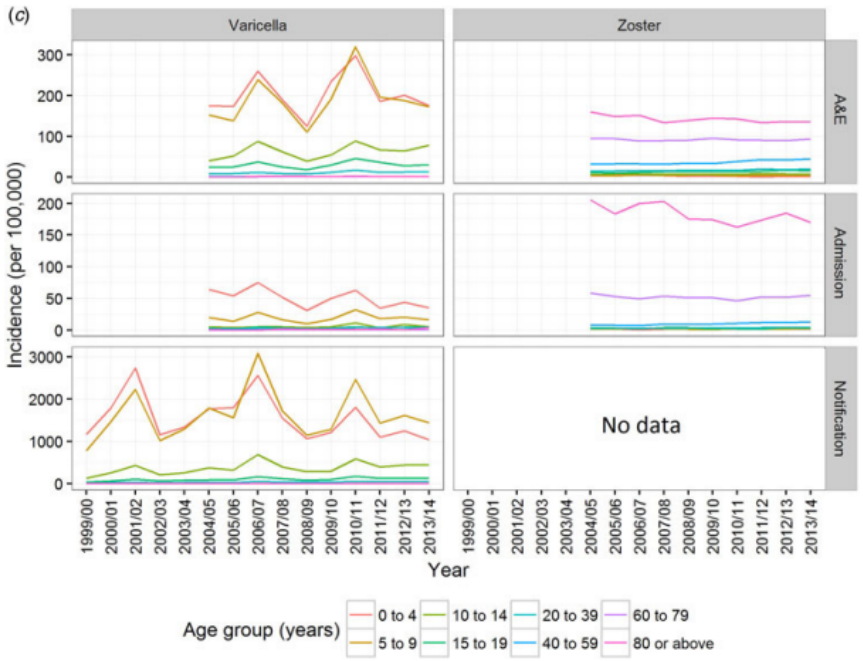

Fig. 2. Continued.

may not be solely associated with the increasing vaccine uptake in the community.

The annual FOI before vaccine use in the private sector was estimated to be 0.22 (95% CI 0.19–0.25), which is high compared with the FOI in Australia before use of varicella vaccine [26] and comparable with some of the estimates from 11 countries in Europe [21]. The difference in the intensity and pattern of population mixing may contribute to the variations in varicella transmission estimates. It should be noted that varicella transmission may be facilitated in a densely populated area. The population density (per square kilometre) in Hong Kong (5758) was much higher than those in Australia (2) and the 11 countries included in the European study (15–378), according to estimates of United Nations in 1995 [27].

The decrease in transmission intensity of varicella was most prominent from 1995 to 1999, but the initial vaccine uptake during this period was low. While the low vaccination uptake might have had some effect on varicella transmission, other factors such as temporal changes in contact mixing could have played an additional role. However, the first published social contact data in Hong Kong were collected in 2009 and 2010 [28] and earlier data are not available for comparison. Nevertheless, we did observe some reduction in the overall number of students and class size in a comparable period from data from the Education Bureau [29] and Social Welfare Department [30] (Fig. S2).

The age shift in varicella infection leaves unvaccinated individuals at increased risk of complications that accompany infection [31]. This includes varicella infection during pregnancy which can result in transplacental transmission of VZV to the foetus and lead to stillbirths or permanent congenital defects [32]. Our analysis of public hospital admissions showed that 19% of women aged 20 years or older with varicella-related admissions were pregnant. This overrepresentation of pregnant women further highlights the need for increased awareness among healthcare workers of the risk of varicella during pregnancy.

Albeit inconclusive from this analysis, if indeed the increased vaccine uptake in the private sector contributed to the age shift in varicella burden, it creates an issue of equity as those older non-immune children not eligible for universal vaccination would be less likely to acquire natural immunity at a young age. With the inclusion of varicella vaccine in the Childhood Immunisation Programme, vaccination uptake should soon exceed 90% and, in the mid-term, likely prevents the majority of varicella illnesses during childhood. However, in the short-term the additional reduction in transmission leaves those cohorts of children who are too old to be eligible for vaccination and who have not been vaccinated through the private market at an even higher risk. We have established a baseline rate which will allow monitoring to identify trends in varicella complications and act on them swiftly.

Furthermore, we found that the burden of zoster A&E attendance and hospitalisations in adults has been on the rise in the pre-universal varicella vaccination era. Circulation of VZV in the community is believed to boost immunity against zoster for individuals previously infected with varicella. It is possible that the gradual increase in varicella vaccination uptake reduced transmission and hence boosting, leading to the observed increase in zoster A&E attendance and hospitalisations among adults. However, the estimated annual decrease in varicella notification and admission for children was 2.5% and 5.6%, and hence effects on transmission may be relatively small. The relationship of childhood varicella vaccination and adult zoster burden continues to be a point for discussion [33]. In addition, other temporal changes might have also contributed to this increase in burden (Fig. S2). In particular, the change in the incentive to code A&E attendance and hospital admissions has made such interpretation difficult.

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Table 2. Underlying medical conditions, complications and outcomes of varicella-related A&E attendance and inpatient admissions

	A&E attendance in public hospitals		Inpatient admission in public hospitals	
	N	%	*N*	%
No. of cases	14 144	–	2860	–
Underlying medical conditions				
Pregnancy[a]	15	1.2	87	19.0
Immunodeficiency (any)[b]	0	–	110	3.8
Lymphoproliferative malignancy	0	–	50	1.7
Malignancy of solid organ/tissue	0	–	21	0.7
Transplant	0	–	22	0.8
HIV	0	–	5	0.2
Other immunodeficiency condition[c]	0	–	25	0.9
Complication[b]	97	0.7	575	20.1
Pneumonia	12	0.1	92	3.2
Varicella pneumonitis	4	0.0	10	0.3
Other pneumonia	8	0.1	82	2.9
Neurological disorder	6	0.0	35	1.2
Encephalitis	0	–	12	0.4
Ataxia	0	–	10	0.3
Meningitis	6	0.0	13	0.5
Myelitis	0	–	2	0.1
Other unspecified viral infection of the central nervous system	0	–	0	–
Septicaemia/sepsis	0	–	21	0.7
Bacterial infections (including scarlet fever and bacterial infection caused by Streptococcal and Staphylococcal species)	0	–	238	8.3
Bacterial superinfection of skin and/or soft tissue	14	0.1	101	3.5
Cellulitis, *abscess* and *erysipelas*	13	0.1	83	2.9
Impetigo	1	0.0	17	0.6
Fasciitis	0	–	3	0.1
Ophthalmic disorders (including conjunctivitis and keratoconjunctivitis)	11	0.1	14	0.5
Congenital varicella infection	0	–	0	–
Outcome				
Hospitalisation	563	4.0	NA	NA
Median length of stay (days)	NA	NA	4	
Among cases with complications	NA	NA	5	
Among cases without complications	NA	NA	4	
ICU admission	NA	NA	19	0.7
Among cases with complications	NA	NA	6	1.0
Among cases without complications	NA	NA	13	0.6
Death	0	0.0	9	0.3
Among cases with complications	–	–	6	1.0
Among cases without complications	–	–	3	0.1

[a]Pregnancy among females aged 20 years or above.
[b]More than one type of immunodeficiency/complications were coded in some episode of A&E attendance and admission.
[c]These include conditions such as white blood cell diseases, Thalassaemia major, aplastic anaemia, asplenia or other splenic diseases, other specified diseases with the participation of lymphoreticular and reticulohistiocytic tissue, patients undergoing chemotherapy or radiotherapy and other conditions affecting the immune system.

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Table 3. Underlying medical conditions, complications and outcomes of zoster-related A&E attendance and inpatient admissions

	A&E attendance in public hospitals		Inpatient admission in public hospitals	
	N	%	*N*	%
No. of cases	23 456	–	12 885	–
Underlying medical conditions				
Pregnancy[a]	3	0.0	38	0.6
Immunodeficiency (any)	11	0.0	1952	15.1
Lymphoproliferative malignancy	2	0.0	691	5.4
Malignancy of solid organ/tissue	5	0.0	855	6.6
Transplant	0	0.0	259	2.0
HIV	3	0.0	68	0.5
Other immunodeficiency condition[b]	1	0.0	303	2.4
Complication	426	1.8	2989	23.2
Neurological disorders	1920	8.2	2047	15.9
Encephalitis	2	0.0	28	0.2
Meningitis	14	0.1	61	0.5
Post herpetic neuralgia	1848	7.9	1646	12.8
Post herpetic trigeminal neuralgia	35	0.2	65	0.5
Post herpetic polyneuropathy	8	0.0	8	0.1
Viral infection of the nervous system	22	0.1	72	0.6
Ophthalmic complications	699	2.9	627	4.9
Geniculate zoster/Ramsay-hunt syndrome	318	1.4	400	3.1
Auricular involvement	31	0.1	37	0.3
Disseminated zoster	13	0.1	77	0.6
Outcome				
Hospitalisation	1485	6.3	NA	NA
Median length of stay (days)	NA	NA	7	
Among cases with complications	NA	NA	8	
Among cases without complications	NA	NA	6	
ICU admission	NA	NA	24	0.2
Among cases with complications	NA	NA	7	0.2
Among cases without complications	NA	NA	17	0.2
Death	0	0.0	484	3.8
Among cases with complications	–	–	117	3.9
Among cases without complications	–	–	367	3.7

[a]Pregnancy among females aged 20 years or above.
[b]These include conditions such as white blood cell diseases, Thalassaemia major, aplastic anaemia, asplenia or other splenic diseases, other specified diseases with the participation of lymphoreticular and reticulohistiocytic tissue, patients undergoing chemotherapy or radiotherapy and other conditions affecting the immune system.

While we accounted for such changes in coding for both primary and secondary diagnoses when estimating the burden of A&E attendance and hospitalisations, we cannot rule out that such changes have contributed to our findings of increasing rate of zoster A&E attendance and hospitalisations among adults.

Based on the existing data, we found no evidence of an increase in zoster A&E attendance and hospitalisation rate among the two oldest age groups, for which the burden of zoster disease is highest. However, this observation may have been affected by a change in healthcare-seeking behaviour instead of zoster vaccination, for which <10% of those aged 60 years or above should have received zoster vaccination (personal communication with Drug Office of the Department of Health). Specifically, since 2009 the Government introduced Health Care Vouchers (HCV) for elders aged 70 years or above to subsidise healthcare costs in the private medical sector (which is not covered by our zoster data) [34]. The amount of annual subsidy has increased from $250 in 2009 to $2000 in 2015.

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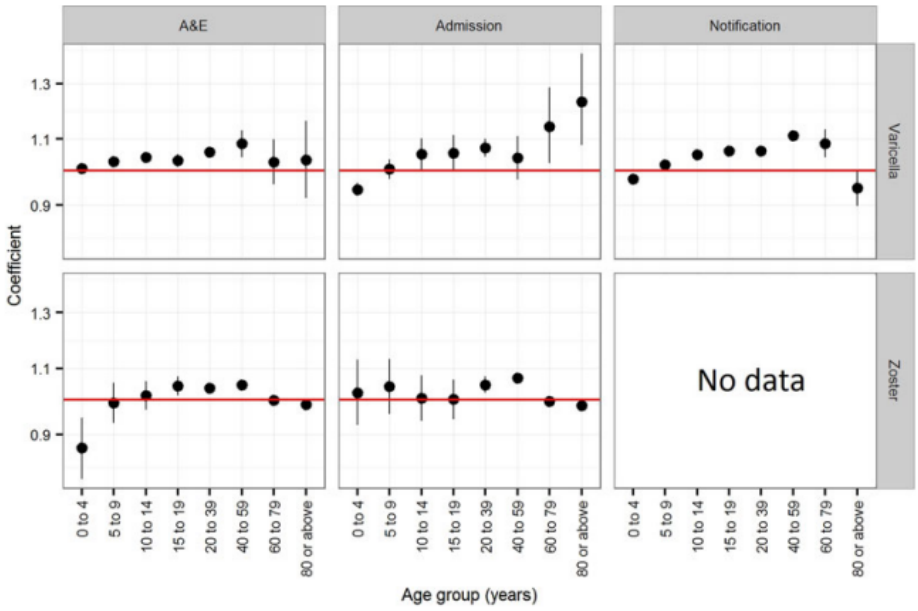

Fig. 3. Coefficients (trends) of the Poisson regression on the annual rate of varicella notification, varicella and zoster A&E attendance and hospitalsations in Hong Kong. Notification is available only for varicella. A coefficient of zero indicates no change.

Cross-sectional surveys showed that the proportion of the elderly having ever used HCV increased from 35% in 2010 [35] to 80% in 2015 [36]. Thematic Household Surveys [16] conducted by the Census & Statistics Department indicated that individuals aged 65 years or above attended more private practitioners but less A&E doctors in recent years (personal communication with Census & Statistics Department). The proportion of inpatient admission at private hospitals increased from 4% in 1999 to 10% in 2014.

Based on the number of varicella infections estimated by fitting the serological data to the catalytic model, only 13–29% of infections were notified. This is comparable with studies in Italy [37] and the USA [38], which similarly found that notification was most complete in children 5–9 years old and that less than half of varicella cases are notified, albeit using different methodologies to estimate underreporting. Varicella is a generally mild disease and hence parents may be reluctant to seek medical consultation. In particular, Hong Kong parents do not need medical confirmation if their child is absent from (pre-) school. Furthermore, doctors may mis-classify particularly mild symptoms of varicella. Reporting was most complete in children 3–6 years old in our study. Under the current reporting system, (pre-) schools are required to report varicella outbreaks and hence cases that are not usually seen by a doctor could be identified this way. We also found that reporting was more complete in later years, potentially related to increased awareness of varicella after the vaccine was more widely available in the community.

There are several limitations of this study. First, A&E attendance and admission with diagnosis codes for VZV in pregnancy/postpartum were not available and this may lead to slight underestimation of the disease burden. Second, clinical notes were not available to ascertain the specificity and accuracy of the ICD codings. For instance, there were one and 21 A&E attendance and hospitalisations coded with both varicella and zoster, respectively. Likewise, fatal outcomes following varicella and zoster A&E attendance and hospitalisations might be attributed to other concurrent diseases, which resulted in an apparently high case-fatality rate of zoster. On the other hand, only 4% and 17% of the hospitalised varicella and zoster cases had codes related to immune-deficient conditions (Table S1), which were lower than one US study using similar methodology [39]. This could be due to the difference in coding practice or criteria in admitting cases, but it is difficult to ascertain without review of clinical records. Third, although we adjusted the estimates of varicella and zoster A&E attendance and admissions rate with the coding rate in respective years, changes in healthcare-seeking behaviour might vary during the study period. Fourth, residual sera for the seroprevalence surveys were sampled conveniently and they might differ from the general population, although a study in Australia [40] showed that sero-immunity against most vaccine-preventable diseases estimated from samples collected through convenient and random sampling were largely comparable. Fifth, while commercially available VZV whole-cell (wc) enzyme-linked immunosorbent assay (ELISA) kits are regarded as sufficient in detecting seroconversion arising from natural infection, its reliability in assessing seroconversion from vaccination is not well documented [41]. In our model, we rely on an estimate from Sauerbrei *et al.* [22] for which 37 of 57 (65% [95% CI 51–77%]) of individuals aged 2–35 years were tested positive by a commercially available wc ELISA kit 4–6 weeks after receiving one or two doses of mVV. We conducted sensitivity analysis on model fitting based on data estimated from the confidence bounds of Sauerbrei *et al.*'s work. This showed that the modelled proportion seropositive was largely comparable even after taking into account variations in the seroconversion among vaccinees (Fig. S3). In addition, circulation of wild-type VZV is believed to boost immunity of previously infected individuals [42]. There is also evidence of such boosting in the

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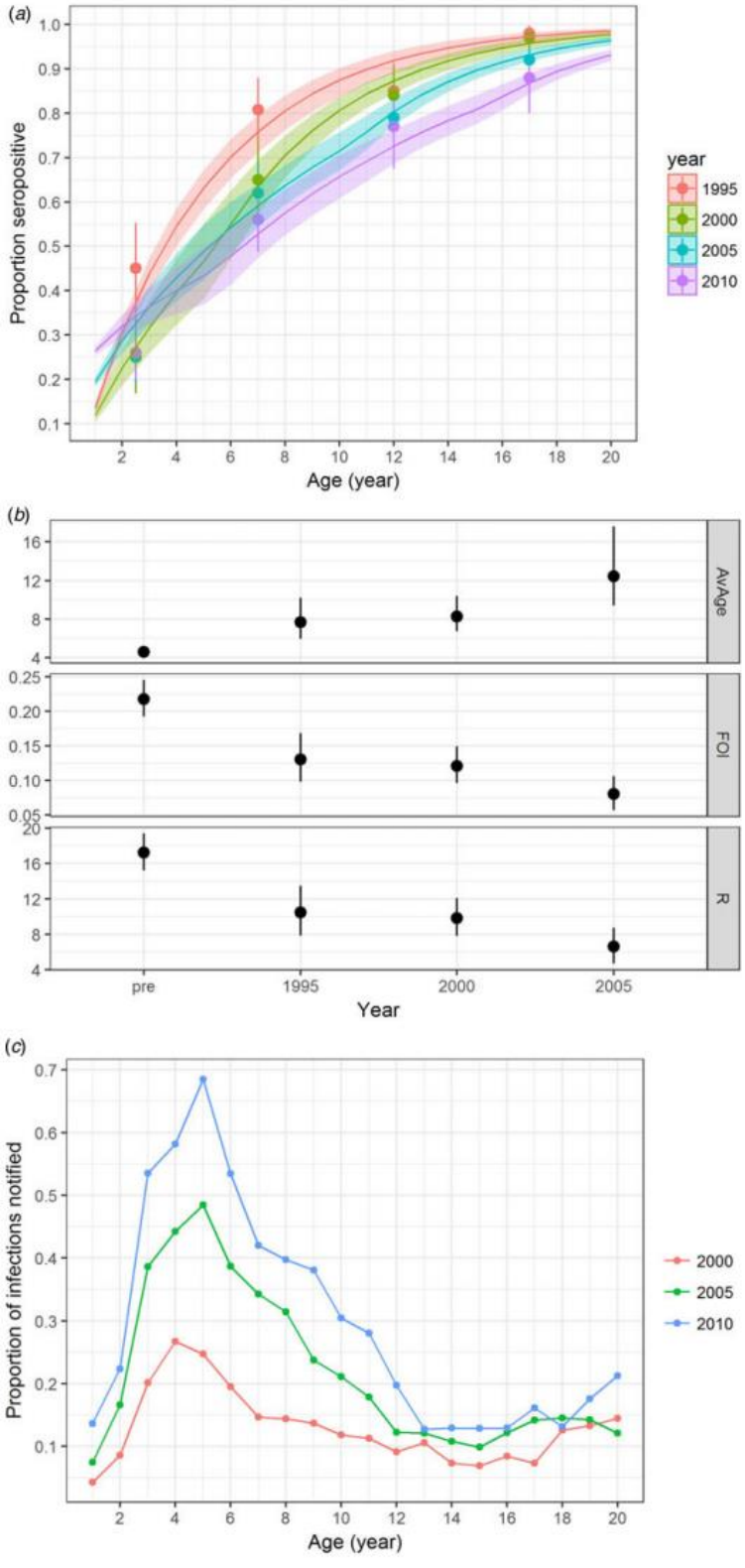

Fig. 4. Varicella serology and estimated transmission parameters in Hong Kong in 1995, 2000, 2005 and 2010. (a) Proportion seropositive against varicella antibody by ELISA test (points with error bars representing 95% CI) and model fitting (line charts with shaded errors bands representing 95% CI), (b) average age of infection [AvAge], annual average force of infection [FOI] and basic reproduction number [R] and (c) reporting ratio between varicella notification and number of infections estimated. Age-specific data on varicella notification are only available for analysis for the year 1999 and onwards.

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persistence of immunity in vaccinees [43]. Therefore, natural infection (as indicated by the FOI) might not only contribute to the seroconversion in those naturally infected but also the vaccinees, especially a few years after vaccination. This is particularly relevant to our study in Hong Kong, as the circulation of VZV continues among those unvaccinated in the absence of universal vaccination. The magnitude of such boosting in vaccinees is not well understood. Sixth, consultations in public and private outpatient settings account for nearly 80% of all consultations [16], but zoster data in these settings were not available for a more comprehensive assessment of the disease burden. Furthermore, non-residents who sought medical care in Hong Kong may contribute to the burden of varicella and zoster as well as varicella serology. Importation status was only available for varicella notifications from 1999 to 2003, but imported cases contributed to only 0.2% of all notifications in this period. This proportion might have increased in recent years as the number of babies born in Hong Kong to mainland women was on the rise until 2013 [44]. Although some of these babies are raised in mainland China, they may later move to Hong Kong for education or continue to reside in mainland China but travel to Hong Kong regularly as cross-border students [45]. The impact of these demographic changes to our observations is unclear as details are not available.

In conclusion, we establish an estimate of the burden of varicella and zoster in Hong Kong in the era before universal childhood vaccination against varicella. We show that vaccination uptake increased substantially through private sector access before universal vaccination; although not to levels that likely interrupt transmission. We present evidence that during the same time period, the disease burden of varicella has shifted towards older children which sees unvaccinated individuals at increased risk of disease complications. Concurrently we observed an increase in zoster A&E attendance and hospitalisation rate among young and middle-aged adults. Serological data extending back to 1995 suggest that age shifts in varicella infections started before licensure of varicella vaccine and hence cannot necessarily be attributed to private market vaccine coverage alone. With the decision taken in 2013 to offer universal varicella vaccination in Hong Kong, we expect the burden of varicella in young children to decline in subsequent years. However, further research is needed to appraise the necessity of a catch-up campaign to protect children not currently eligible for vaccination, the likely impact of different vaccination schedules, and the cost-effectiveness of the programme.

Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1017/S0950268818000444.

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Declaration of interest. None.

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2.3 Supplementary Materials

Epidemiology and Infection

Title: The changing epidemiology of varicella and herpes zoster in Hong Kong before universal varicella vaccination in 2014

Authors

D.Y.W. CHAN, W. J. EDMUNDS, H.L. CHAN, V. CHAN, Y.C.K. LAM, S.L. THOMAS, A. J. VAN HOEK, S. FLASCHE

Supplementary Material

Supplementary Table S1. ICD-9-CM codes related to disease and common complications of varicella and zoster, as well as underlying conditions of pregnancy and immunodeficiency

Supplementary Table S2. Estimation of proportion seroconverted among vaccinees in different serological surveys

Supplementary Figure S1. Coding practice of A&E attendance and inpatient admission in public hospitals of Hong Kong, 2004/05 to 2013/14. (a) Proportion of A&E attendance coded, (b) average number of codes per A&E attendance, (c) proportion of A&E referred admission coded and (d) average number of codes per A&E referred admission

Supplementary Figure S2. No. of enrolment, average no. of enrolment per school and per class in preschools^, primary and secondary schools in Hong Kong, 1990 to 2015 (Source: Education Bureau and Social Welfare Department, Hong Kong SAR Government).

Supplementary Figure S3. Proportion seropositive against varicella antibody and model fitting with sensitivity analysis.

Supplementary Table S1. ICD-9-CM codes related to disease and common complications of varicella and zoster, as well as underlying conditions of pregnancy and immunodeficiency

Condition	Description	ICD-9-CM Codes
Varicella		
Varicella without complication		052.9^
Varicella with complication		052.7^*, 052.8^
Neurological complications	Encephalitis	052.0^, 049.8, 049.9, 136.9, 294.1, 323.0, 323.4, 323.6, 323.8, 323.9
	Meningitis	052.7^*, 047.8, 047.9, 321.2, 321.8, 322.0, 322.9
	Demyelineating disease	323.9, 341.0, 341.8, 341.9, 377.3
	Cerebellar ataxia	334.3, 334.4
	Viral infection of the central nervous system	049.9
Pneumonia/ Pneumonitis	Varicella pneumonitis	052.1^
	Pneumococcal pneumonia	481*
	Streptococcal pneumonia	482.30-482.39
	Staphylococcal pneumonia	482.4
	Other pneumonia/ pneumonitis	136.9, 480, 480.8, 480.9, 481*, 482.9, 483.8, 484, 484.8, 485, 486
Septicaemia		038.0-038.3, 038.40-038.49,

		038.8-038.9
Other bacterial infections	Toxic shock syndrome	040.89,
	Pneumococcal infection	041.06, 041.2, 711.00
	Streptococcal infection	034.0, 034.1, 041.00-041.05, 041.09
	Staphylococcal infection	041.10, 041.11, 041.19, 711.00
Skin and soft tissue infections	Cellulitis, abscess and erysipelas	035, 681.0-681.9, 682.0-682.9
	Impetigo	684, 686.8
	Fasciitis	728.86, 729.4
		370.40, 370.49, 372.00, 372.02, 372.03, 372.05, 372.20, 372.30, 372.33, 372.39
Congenital varicella infection		771.8
VZV in pregnancy/ postpartum		647.60, 647.63, 647.64
Zoster		
Zoster (without mention of complication)		053.9^
Zoster with complications		053.7^, 053.79^, 053.8^
Geniculate herpes zoster/ Ramsay Hunt syndrome		053.11^
Neurological complications	Encephalitis	053.19^, 049.8, 049.9, 136.9, 294.1, 323.0, 323.4, 323.6, 323.8, 323.9
	Meningitis	053.0^, 047.8, 047.9,

		321.2, 321.8, 322.0, 322.9
	Postherpetic neuralgia	053.19^
	Postherpetic polyneuropathy	053.13^
	Postherpetic trigeminal neuralgia	053.12^
	Viral infection of the nervous system	053.1^, 053.10^, 053.19^, 049.9
Zoster with auricular involvement		053.71^
Zoster with ophthalmic complications		053.20-053.29
VZV in pregnancy/ postpartum		647.60, 647.63, 647.64
Immunodeficiency		
	Malignancy involving solid organ/ tissue	140-165, 170-176, 179-199, 573.8
	Lymphoproliferative malignancy	200-208
	Transplantation#	996.8, V42.0-V42.4, V42.6-V42.9, V58.49
	Human immunodeficiency virus	042-044, 294.1, 647.60, 647.61, 647.63, 647.64, 795.8, V02.9, V08
	Chemotherapy	277.8, 799.8, V07.3, V07.39, V58.1, V66.1, V66.2, V67.2
	Radiotherapy	253.7, 457.1, 558.1, 990, E879.2, V58.0, V67.1
	Asplenia or other splenic	289.4, 289.5, 759.0,

	disease	V45.89
	Other conditions affecting immune system**	277.8, 279.01-279.09, 279.1-279.9, 282.4, 284, 284.8, 284.9, 288, 288.8, 648.2, 648.23, V02.9
Pregnancy		633.8, 634-677, 694.3, 694.4, 760-763, 773.2, 779.9, 799.9, V22-V24, V27-V39, V41.9, V61.7, V65.9

Remarks:

^ICD-9-CM codes specific to varicella and zoster

**An extension code known as Term ID is adopted by the Hospital Authority to supplement the ICD-9-CM codes. Thus the same ICD-9-CM code may represent different description as their Term ID differs*

#excluding corneal transplantation

***Including primary immunodeficiency, WBC diseases, aplastic anaemia, thalassaemia major, and other specified diseases with participation of lymphoreticular and reticulohistiocytic tissue*

Supplementary Table S2. Estimation of proportion seroconverted among vaccinees in different serological surveys

Year of survey	Age group	Birth cohort[1]	Proportion vaccinated[2]	Proportion seroconverted due to vaccination[3]
1995	1 to 4	1991-1994	5.7%	3.7%
	5 to 9	1986-1990	0.0%	0.0%
	10 to 14	1981-1985	0.0%	0.0%
	15 to 19	1976-1980	0.0%	0.0%
2000	1 to 4	1996-1999	9.3%	6.1%
	5 to 9	1991-1995	5.7%	3.7%
	10 to 14	1986-1990	0.0%	0.0%
	15 to 19	1981-1985	0.0%	0.0%
2005	1 to 4	2001-2004	22.1%	14.3%
	5 to 9	1996-2000	12.7%	8.2%
	10 to 14	1991-1995	5.7%	3.7%
	15 to 19	1986-1990	0.0%	0.0%
2010	1 to 4	2006-2009	36.1%	23.4%
	5 to 9	2001-2005	24.4%	15.9%
	10 to 14	1996-2000	12.7%	8.2%
	15 to 19	1991-1995	5.7%	3.7%

Remarks:

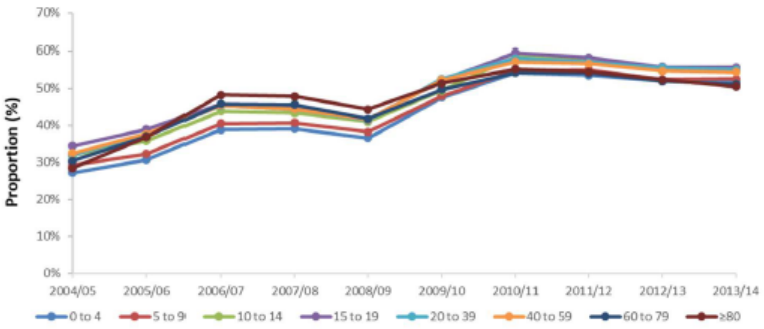
1. Birth cohort deduced from age group and corresponding survey year.

2.Proportion vaccinated was obtained from first dose varicella vaccination uptake in the immunisation coverage surveys on preschool children in 2001, 2003, 2006, 2009, 2012 and 2015, which covered birth cohorts between 1995 to 2011(please refer to Fig 1a of this manuscript). Children of birth cohorts 1991 to 1994 were assumed to have same vaccination uptake as the 1995 cohort (i.e. 5.7%). Individuals born in 1990 or before were assumed to be unvaccinated as varicella vaccine were only available in the private market in 1996.

3. Sauerbrei et al. compared different laboratory tests for assessing varicella immunity. Blood samples of 57 vaccinees aged 2 to 35 years were obtained 4 to 6 weeks after one or two doses of monovalent varicella vaccine (mVV). 37 (65%) tested positive by a commercially available whole-cell ELISA kit. Numbers in these columns were obtained by multiplying this proportion with the proportion vaccinated.

Supplementary Figure S1. Coding practice of A&E attendance and inpatient admission in public hospitals of Hong Kong, 2004/05 to 2013/14. (a) Proportion of A&E attendance coded, (b) average number of codes per A&E attendance, (c) proportion of A&E referred admission coded and (d) average number of codes per A&E referred admission

(a)



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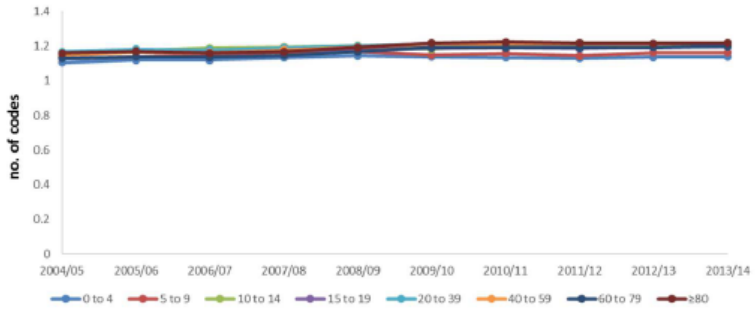

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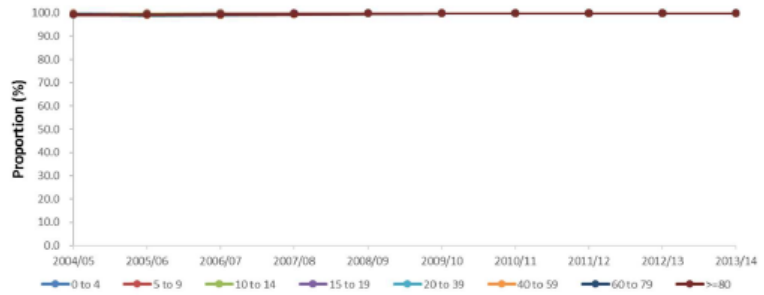

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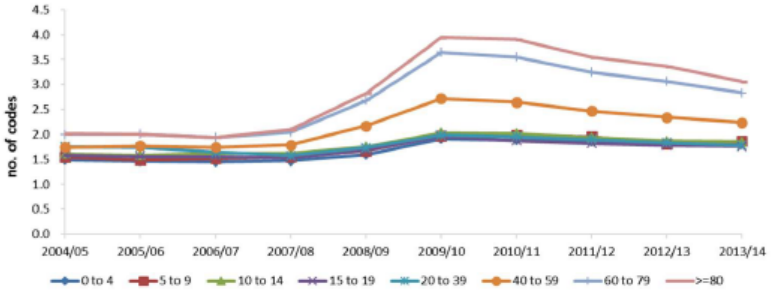
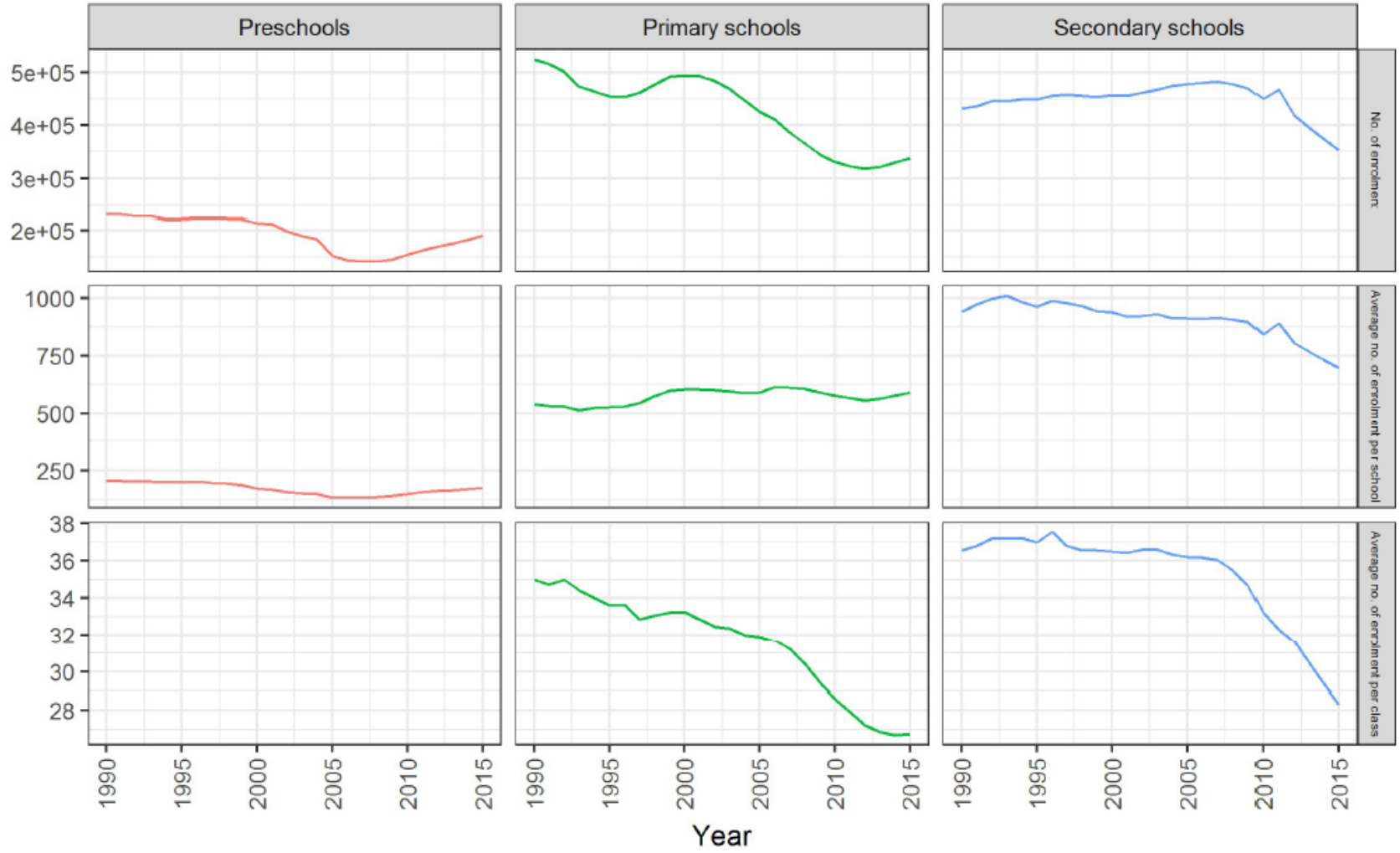


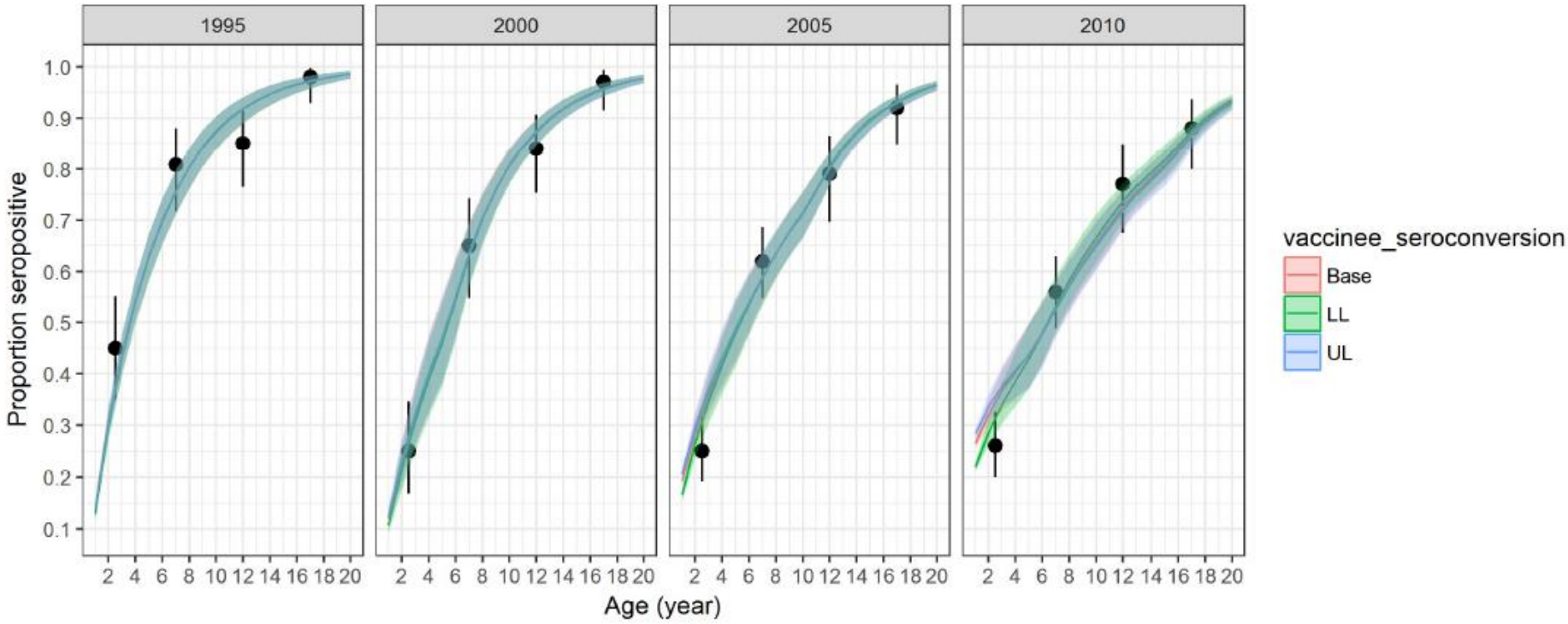
Supplementary Figure S2. No. of enrolment, average no. of enrolment per school and per class in preschools^, primary and secondary schools in Hong Kong, 1990 to 2015 (Source: Education Bureau and Social Welfare Department, Hong Kong SAR Government).



Remarks:

^Preschools include kindergartens (KG), child-care-centres (CCC) and KG-cum-CCC. Data regarding no. of enrolment per class is not available for preschools.

Supplementary Figure S3. Proportion seropositive against varicella antibody and model fitting with sensitivity analysis^



Remarks:

^Sensitivity analysis was carried out based on the proportion of vaccinee seroconverted and its 95%CI from Sauerbrei et al., for which 37 of 57 (65%) of individuals aged 2 to 35 years were tested positive by a commercially available wc ELISA kit, 4 to 6 weeks after receiving one or two doses of mVV. Base: 65%, lower limit (LL): 51% and upper limit (UL): 77%.

Chapter 3. Dose dependent varicella vaccine effectiveness

In this Chapter, I conducted an observational study to estimate the varicella vaccine effectiveness (VE) in preschool children of Hong Kong, using the screening method or case-population method. I made use of two data sources that have been described in detail in Chapter 2, the immunisation coverage surveys in 2009, 2012 and 2015 and varicella notification data in corresponding years. I led the surveys in these three years at DH, and I was the surveillance officer overlooking the collection of varicella notifications during this period. However, several key aspects of vaccine effectiveness were not readily available from the surveys. Therefore, I led the digitalisation of the dose number and date of varicella vaccination of over 10,000 immunisation records in the 2009 and 2012 surveys. I also cleaned and validated all varicella notification data included in the VE estimation. I conducted all analyses of the VE estimation, including multiple imputation which was described in detail in the supplementary materials. I estimated the VE by dose (1- or 2-dose) and by severity of outcomes (all notification, hospitalised cases and cases with complications).

I found that 1- and 2-dose varicella vaccination was moderately and highly effective in preventing notified varicella cases respectively (1-dose VE: 69.4% [95%CI: 67.5 to 71.2%] and 2-dose VE: 93.4% [95%CI: 91.7 to 94.7%]). Compared to the effectiveness against notified varicella, one dose of the vaccine was more effective against complications (86.0% [95%CI: 48.8 to 95.8%]) and hospitalisations (75.2% [95%CI: 53.4 to 86.8%]). There was no evidence of waning protection within the first four years after vaccination, as the VE estimates were not significantly different in this period. The work was published in Human Vaccines and Immunotherapeutics in 2019 (156). The VE estimates in this Chapter are referenced as a prior

of the estimation of one of the VE parameters in Chapter 5 of this PhD thesis. A discussion and comparison of the estimates are made in a later part of the thesis.

3.1 Research paper cover sheet

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Student ID Number	414373	**Title**	Mr
First Name(s)	Yung Wai		
Surname/Family Name	Chan		
Thesis Title	Varicella vaccine dose depended effectiveness and waning among preschool children in Hong Kong		
Primary Supervisor	Stefan Flasche		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Human Vaccines & Immunotherapeutics		
When was the work published?	23 October 2019		
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Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	The study involved two data sources from the Department of Health (DH) Hong Kong, the immunisation surveys and varicella notification. I was the Scientific Officer of DH and I led the immunisation surveys conducted by Department of Health Hong Kong in 2009, 2012 and 2015. This involved planning, training of field staff, data collection, validation and analyses. To obtain additional data essential for vaccine effectiveness estimation, I led the digitialisation of the 2009 and 2012 surveys from paper forms. The second data source was varicella notification in Hong Kong, of which I overlooked as the lead scientist on varicella. I collated the data from different health protection teams, carried out data quality check and cleaning. I designed and conducted the vaccine effectiveness estimation, including imputation of missing variables. I drafted the manuscript and managed the article submission.

SECTION E

Student Signature	Yung-Wai Chan
Date	1 December 2024

Supervisor Signature	
Date	3 dec 2025

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RESEARCH PAPER

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Varicella vaccine dose depended effectiveness and waning among preschool children in Hong Kong

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ABSTRACT

In Hong Kong, universal varicella vaccination was introduced in July 2014 with a two-dose schedule but the vaccines had been available in the private market since 1996. With data from varicella notification and surveys on immunization coverage, we used the screening method to estimate dose-specific varicella vaccine effectiveness (VE) among preschool children in Hong Kong before universal vaccination. We estimated the VE of one- and two-dose varicella vaccination against all notified varicella as 69.4% (95% confidence interval (95% CI) 69.5–71.2) and 93.4% (95% CI 91.7–94.7), respectively. We found that VE did not decrease with time since receipt. Varicella vaccine was more effective against complications (85.4% [95% CI 48.8–95.8] for one dose and 100% [95% CI –Inf to 100] for two doses) and against hospital admission (75.2% [95% CI 53.4–86.8] for one dose and 93.1% [95% CI 47.1–99.1] for two doses). Lower protection of one-dose varicella vaccine resulted in breakthrough varicella. Under universal vaccination, second-dose varicella vaccine (given as combined measles, mumps, rubella and varicella vaccine) was first scheduled for children when they reach primary one (about 6 years of age) and was recently advanced to 18 months of age. Shortening the interval between the first dose and second dose of varicella vaccination should reduce breakthrough varicella and outbreaks in preschool.

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Chickenpox; chickenpox vaccine; immunity; vaccine effectiveness

Introduction

Universal varicella vaccination (UVV) in Hong Kong was introduced in July 2014 for children born in 2013 and after with a two-dose schedule at 12 months and around 6 years of age (at the start of primary school).[1] Monovalent varicella vaccine (mVV) is provided as the first dose whilst combined measles, mumps, rubella, and varicella (MMRV) is provided as the second dose. However, before the start of UVV, varicella vaccine was licensed for private market use in 1996 with no clear schedule and the first dose vaccination uptake gradually reached up to 50% among preschool children.[2] The private market was dominated by mVV from GSK, Sanofi, and MSD (Table 1). All three products consisted of live attenuated varicella virus (Oka strain) with at least 1350 plaque-forming unit.[3] We found that most vaccinated preschool children only received one dose of vaccine, with median age of vaccination ranging from about 15 to 20 months of age.[2] We previously reported the burden of varicella shifting to older children during the period of increasing vaccination uptake in the private market. However, the extent to which this increase in varicella vaccination contributed to the change in epidemiology remains uncertain.[2]

Vaccinees developing modified (less severe) varicella is often referred to as breakthrough infections.[3] In the United States, the frequent reporting of breakthrough infections in one-dose recipients with low protection against varicella[4,5] has led to the implementation of two-dose program, with the first dose scheduled at 12–15 months while the second dose was scheduled at 4–6 years. Yet, in Hong Kong, the second dose was first scheduled at about 6 years of age and hence at least 5 years following the first dose of varicella vaccine. The decision to space out the two doses was largely on programmatic grounds and this schedule may result in a high number of breakthrough cases before receipt of a second dose because of limited effectiveness[6] or potential waning following a single dose of varicella vaccine.

We used the screening method to estimate the direct effect of varicella vaccine in Hong Kong before UVV. The primary objective of this study is to estimate the effectiveness of varicella vaccine against varicella infections of all severity in preschool children in Hong Kong. Secondary objectives include estimating varicella vaccine dose-specific effectiveness, whether vaccine effectiveness (VE) waned with time and VE against complications and severe diseases.

Patients and methods

We used the screening method[7,8] to estimate the effectiveness of varicella vaccine among children aged 3–5 years in Hong Kong. In contrast to vaccine efficacy, which is typically defined as the direct effect of a vaccine measured in pre-

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Supplementary data for this article can be accessed here

Table 1. Type of varicella vaccine received for vaccinated survey participants, 2009 and 2012 immunization survey for preschool children, Hong Kong.

		First dose				Second dose			
		2009		2012		2009		2012	
Type of varicella vaccine		*N*	%	*N*	%	*N*	%	*N*	%
mVV	Varilix (GSK)	496	32.7	658	39.7	12	54.5	13	19.7
	Okavax (Sanofi)	195	12.8	171	10.3	0	0.0	8	12.1
	Varivax (MSD)	68	4.5	118	7.1	3	13.6	5	7.6
	Manufacturers from mainland China	14	0.9	13	0.8	0	0.0	0	0.0
	GreenCross Korea	0	0.0	1	0.1	0	0.0	0	0.0
MMRV	PriorixTetra (GSK)	0	0.0	0	0.0	0	0.0	4	6.1
	Exact brand and manufacturer unclear	0	0.0	0	0.0	0	0.0	3	4.5
Unknown		746	49.1	695	42.0	7	31.8	33	50.0
Total		1519	100.0	1656	100.0	22	100.0	66	100.0

mVV: monovalent varicella vaccine
MMRV: combined measles, mumps, rubella and varicella vaccine

licensure clinical trials, VE commonly referred to the estimated protection attributed to a vaccine under postlicensure, field conditions.[9] Post-licensure VE is commonly estimated using case–control and cohort studies by comparing the attack rate or incidence rate among vaccinated and unvaccinated cases. On the other hand, the screening method is used to estimate VE by making use of surveillance data consisting of the vaccination coverage among the cases and the source population.[7,8] In our study, we compared the proportion of childhood varicella cases who were vaccinated (Proportion of Cases Vaccinated [PCV]) with the proportion of the children vaccinated in the source population (Proportion of Population Vaccinated [PPV]) for the corresponding age cohort to obtain the VE.

Data sources

PPV was obtained from territory-wide immunization surveys on preschool children conducted by the Department of Health (DH). The surveys were cross-sectional studies using stratified cluster sampling of preschools in Hong Kong to estimate vaccine uptake, which was the proportion of children receiving a particular vaccine. Vaccination status was ascertained by reviewing documented vaccination records. As the screening method is disproportionately prone to error when the PPV and PCV is very high or very low,[7] we chose surveys conducted in 2009, 2012, and 2015 covering cohorts with an intermediate uptake of 23.8–51.0% in the private market. This provided us with additional confidence for a robust VE estimation before UVV as first dose uptake for children eligible for universal vaccination has reached 99%.[10] About 5% of preschools were selected in these three surveys, with 6051–8522 children aged 2–5 from sampled preschools were recruited in these three surveys. We used varicella vaccine uptake of children aged 3–5 only as preschool attendance rate for children of these ages were high,[11] compared to the 50% attendance rate for those aged 2 years. Details of the surveys have been reported elsewhere.[2] Survey data readily available for analysis included demographics (including birth year, sex, place of birth, and residence) and varicella vaccination history (including vaccination status, number of dose(s) received, and date of vaccination (for 2015)). Two independent reviewers retrospectively digitalized the number of dose(s), date of vaccination, and vaccine product for the 2009 and 2012 surveys from stored paper forms. We described the varicella vaccination uptake for different birth cohorts, including the number and proportion of surveyed children that received varicella vaccine, as well as the timeliness of vaccination, as indicated by median and interquartile range of the age of vaccination.

Varicella is a notifiable disease in Hong Kong. The DH receives varicella notifications from doctors in public and private sectors, as well as from varicella outbreaks from schools and institutions. Probable cases were defined as those with the clinical presentation of acute onset of diffuse (generalized) papulovesicular rash without other apparent cause or atypical (milder) clinical presentation for those with varicella vaccination history. Confirmed cases were defined as probable cases with either laboratory confirmation or epidemiologically linked to a confirmed case. We included all confirmed and probable cases in our analyses. Parents and/or doctors were interviewed using a standard questionnaire to obtain the demographics (including age, gender, place of residence, and travel history during the incubation period), clinical information (including date of onset, any varicella-related complications, hospitalization, and fatality), and varicella vaccination history (vaccination status, number of dose(s) received, and age of last varicella vaccination). Number of dose(s) was recorded for cases reported in 2012 onwards. However, since second-dose varicella vaccination uptake for children surveyed in 2009 was only 0.5% or below (Table 2) and the information on number of dose(s) was not collected for varicella cases reported in 2009, we assumed that all vaccinated varicella cases in 2009 received only one dose. Doctors and/or hospitals were contacted to obtain clinical information when parents reported that their children developing varicella-related complications and/or were admitted to hospitals. We extracted information from the questionnaire into an electronic database. To match with the children captured by the immunization surveys (source population), we selected reported cases aged 3–5 years attending preschools in 2009, 2012, and 2015. We excluded cases who did not attend preschools, who did not reside in Hong Kong or imported cases (i.e. those who had a travel history during the incubation period), or who resided in residential homes from our analyses as these children were unlikely to be sampled in the immunization surveys. Children fulfilling one of the following criteria were regarded as attending preschools: attendance being confirmed by parents, notifications by preschools, or cases identified during investigation of varicella outbreaks in preschools. We described the demographics of varicella cases included in our analysis.

Assessing waning immunity

To assess whether the effectiveness of varicella vaccine waned with time, time since last vaccination was computed for vaccinated cases by subtracting the age at most recent varicella vaccination by the age at disease onset. Waning refers to the loss of vaccine protection with time. Similar computation is needed for unvaccinated cases when VE is estimated by the screening method.[12,13] Studies carried out when a common vaccination schedule was in place could impute the time of vaccination by assuming that unvaccinated cases would have received the vaccine under the recommended schedule.[12,13] In our study,

Table 2. Varicella vaccination uptake and age of vaccination in preschool children surveyed and preschool children with varicella reported in Hong Kong, 2009, 2012, and 2015.

Varicella vaccination among preschool children surveyed							
			At least 1 dose	1st dose		2nd dose	
Survey year	Age (years)/ cohort	Number surveyed	Number received (%)	Number received (%)	Median age (months) at 1st dose (IQR)	Number received (%)	Median age (months) at 2nd dose (IQR)
2009	5/2003	1666	397 (23.8)	375 (22.5)	25.5 (16.7–34.5)	7 (0.4)	40.0 (38.7–64.1)
	4/2004	1726	509 (29.5)	405 (23.5)	24.9 (16.5–32.4)	9 (0.5)	40.7 (35.9–49.7)
	3/2005	1819	613 (33.7)	526 (28.9)	23.0 (15.6–28.8)	6 (0.3)	37.0 (35.2–37.4)
2012	5/2006	1596	430 (26.9)	375 (23.5)	20.6 (14.7–29.5)	24 (1.5)	62.0 (39.3–65.5)
	4/2007	1834	614 (33.5)	546 (29.8)	19.0 (14.2–27.9)	22 (1.2)	48.7 (36.6–51.7)
	3/2008	1815	612 (33.7)	575 (31.7)	18.4 (14.1–25.9)	20 (1.1)	35.4 (27.0–40.9)
2015	5/2009	2276	1034 (45.4)	924 (40.6)	19.2 (14.3–27.4)	110 (4.8)	51.0 (39.9–59.2)
	4/2010	2488	1216 (48.9)	1046 (42.0)	16.3 (14.0–23.5)	170 (6.8)	34.9 (24.6–50.4)
	3/2011	2831	1443 (51.0)	1172 (41.4)	15.6 (13.5–21.9)	271 (9.6)	22.6 (17.2–30.4)
Varicella vaccination among cases reported to the DH							
			At least 1 dose	1st dose		2nd dose	
Notification year	Age (years)	Number reported	Number received (%)	Number received (%)	Median age (year) at 1st dose (IQR)	Number received (%)	Median age (month) at 2nd dose (IQR)
2009[4]	5	684	130 (19.0)	130 (19.0)	2.0 (1.0–3.0)	–	–
	4	751	121 (16.1)	121 (16.1)	2.0 (1.0–2.0)	–	–
	3	653	95 (14.5)	95 (14.5)	1.0 (1.0–2.0)	–	–
2012	5	861	177 (20.6)	147 (17.1)	1.0 (1.0–2.0)	6 (0.7)	3.0 (2.5–3.0)
	4	951	182 (19.1)	146 (15.4)	2.0 (1.0–2.0)	7 (0.7)	3.0 (2.0–3.0)
	3	727	126 (17.3)	105 (14.4)	1.0 (1.0–2.0)	3 (0.4)	1.0 (1.0–1.5)
2015	5	838	171 (20.4)	136 (16.2)	1.0 (1.0–2.0)	15 (1.8)	2.0 (2.0–5.0)
	4	866	189 (21.8)	143 (16.5)	1.0 (1.0–2.0)	20 (2.3)	2.0 (1.0–2.0)
	3	675	110 (16.3)	89 (13.2)	1.0 (1.0–1.3)	11 (1.6)	2.0 (1.0–2.0)

Note:
(1) Survey respondents and reported cases aged three to five were included in this study.
(2) Survey respondents and reported cases with missing vaccination information were not included in the above table. Those who were vaccinated with unknown dose was not shown.
(3) Number and the proportion (%) of children received varicella vaccine for different doses was presented in the above table. Proportion was computed by the number of children received the vaccine divided by the number surveyed/ reported in each stratum.
(4) Number of varicella vaccine received was not collected for cases reported in 2009. In view of low second-dose uptake for children surveyed in 2009, all vaccinated varicella cases reported in 2009 were assumed to have received only one dose.
(5) Age of vaccination for survey respondents was computed by subtracting date of vaccination with date of birth. Median and interquartile range (IQR) of the age of vaccination was presented in the above table to indicate timeliness of vaccination.
(6) Age of vaccination for varicella cases was collected by a standardized questionnaire for which the precision is up to year only.

varicella VE was estimated before universal vaccination and the age of vaccination through private market in the source population was highly diverse (Table 2). Therefore, the time since last (hypothetical) vaccination for unvaccinated cases cannot be approximated by simply using the recommended age of vaccination or the median age of vaccination in the healthy population. Assuming the time of vaccination for unvaccinated cases would have been comparable to those in the population should they choose to vaccinate, we imputed the age of (hypothetical) vaccination for unvaccinated cases from the observed vaccination timing in the population, i.e. survey respondents vaccinated against varicella (Supplementary Figure 1). In order to obtain a dataset with the age of (hypothetical) vaccination for unvaccinated cases completely imputed, we first imputed missing values of vaccination-related variables among vaccination survey respondents and varicella cases to obtain complete datasets. The imputation process is described in detail in Supplementary Figure 1. A maximum number of 25 iterations for each imputation was chosen as 20–30 iterations were suggested to be sufficient in achieving convergence of variables under imputation, which is fewer than other Gibbs sampling methods.[14] We created 500 multiply imputed datasets.

Estimation of VE

Following Orenstein,[7] we estimated VE via:

$$\mathbf{VE} = \mathbf{1} - (\mathbf{PCV})(\mathbf{1} - \mathbf{PPV})/[(\mathbf{1} - \mathbf{PCV})(\mathbf{PPV})]$$

We computed PPV specific to different years (2009, 2012, and 2015), age (3, 4, and 5 years), and dose (at least one, one and two doses). PPV were then matched to each varicella cases based on their year of survey/notification, age, and number of dose(s) received. We computed the VE following the approach suggested by Farrington,[15] which was also adopted and described in detail in other VE studies:[12,16,17]

$$\mathbf{In}[\mathbf{P}/(\mathbf{1} - \mathbf{P})] = \boldsymbol{c} + \mathbf{In}[\mathbf{PPV}/(\mathbf{1} - \mathbf{PPV})]$$

where P is the probability of vaccination status of reported cases fitted as a binary outcome (vaccinated or not), with log odds of the matched PPV (In[PPV/(1-PPV)]) as an offset in a logistic regression model. VE was obtained as VE = 1 – exp(c) where c was the estimated constant in the regression model.

VE estimates were obtained for each imputed dataset and then pooled to give a single estimate for which the within- and between-imputation variance was accounted for according to

Rubin's rules.[14] We reported the pooled VE estimates alongside their 95% confidence intervals in our results.

We computed the varicella VE of different doses (any, one and two doses (for 2012 and 2015)) against different outcomes including all varicella infections, varicella with complications, and varicella-related hospitalizations. In addition, we included time since vaccination as a covariate in the logistic regression model for VE against all varicella infections and obtained the VE at different time periods since vaccination (0, 1, 2, 3, and 4 years) to assess whether there was evidence of waning immunity.

Software

All analyses were done in R[18] including the multiple imputation via the MICE package.[14]

Ethical approval

Ethical approval was obtained from the Observational/Interventions Research Ethics Committee of the London School of Hygiene & Tropical Medicine as part of a modeling study of varicella vaccination in Hong Kong (LSHTM ethics ref: 11852).

Results

Varicella vaccination uptake in the community

Uptake for at least one dose of varicella vaccine gradually increased from about 25% for preschool children surveyed in 2009 to about 50% for those surveyed in 2015 (Table 2). Most preschool children only received one dose of varicella vaccine. Second-dose vaccine uptake was about 1% or less in 2009 and 2012, and it increased to 5–10% in 2015. Age at vaccination varied greatly among different cohorts, especially for the second dose (Table 2).

Varicella notifications

A total of 7302 varicella cases aged 3–5 years were recorded in 2009, 2012, and 2015, corresponding to a notification rate of 1534 per 100,000. After excluding cases that were imported (i.e. those who had a travel history during the incubation period) (33), lived in residential care homes (4), and did not attend preschools (259), we included 7006 cases in our analyses. Only two cases were immunosuppressed (one case of nephritis and one case of pre-B acute lymphoblastic leukemia). Twenty-nine cases (0.4%) had complications, among which 18 were scarlet fever, one case each of pneumonia, febrile convulsion, cellulitis and abscess due to methicillin-resistant *Staphylococcus aureus*, and mild skin infection. Exact complication type was not known for the remaining seven cases. Seventy-five cases (1.1%) were admitted to hospitals but no fatal case was identified.

The vaccination uptake for varicella cases slightly increased from 16.6% in 2009 to 19.1% in 2012 and 19.8% in 2015 (Table 3). For cases reported in 2012 and 2015, less than 3% had received a second dose (Table 2). The proportion of hospital admissions was comparable for children of different vaccination status albeit sample size was small (1.1% (95% CI 0.9–1.4) among unvaccinated, compared to 1.0% (95% CI 0.6–1.8) and 1.6% (95% CI 0.3–8.6) among one- and two-dose recipients). Among two-dose recipients, there was no case with complication and only one case was admitted to hospital.

Varicella VE

We estimated the VE of one-dose varicella vaccination against all notified varicella as 69.4% (95%CI 67.5%–71.2). The respective two-dose VE was substantially higher at 93.4% (95%CI 91.7–94.7). We did not find evidence for waning immunity of varicella vaccination against all notified varicella. For one-dose recipients, the estimated VE did not decrease significantly with time since receipt (Table 4). On the other hand, we found that two-dose VE

Table 3. Characteristics of varicella notifications aged 3–5 years[1], Hong Kong, 2009, 2012, and 2015.

		2009 (n = 2088)		2012 (n = 2539)		2015 (n = 2379)		Total (n = 7006)	
Characteristics		*N*	%	*N*	%	*N*	%	*N*	%
Female gender		923	44.2	1156	45.5	1063	44.7	3142	44.8
Age (years)	3	653	31.3	727	28.6	675	28.4	2055	29.3
	4	751	36.0	951	37.5	866	36.4	2568	36.7
	5	684	32.8	861	33.9	838	35.2	2383	34.0
Clinical condition	Immunosuppression	0	0.0	1	0.0	1	0.0	2	0.0
	Complications	3	0.1	13	0.5	13	0.5	29	0.4
	Hospitalization	19	0.9	26	1.0	30	1.3	75	1.1
Varicella vaccination		346	16.6	485	19.1	470	19.8	1301	18.6
No. of dose received[2]	1	NA	NA	398	82.1	368	78.3	766	58.9
	2	NA	NA	16	3.3	46	9.8	62	4.8
	Unknown	346	100.0	71	14.6	56	11.9	473	36.4
Age of last vaccination (year)[2]	<1	1	0.3	2	0.4	2	0.4	5	0.4
	1	122	35.3	215	44.3	234	49.8	571	43.9
	2	142	41.0	142	29.3	123	26.2	407	31.3
	3	40	11.6	55	11.3	37	7.9	132	10.1
	4	16	4.6	15	3.1	10	2.1	41	3.2
	5	2	0.6	2	0.4	7	1.5	11	0.8
	Unknown	23	6.6	54	11.1	57	12.1	134	10.3

Note:
[1]Two hundred and ninety-six cases were excluded from the analyses and thus not included in the above table (imported: 33, residential care homes: 4, did not attend preschool: 259).
[2]Among those vaccinated with varicella vaccines.

Table 4. Vaccine effectiveness for different doses of varicella vaccine against all varicella, varicella with complications, and varicella admissions among preschool children aged 3–5 years in Hong Kong.

Outcome/dose		Vaccine effectiveness % (95% CI)
All varicella		
Any dose		68.7 (66.8–70.5)
Time since vaccination (year)	0	68.7 (63.4–73.3)
	1	68.7 (61.1–74.8)
	2	68.7 (58.7–76.3)
	3	68.7 (56.1–77.7)
	4	68.7 (53.3–79.0)
1 dose		69.4 (67.5–71.2)
Time since vaccination (year)	0	70.8 (65.7–75.2)
	1	70.2 (62.8–76.2)
	2	69.7 (59.8–77.3)
	3	69.2 (56.4–78.3)
	4	68.7 (52.8–79.2)
2 doses		93.4 (91.7–94.7)
Time since vaccination (year)	0	86.4 (77.2–92.0)
	1	90.6 (80.0–95.6)
	2	93.5 (82.5–97.6)
	3	95.5 (84.7–98.7)
	4	96.9 (86.6–99.3)
Complication		
Any dose		86.0 (50.9–96.0)
1 dose		85.4 (48.8–95.8)
2 doses		100.0 (–Inf to 100.0)
Hospital admission		
Any dose		74.2 (52.6–86.0)
1 dose		75.2 (53.4–86.8)
2 doses		93.1 (47.1–99.1)

Note:
- Time since vaccination was included as a covariate only in the logistic regression model for VE against all varicella infections.
- Since dose of vaccine received was not collected for varicella cases reported in 2009 and the second-dose varicella vaccination uptake in the population is very low, all vaccinated cases reported in 2009 were assumed to have only received one dose of vaccine. As such, VE estimation for any dose (ever vaccinated) and one dose was based on all 3 study years (2009, 2012, and 2015) whereas two doses was based on data from 2012 and 2015 only.
- Variable "dose no." was not added in the regression model when estimating VE for any dose due to issue in model convergence. As such, VE for any dose was not adjusted for no. of doses received.

increased with time since receipt. Varicella vaccine was more effective against complications: 85.4% (95%CI 48.8–95.8) for one dose and 100% (95%CI –Inf to 100) for two doses. The effectiveness of varicella vaccines against hospital admission was 75.2% (95% CI 53.4–86.8) and 93.1% (95% CI 47.1–99.1) for one- and two-dose recipients, respectively (Table 4).

Discussion

We used the screening method to estimate the varicella VE among preschool children in Hong Kong. We showed that one-dose varicella vaccination conferred moderate direct protection [69.4% (95% CI 67.5–71.2)] against notified varicella whilst two doses conferred strong direct protection [93.4% (95% CI 91.7–94.7)]. VE against complications and hospital admissions was also generally higher for those who received two doses, though numbers were too small to conclude of superiority. We did not find any evidence to support concerns that vaccine protection from one dose would wane before children entering primary school.

Our VE estimates are largely comparable to a recent meta-analysis of post-licensure VE studies[6] which also showed that one-dose varicella vaccine (mostly mVV) is moderately effective for preventing disease of any severity [81% (95% CI 78–84%)] but two-dose varicella vaccine is highly effective at 98% (95% CI 97–99%). We also found that the effect of varicella vaccination persisted in the first few years after vaccination with no apparent decline in VE. For two-dose vaccinees, there was a general trend of increasing effectiveness with time since vaccine receipt. There are a few possible explanations behind this observation. First, as children aged, they had more exposure to circulating wild-type varicella, which might boost up their immunity. Second, vaccinees who failed to develop adequate immunity would be infected and became immune to further varicella infections. Thus, the number of vaccinated yet susceptible children would decrease with time and contribute less to the varicella reported in later years. This would result in lower PCV and higher VE in later years. Third, there were only 62 reported cases having received two doses of varicella vaccine and the estimation of two-dose VE by year since vaccination was more prone to error due to small sample size. Clinical trials of Varivax showed that vaccinees who were initially protected lost their protection rather quickly,[19] while some studies showed that antibodies against varicella were persistent among vaccinees after 10- to 20-year follow-up, though boosting by circulating wild-type VZV cannot be ruled out.[20] Systematic review found that waning immunity for single-dose vaccination was not conclusive,[20,21] and long-term protection of up to 14 years had been demonstrated for two-dose regimen in the World Health Organization's systematic review.[22]

As one-dose varicella vaccine induces only moderate protection, breakthrough infections are often observed in one-dose vaccinees.[4,5] Although waning immunity after first dose varicella vaccination remains inconclusive, the lower VE is generally believed to be a result of primary vaccine failure which mainly occurred after first dose, as evidenced by only 76–84% of one-dose recipients seroconverted (assessed by fluorescent antibody to membrane antigen test, the most specific laboratory test for serological correlates of varicella infection and vaccination).[21] Furthermore, IgG geometric mean concentration of subjects receiving the first dose MMRV of MSD (ProQuad) was lowest for varicella and the boosting effect after the second dose was much more profound for varicella,[3] suggesting that immune response following only one dose against varicella is likely incomplete. In addition to nonconverter (primary vaccine failure), mild breakthrough infections occurring among seroconverted vaccinees (commonly defined as those who had >5 glycoprotein enzyme-linked immunosorbent assay units/mL) may be a result of partial or "leaky" protection.[4,21] Thus, second-dose varicella vaccination is important in completing the incomplete immune response following first-dose vaccination and maximizing the impact of varicella vaccination. After the start of a one-dose program in 1995, the United States switched to a two-dose regimen in 2006 as varicella outbreaks persisted even among the highly vaccinated parts of the population.[23] Providing second-dose vaccination at 4–6 years of age led to further declines in varicella incidence, hospitalizations, and outbreaks in the US.[24] It should be noted that, however, more than half of the 29 countries or areas with funded varicella vaccination adopt a one-dose schedule and most of those with two-dose vaccination have a second dose scheduled at ≥4 years [Information summarized from WHO, European Center for Disease Control, MSD and GSK].

In Hong Kong, the implementation of UVV has rapidly increased the first dose varicella vaccination uptake to about 99% for eligible preschool children.[10] Reduction in varicella notification was observed shortly after universal vaccination, as the annual notification rate per 100,000 among children aged 3–5 had decreased from 1670 to 2916 between 2011 and 2013 and to 934–1256 between 2015 and 2018 (Supplementary Figure 3). Preschool outbreaks also decreased to a lower level but persisted in recent years (292–442 outbreaks annually from 2011 to 2013 compared with 111–284 outbreaks annually from 2015 to 2018). The Scientific Committee on Vaccine Preventable Diseases, the advisory body on immunization in Hong Kong, recently recommended advancing second-dose vaccines against measles, mumps, rubella, and varicella (given as combined MMRV) from Primary One to 18 months of age.[25] Given the higher effectiveness of second-dose vaccination, this change in the program should reduce breakthrough infection and accumulation of susceptible children who experienced primary vaccine failure, and it would further limit varicella transmission and outbreaks in preschools. In addition, herpes zoster appeared to be less common among children vaccinated against varicella.[26,27] Therefore, advancing the second-dose vaccine to 18 months of age should also bring a long-term impact of decreasing the probability of vaccinated children developing zoster later in their life.

We previously reported the burden of varicella having shifted to older children before UVV.[2] The epidemiology of varicella and zoster is expected to change further as high varicella vaccination uptake has been achieved for children eligible for UVV. To assess the potential long-term impact of UVV on varicella and zoster, as well as different options to maximize the benefits of the vaccination program, we will model the transmission of VZV mechanistically. These local VE estimates provided important baseline data to monitor the impact of the UVV and could serve as important inputs for the mathematical model.

There were some limitations to this study. First, most varicella cases were ascertained clinically without laboratory confirmation. Breakthrough varicella with modified (less severe) symptoms is more difficult to be diagnosed clinically and is expected to increase with higher vaccination uptake. Inclusion of non-varicella cases will underestimate the VE. Second, varicella is generally a nonsevere disease and underreporting exists. We previously estimated that less than 50% of varicella infections were notified among those aged 3–5 years and the reporting sensitivity varied with time and age.[2] This may bias our VE in different directions, depending on whether vaccinated cases are more likely to be reported. For instance, those who chose to actively vaccinate might be more aware of varicella and hence more likely to seek medical consultation and be reported. This would bias our VE estimates toward null. On the other hand, breakthrough varicella cases with milder symptoms may be less likely to seek medical consultation or require hospital admission. This will underestimate PCV and overestimate the VE. To our knowledge, we are not aware of reports on how varicella vaccination affects health-seeking and reporting behavior, though severe varicella in vaccinated children are rare.[28] Third, complication and hospitalization alone might not be representative of clinical severity, as we did not collect further details such as the number of vesicles developed and the duration of hospitalization. Young children with varicella might be hospitalized for fever work-up instead of clinical severity. This would lead to underestimation of VE against admissions. Our VE estimates against complications were higher than that against hospital admissions. Varicella vaccine was shown to be more effective against severe outcomes, but severe disease in some observational studies was defined as varicella with ≥500 lesions or presence of complications/hospitalization.[6,22] It should be noted that the median interval between interview and disease onset was only 3 days (interquartile range: 2–8 days) for cases included in our study. Cases that developed complications or hospitalized after data collection would not be counted as severe cases. Fourth, although adequate immunity against clinical disease might not have developed until 1 month after vaccination,[3] cases that developed disease shortly after vaccination would still be regarded as vaccinated as the exact date of vaccination was not available for most varicella notifications. This will overestimate the PCV and underestimate the VE. Fifth, information on the exact vaccine product received by varicella cases was not collected and we were unable to estimate VE specific to different formulations. As children received varicella vaccines from different manufacturers (Table 1), our VE estimates were the effect of mixed vaccine products. Nevertheless, with the exception of varicella vaccine manufactured in South Korea, varicella vaccines available in Hong Kong are based on the Oka strain and their effectiveness are generally comparable.[6] Sixth, ascertainment of vaccination status was different for the survey and notification. Vaccination status for surveyed children was ascertained by reviewing medical records, while that for most varicella notification was ascertained by parental recall. Thus, vaccination status of varicella cases was more prone to recall bias and it might affect the accuracy of PCV.

Conclusion

We showed that varicella vaccine is effective in preventing varicella infection, complication, and hospitalization in Hong Kong, especially for two-dose vaccination. Countries with UVV should consider adopting a two-dose strategy with a short interval between the first and second doses to reduce breakthrough varicella and outbreaks in preschool. In view of the high VE, the epidemiology of varicella and herpes zoster is expected to change as universal vaccination program successfully rolls out in Hong Kong.

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Author contribution

Conception and design of the study: Chan YWD, Edmunds WJ and Flasche S; Planning and data collection on varicella surveillance and immunization surveys: Chan YWD, Chan HL, Wong ML, Au KWA and Chuang SK; Data analysis and interpretation: Chan YWD and Flasche S; Preparation of article: Chan YWD and Flasche S; Critical appraisal: Flasche S and van Hoek AJ; All authors approved the final article. All authors attest they meet the ICMJE criteria for authorship.

Disclosure of potential conflicts of interest

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3.3 Supplementary Materials

Varicella Vaccine Dose Depended Effectiveness and Waning Among Preschool Children in Hong Kong

Supplementary materials

Supplementary Figure 1. Imputation and data analysis for estimating varicella vaccine effectiveness in Hong Kong using the screening method

Supplementary Figure 2. Varicella vaccine effectiveness among preschool children aged 3 to 5 years in Hong Kong with different combinations on imputations and iterations

Supplementary Figure 3. Varicella vaccination uptake and varicella notification rate in Hong Kong. (a) First dose varicella vaccination uptake for preschool children aged three to five years in Hong Kong (except for 2001 when children included were aged four to five years). Annual varicella notification rate in Hong Kong from 1999 to 2018 for (b) children aged three to five years and (c) all ages.

Supplementary Figure 1. Imputation and data analysis for estimating varicella vaccine effectiveness in Hong Kong using the screening method

The main purpose of the imputation is to obtain the age of (hypothetical) vaccination for unvaccinated cases from the observed vaccination timing in the population i.e. survey respondents vaccinated against varicella. In order to obtain a dataset with the age of (hypothetical) vaccination for unvaccinated cases completely imputed, we first imputed missing values of vaccination-related variables among vaccination survey respondents and varicella cases to obtain complete datasets.

Imputation of survey dataset (multiple imputation 1)

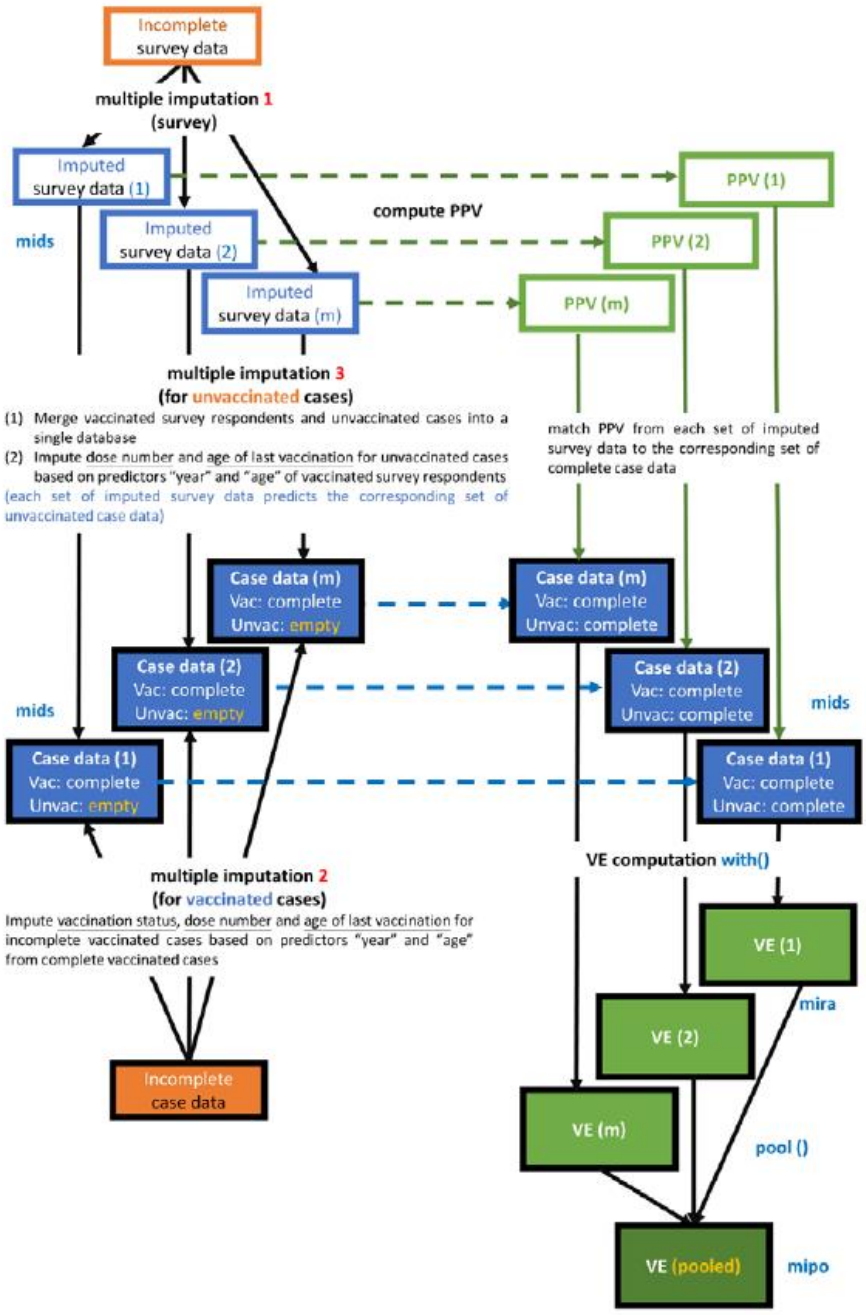
Vaccination status was complete for all survey respondents. Among vaccinated survey respondents, less than 5% had no information on the received number of doses, the time of receiving first dose and the time of receiving their second dose. For imputation of survey data, dependent variables including vaccination status for second dose and age of vaccination for first and second dose was imputed based on predictor variables including survey year, age, type of preschool attended, place of birth, usual place of residence before 2 years of age and usual place of residence after 2 years of age (for 2015 survey only).

Imputation of varicella notification dataset (multiple imputation 2)

Across the three years of notification data in 2009, 2012 and 2015, between 6 and 15% of cases reported had missing information on either one of the vaccination-related variables (varicella vaccination status, number of doses (excluding year 2009 as this information was not collected) and age of last vaccination). We imputed missing values in varicella vaccination status, number of dose, and age of last varicella vaccination in the notification dataset, based on predictor variables including notification year and age (predictors used in imputing survey database such as type of preschool attended, place of birth, usual place of residence before 2 years of age and usual place of residence at time of survey was not available in the notification database).

Imputation of age of (hypothetical) vaccination for unvaccinated cases (multiple imputation 3)

After completing missing values of the survey and notification databases, we imputed the age of (hypothetical) vaccination for unvaccinated cases from vaccinated survey respondents using year and age as predictors.



Note:

- All imputations was carried out using the mice (Multivariate Imputation by Chained Equations) v3.3.0 package from R. with() and pool() corresponds to the R syntax.
- Imputations 1 and 2 aimed at completing missing values related to vaccination variables in the survey and notification datasets.
- Imputation 3 aimed at imputing dose and age of vaccination for unvaccinated cases from notification dataset, with vaccinated respondents from the survey dataset as predictors.
- There was multiple number of imputations (m), which equaled to 500 (main result), 250 and 25 (as validity testing, please refer to Supplementary Figure 2). For simplicity only 3 boxes are drawn in the above figure.

Abbreviations:

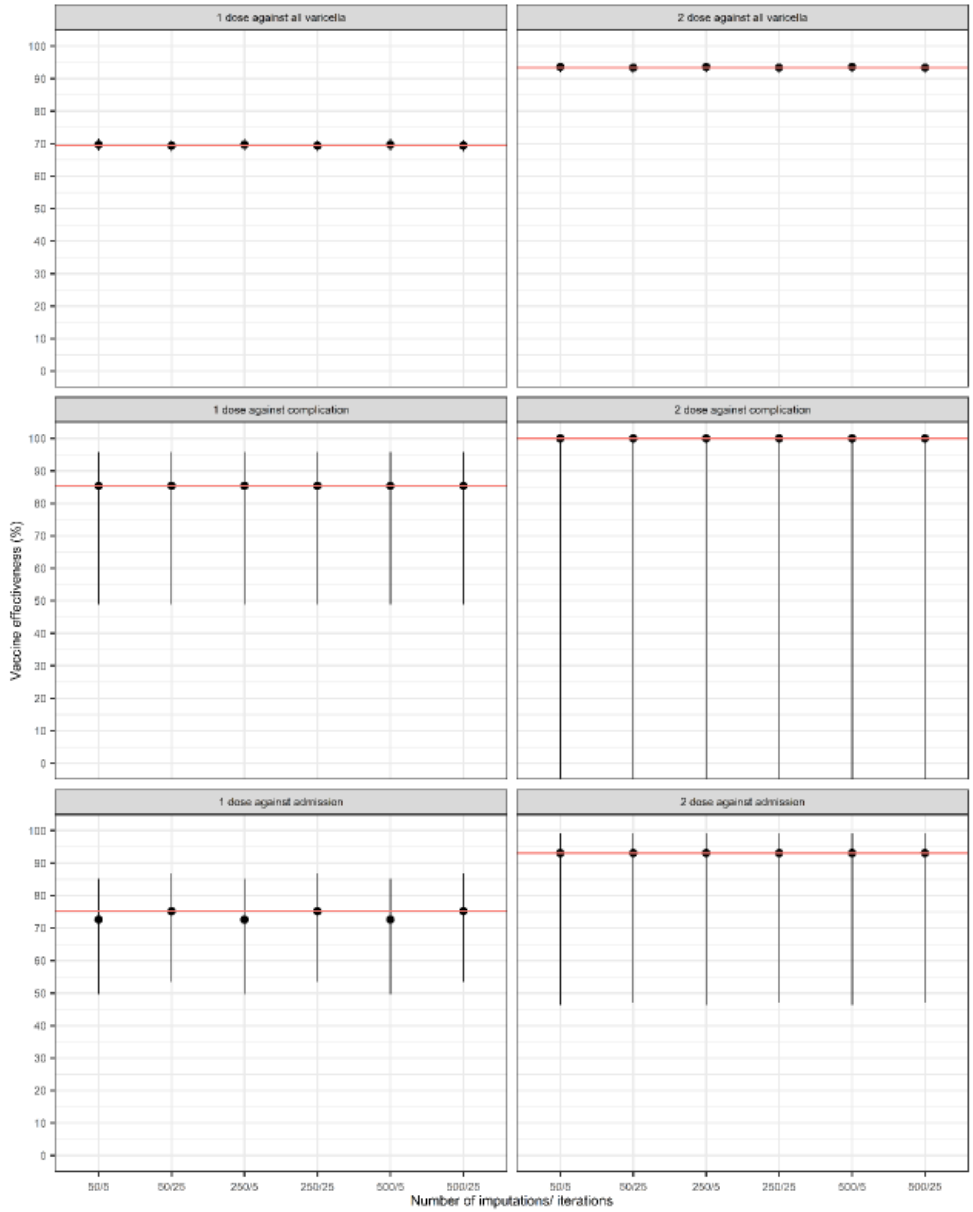
PPV: proportion of population vaccinated

mids: Multiply Imputed Dataset

mira: Multiply Imputed Repeated Analyses

mipo: Multiple Imputation Pooled Object

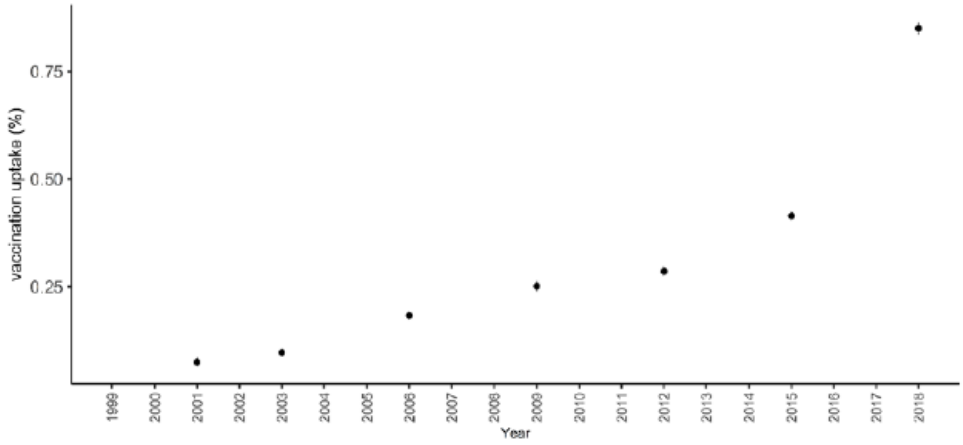
Supplementary Figure 2. Varicella vaccine effectiveness among preschool children aged 3 to 5 years in Hong Kong with different combinations on imputations and iterations



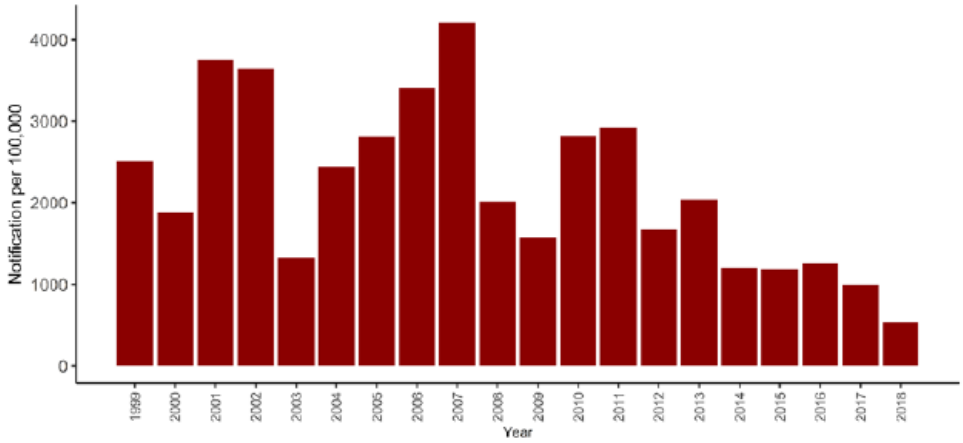
Note: reference lines are the point estimate of the VE presented as main result in the manuscript (i.e. 500 imputations with 25 iterations in each imputation). Confidence intervals for "2 dose against complication" were –Inf to 100 for all combination of imputations and iterations.

Supplementary Figure 3. Varicella vaccination uptake and varicella notification rate in Hong Kong. (a) First dose varicella vaccination uptake for preschool children aged three to five years in Hong Kong (except for 2001 when children included were aged four to five years). Annual varicella notification rate in Hong Kong from 1999 to 2018 for (b) children aged three to five years and (c) all ages.

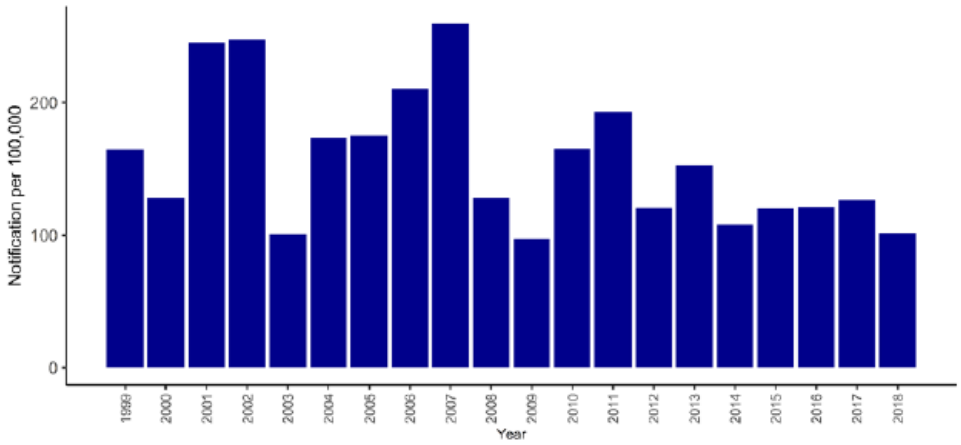
(a) Varicella vaccination uptake among preschool children aged 3 to 5 years



(b) 3 to 5 years



(c) All age



Note: varicella notification for 1999 started in February.

Chapter 4. UVV in Hong Kong and post-UVV varicella epidemiology

This chapter focuses on the changes in epidemiology of varicella in Hong Kong coinciding with the introduction of universal varicella vaccination in 2014. Varicella vaccine uptake increased quickly for eligible children, with first dose uptake reaching 98% [Chapter 4.1]. In Chapter 2, varicella immunity and transmission in the population was shown to be changing with the use of vaccine in the private market. To understand the incremental impact of universal vaccination which led to rapidly increasing varicella vaccine uptake, both serology and surveillance data in the post-UVV era were analysed. The seroprevalence studies reflected changes in population immunity in Hong Kong, with an increase in seroprevalence in very young children that were UVV-eligible but decrease in seroprevalence among older children, adolescents and young adults [Chapter 4.2]. Varicella surveillance data, including notifications, AED attendance and hospital admissions in public hospitals, showed reductions of varicella in eligible children but infections persisted in the community for at least the first five years after UVV, contrasting the seroprevalence data [Chapter 4.3].

4.1 Uptake of the universal varicella vaccination programme in Hong Kong

Changes of varicella vaccination recommendation in Hong Kong

The evolution of varicella vaccination policy in Hong Kong has been described in detail in Chapter 1. In brief, varicella vaccine has been available in the private market since 1996. The Scientific Committee on Vaccine-Preventable Diseases (SCVPD) recommended a 2-dose UVV and the programme was launched in 2014. The 2-dose programme consists of the first dose using mVV for children at age 12 months and a second dose using MMRV when eligible children enter primary school (approximately six years of age) (78). Only children born in 2013 and after were eligible for UVV (78). The SCVPD advised, in 2018, bringing forward the second dose of MMRV from primary one to 18 months of age (79). Both children eligible for the original schedule (born between January 2013 and June 2018) and the first cohort under the new schedule (born in July 2018) would have their second dose administered in 2020.

As reported in Chapter 2, increasing varicella vaccine uptake among non-UVV eligible children was captured by the immunisation coverage surveys between 2001 and 2015. The immunisation coverage surveys were repeated in 2018 and 2021 with a similar methodology to previous surveys (155), using stratified cluster sampling to recruit children attending sampled preschools (including kindergarten (KG) and kindergarten-cum-childcare (KG-cum-CCC)). The 2018 and 2021 surveys included birth cohorts between 2012 and 2017 [Table 4.1.1] (157, 158). Demographics were collected from parents using a self-administered questionnaire, which was extended to include

attitudes to childhood vaccination in the 2018 and 2021 surveys. Documentation on immunisation records of consented children were reviewed and cross-checked with electronic vaccination records from the MCHC, if available. For vaccines not included in the routine Hong Kong childhood immunisation, only the first dose was routinely captured. To support varicella vaccine effectiveness estimation [Chapter 3], additional effort was made to record the second dose uptake, timeliness of vaccination, as well as vaccine manufacturers of varicella vaccines in the 2009, 2012 and 2015 surveys (156).

High first-dose varicella vaccine uptake achieved for UVV-eligible children

Among cohorts born before 2013 and not eligible for UVV, first dose varicella vaccine uptake among preschool children increased gradually from 6% for those born in 1995 to 55% for those born in 2012 [Table 4.1.1 & Figure 4.1.1a]. The median age of first dose vaccination for these children reduced from 25.5 months for those born in 2003, to 14.6 months for those born in 2012 [Table 4.1.1 & Figure 4.1.1b]. Information on the type of vaccine from the 2009 and 2012 surveys showed that most children received mVV from different manufacturers before UVV implementation (156). On the other hand, first dose uptake was remarkably high at 98% for UVV-eligible cohorts between 2013 and 2017 [Table 4.1.1 & Figure 4.1.1a]. The median age of vaccination for children born in 2013 and 2014 ranged from 12.1 to 12.6 months, close to the recommended 12 months [Table 4.1.1]. With the introduction of the universal vaccination programme, first dose uptake was high at 98% or above irrespective of place of birth and/ or residence, though slightly lower for non-local children (UVV eligible cohorts 2013 to 2018: 94.3% to 97.6% for non-local children vs. 99.1 to 99.7% for local children).

Attitudes on vaccine confidence were included in the 2018 and 2021 surveys. Parents surveyed in both 2018 and 2021 are confident in HKCIP vaccines, aligning with the high varicella vaccine uptake upon introduction to the routine programme (159). There was a slight increase in the concern in vaccine safety and a desire to receive fewer vaccines in the same visit (159). Increase in vaccine hesitancy on routine vaccination after COVID-19 pandemic has been reported elsewhere (160).

Variation of two-dose vaccine schedule by cohorts

The second dose varicella vaccine uptake for UVV cohort-ineligible children was lower than 10%, with the exception of the 2012 cohort (17%) [Table 4.1.1 and Figure 4.1.1a]. For UVV-eligible children, their second dose vaccine uptake is captured differently by the age of their scheduled vaccination. As those born in July 2018 or after are meant to receive their second dose vaccine at 18 months of age, their uptake will not be captured until the 2024 immunisation coverage survey, which includes birth cohorts between 2018 and 2021. On the other hand, children born between January 2013 and June 2018 received their second dose at primary one, which started in school year 2019/20. SIT administrative statistics in 2021 showed that second dose uptake of MMR (for those born before 2013)/ MMRV (for those born between 1 January 2013 and 30 June 2018) was 91% among primary one children in the 2019/20 school year [Figure 4.1.1c]. This was considerably lower than the second dose MMR uptake in previous years (98% or above in 2017/18 and 2018/19) (161), as school visits was disrupted in 2020 by school closure due to the COVID-19 pandemic (162). A MMR/ MMRV catch-up vaccination for primary one student in the 2019/20 year was arranged in 2022 (163). The long-term

impact of the pandemic on routine vaccination remains to be seen.

Table 4.1.1. Varicella vaccination uptake and age of vaccination in preschool children surveyed in Hong Kong, 2001 to 2021.

Survey year	Age (years)[1]/ cohort[2]	Number surveyed	Number received at least 1 dose (%)[3]	Median age (months) at 1st dose (IQR)[4]	Number received 2 dose (%)[5]	Median age (months) at 2nd dose (IQR)[4]
2001	5/ 1995	1176	67 (5.7)	NA	NA	NA
	4/ 1996	1257	112 (8.9)	NA	NA	NA
2003	5/ 1997	1245	120 (9.6)	NA	NA	NA
	4/ 1998	926	97 (10.5)	NA	NA	NA
	3/ 1999	868	73 (8.4)	NA	NA	NA
2006	5/ 2000	2314	435 (18.8)	NA	NA	NA
	4/ 2001	1928	322 (16.7)	NA	NA	NA
	3/ 2002	1840	350 (19.0)	NA	NA	NA
2009	5/ 2003	1666	397 (23.8)	25.5 (16.7 – 34.5)	7 (0.4)	40.0 (38.7 – 64.1)
	4/ 2004	1726	509 (29.5)	24.9 (16.5 – 32.4)	9 (0.5)	40.7 (35.9 – 49.7)
	3/ 2005	1819	613 (33.7)	23.0 (15.6 – 28.8)	6 (0.3)	37.0 (35.2 – 37.4)
2012	5/ 2006	1596	430 (26.9)	20.6 (14.7 – 29.5)	24 (1.5)	62.0 (39.3 – 65.5)
	4/ 2007	1834	614 (33.5)	19.0 (14.2 – 27.9)	22 (1.2)	48.7 (36.6 – 51.7)
	3/ 2008	1815	612 (33.7)	18.4 (14.1 – 25.9)	20 (1.1)	35.4 (27.0 – 40.9)
2015	5/ 2009	2276	1034 (45.4)	19.2 (14.3 – 27.4)	110 (4.8)	51.0 (39.9 – 59.2)
	4/ 2010	2488	1216 (48.9)	16.3 (14.0 – 23.5)	170 (6.8)	34.9 (24.6 – 50.4)
	3/ 2011	2831	1443 (51.0)	15.6 (13.5 – 21.9)	271 (9.6)	22.6 (17.2 – 30.4)
2018	5/ 2012	832	458 (55.1)	14.6 (12.7 - 23.9)	144 (17.3)	23.7 (17.2 - 40.0)
	4/ 2013	814	806 (99.0)	12.6 (12.1 - 18.0)	60 (7.4)	19.0 (16.7 - 24.2)
	3/ 2014	976	970 (99.4)	12.1 (12.0 - 12.2)	23 (2.4)	19.9 (18.0 - 25.0)
2021	5/ 2015	799	792 (99.1)	NA	NA (NA)	NA
	4/ 2016	946	934 (98.7)	NA	NA (NA)	NA
	3/ 2017	820	809 (98.7)	NA	NA (NA)	NA

Note:

(1) Surveys between 2001 and 2015 recruited children aged two to five years. As the preschool attendance rate of two-year-olds was only 50%, they were less representative of the population and only those aged three to five years were included in the analysis.

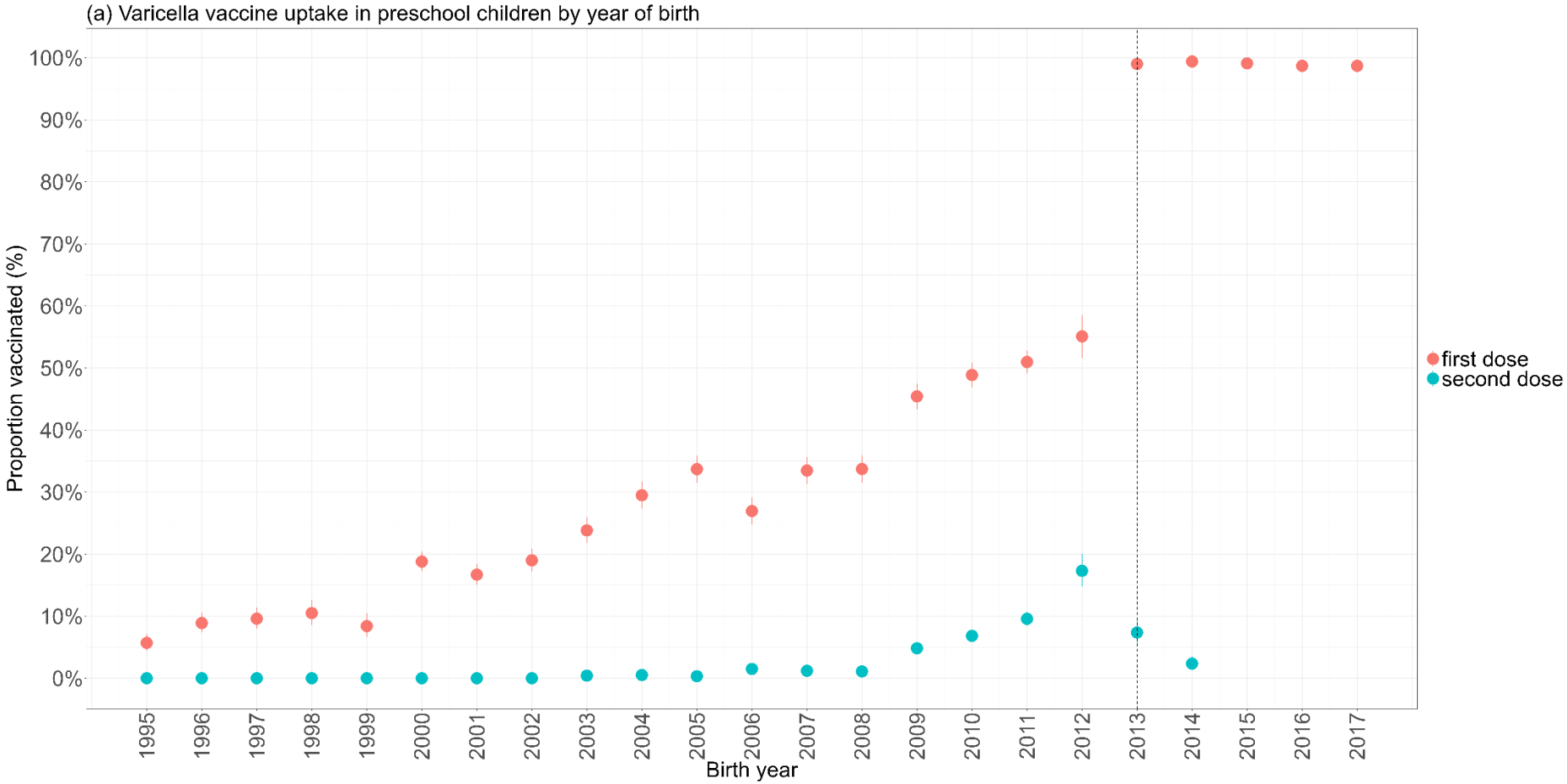
(2) Children born in 2013 or after are eligible for universal varicella vaccination (UVV). At the time of surveys, all UVV-eligible children had been due for their first dose but not the second dose of varicella vaccines. Therefore, the uptake and age at receiving second dose varicella vaccine for children born in 2013 and after represented those who received the vaccines earlier than scheduled in the private sector.

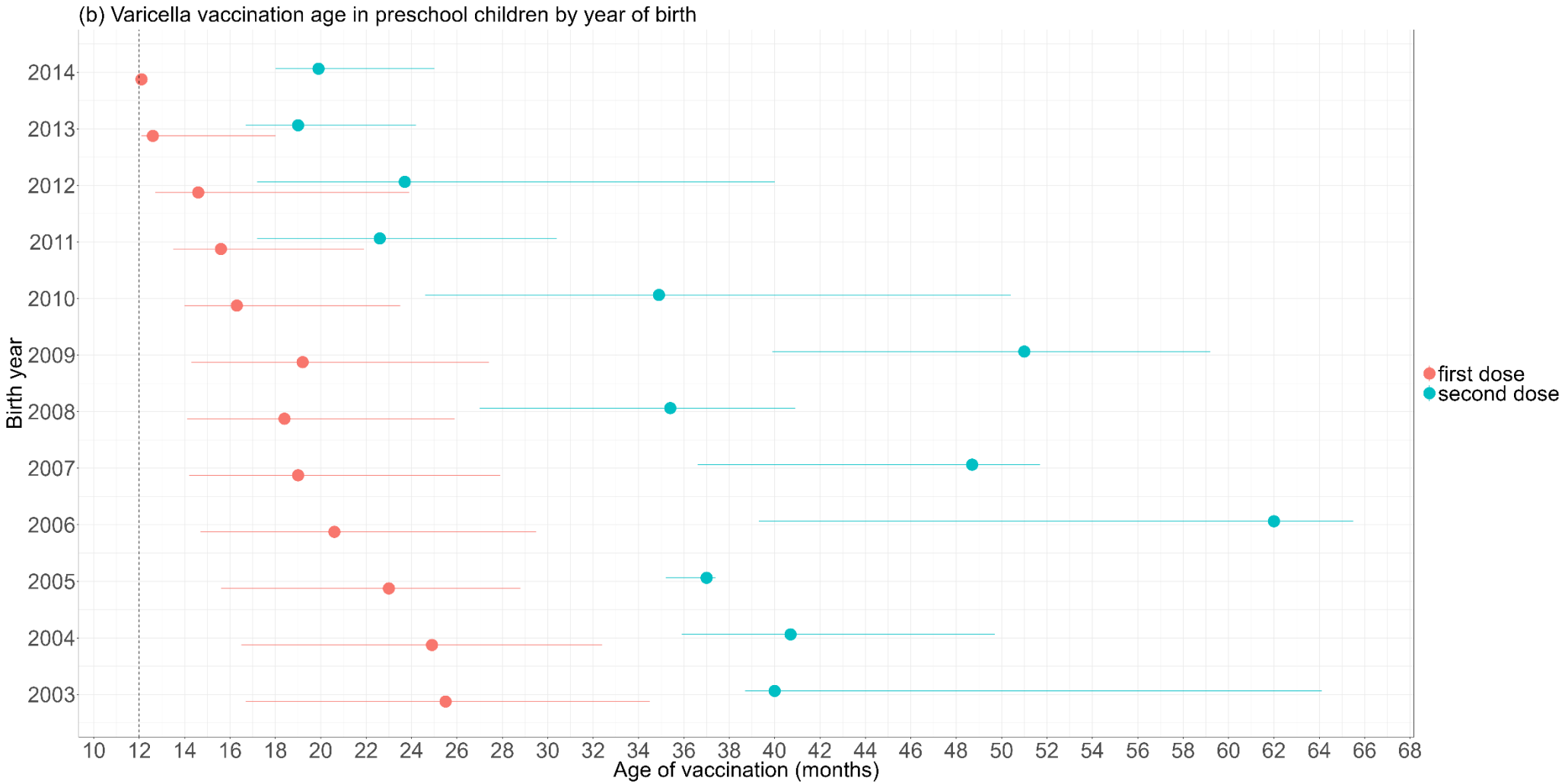
(3) Number and the proportion (%) of children ever received varicella vaccine. Some children might have received multiple vaccines but there was no data available for second dose vaccination in the surveys of 2001, 2003, 2006 and 2021. Survey respondents and reported cases with missing vaccination information were not included in the above table. Those who were vaccinated with unknown dose was not shown.

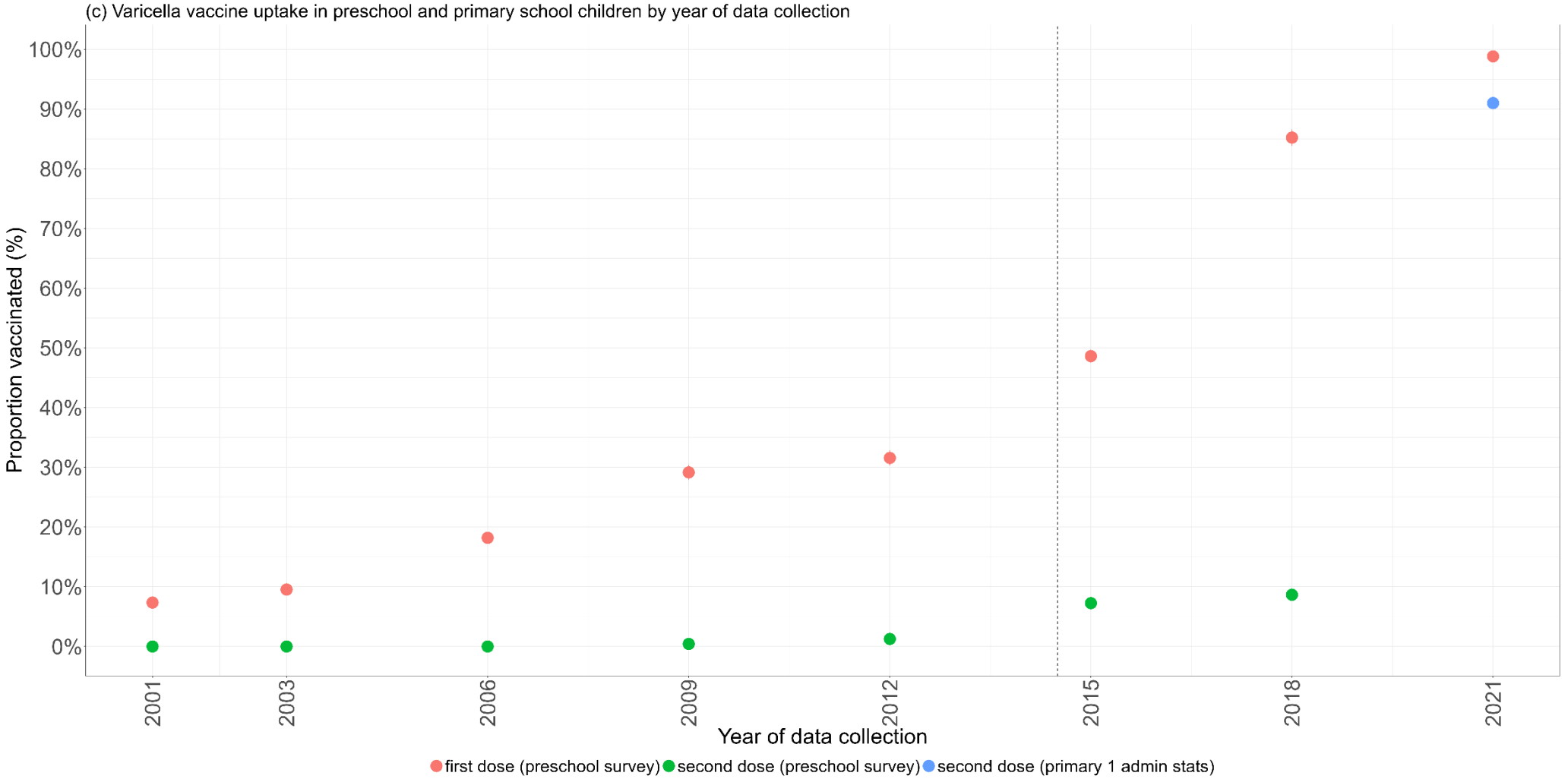
(4) Age of vaccination for survey respondents was computed by subtracting date of vaccination with date of birth. Median and interquartile range (IQR) of the age of vaccination was presented in the above table to indicate timeliness of vaccination. These data were not available in the surveys of 2001, 2003, 2006 and 2021.

(5) Number of varicella vaccine received was not collected for cases reported in 2001, 2003 and 2006 surveys and the data were not released by DH for the 2021 survey.

Figure 4.1.1. Varicella vaccination uptake and timeliness in Hong Kong. (a) Proportion of preschool children aged 3 to 5 years receiving varicella vaccine by birth cohort, 1995–2017 (dashed reference line: cohort eligible for UVV (2013)) (b) Interquartile range of age at receipt of varicella vaccination (months) for preschool children born between 2003 and 2018 by birth cohort and vaccine dose (dashed reference line: first dose schedule under UVV (12 months) (c) Proportion of preschool/ primary one children receiving varicella vaccine by year of data collection, 2001–2021 (dashed reference line: UVV introduction (July 2014))




(b) Varicella vaccination age in preschool children by year of birth
Birth year
2014
2013
2012
2011
2010
2009
2008
2007
2006
2005
2004
2003
10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56 58 60 62 64 66 68
Age of vaccination (months)
first dose
second dose



Note:

Children born in 2013 or after are eligible for universal varicella vaccination (UVV). At the time of surveys, all UVV-eligible children had been due for their first dose but not the second dose of varicella vaccines. Therefore, data from the preschool surveys including the uptake and age at receiving second dose varicella vaccine for children born in 2013 and after represented those who received the vaccines earlier than scheduled in the private sector [Figure 4.1.1a to 4.1.1c].

On the other hand, the primary 1 administrative statistic shown in Figure 4.1.1c was collected when UVV-eligible children were due for their second dose as they reached primary 1. Hence, this data reflected the second dose uptake of primary school children according to the originally recommended schedule.

Varicella vaccine uptake estimates in other studies

Varicella vaccine uptake among preschool children was also assessed in two other cross-sectional surveys in Hong Kong (164, 165). Varicella vaccine uptake among preschool children was estimated to be 57.6% in 2012 by Chan J *et al*. (164), compared with 31.6% in DH's 2012 survey [Table 4.1.1]. The survey by Huang *et al*. found that the first and second dose varicella vaccine uptake was 66.4% and 15.5% among preschool children aged two to five years between 2015 and 2016 (165), which was also higher than the 48.6% estimate in DH's 2015 survey (first does: 48.6% and second dose: 7.3%) [Table 4.1.1]. There are three factors that may lead to these differences. First, the DH surveys ascertain vaccination status by reviewing documented proof of vaccination records, whereas the other two surveys relied on parental recall, which is less specific albeit potentially more sensitive. Second, children aged two years attending preschools in Hong Kong may not be fully representative of the population. Subsidy for preschool fees is only available for those aged three to five years and only 50% of children aged two years attend preschool. Hence children aged two years sampled in preschools are more likely to be from families of higher incomes, who are associated with higher varicella vaccine uptake in the private market (164). Third, Huang *et al*'s study included children aged two years in 2015 and 2016, which would include UVV eligible cohorts of 2013 and 2014. The DH survey in 2015 only included non-UVV eligible cohorts born between 2009 and 2011. Thus, in this thesis, I will rely only on the estimates of vaccine coverage from DH surveys for all subsequent analyses.

Summary

Between 2001 and 2015, one-dose varicella vaccine uptake in Hong Kong increased from less than 10% to 50% for children not eligible for UVV. With the implementation of UVV in 2014, the uptake quickly rose to 99% or above for eligible children. Before 2020, most vaccinees received only one dose of varicella vaccine. The second dose uptake for eligible primary school children was still high at 91% in 2021 but the uptake was adversely affected by the COVID-19 pandemic.

4.2 Changes in Varicella-Zoster Virus (VZV) seroprevalence in Hong Kong, 1995 to 2020

Introduction

Between 1995 and 2020, the Public Health Laboratory Services Branch (PHLSB) of the Department of Health in Hong Kong conducted six varicella seroprevalence surveys, one every five years. Details of the serosurveys were given previously in Chapter 2 and Chan *et al*. (155). These serosurveys aim at detecting the prevalence of IgG antibodies against varicella-zoster virus (VZV) to reflect the population immunity against varicella. As VZV antibody elicited after natural infection persists for decades and through adulthood (166), the seroprevalence of VZV can be a good proxy of the prevalence of past VZV infections in the community in the pre-vaccine era. Existing commercial enzyme immunoassays (EIAs) are less sensitive to vaccine-induced immunity (35). Hence, VZV seroprevalence in a population with high vaccination uptake will likely be under-estimated.

In Hong Kong, varicella vaccine uptake increased steadily to 50% before the implementation of universal varicella vaccination (UVV) for children in 2014 (155), and first dose uptake quickly increased to at least 98% for eligible children born between 2013 and 2017 in 2018 (157) and 2021 (158) [Figure 4.1.1a]. The first serosurvey in 1995 represents the pre-vaccine era sero-epidemiology of VZV in Hong Kong, whilst later surveys were collected with samples covering children of increasing vaccine uptake, transitioning from private to publicly funded vaccination. In this

analysis, the change in VZV seroprevalence in Hong Kong under the increasing vaccine uptake was described, with consideration of vaccine uptake of children sampled in different years. The force-of-infection (FOI) was also estimated to understand the change in transmission intensity of varicella.

Methods

Sampling and descriptive analyses

Samples for the serosurveys were left-over sera submitted for clinical diagnoses and not clinically indicated for varicella or herpes zoster. Samples for different age groups were included until the pre-defined quotas of sera were reached. Commercial EIAs were used to test the IgG antibodies to VZV [Table 4.2.1]. Samples with results falling in the equivocal/ indeterminate range by the first EIA were repeated in duplicates with a second EIA to determine the positivity of these samples [Personal communication, Department of Health Hong Kong]. Results of the serosurveys, including the number of samples and percentage tested positive in each age group and survey year, were released by the Department of Health Hong Kong (167). The proportion tested positive, or seroprevalence, was analysed by mean age of each age group and survey year. Exact binomial proportion confidence intervals for each age group and survey year were generated using R package *binom* (168).

Table 4.2.1. Enzyme immune-assays used in seroprevalence surveys of varicella-zoster virus antibodies in Hong Kong.

Year	Test kit 1	Test kit 2[1]
1995	Human Elisa	Unknown[2]
2000	Unknown[3]	Unknown[3]
2005	Siemens[4]	VIDAS
2010		
2015	Siemens[4]	Siemens[4]
2020	Novalisa	Novalisa

Note:

1) Second test kit was used to test samples that were indeterminate by the first test kit.

2) No information on whether second test kits were used for the 1995 survey.

3) No information on test kits for the 2000 survey.

4) Production of Siemens test kit ceased in 2020.

Analysis of seroprevalence in conjunction with vaccine uptake

Using the cohort-specific varicella vaccination uptake captured in the immunisation coverage surveys on preschool children [Chapter 4.1], the expected vaccine-induced seroprevalence (*PV*) was estimated by multiplying the varicella vaccine uptake with a 5% primary vaccine failure and three different sensitivities of EIA to vaccine-induced antibody (50% (worst-case), 88% (base-case) and 100% (best-case)). This estimation assumed the seroprevalence for the sero-converted vaccinees were contributed only from vaccination but not from infections. On the other hand, the expected infection-induced seroprevalence (*PI*) was obtained by subtracting the observed seroprevalence with the estimated vaccine-induced seroprevalence (*PV*). Maple *et al*. compared 15 EIAs with time-resolved immuno-fluorescent assay (TRIFA) and found that the

sensitivity of these assays on unvaccinated individuals with natural infection ranged from 69% to 97%, with the Siemens (Dade Behring) EIA being the most sensitive (169). In another study by Sauerbrei *et al*. (35), the Siemens EIA had a lower sensitivity of 76% in detecting vaccine-induced antibody (with equivocal results being counted as negative) when compared to the Fluoresecent Antibody to Membrane Antigen (FAMA) assay (FAMA is generally regarded as the most sensitive serology test for varicella and a FAMA titer of >= 1:4 has a good correlation with protection against symptomatic varicella (33)). A sensitivity of 50% was assumed as the worst-case scenario for the sensitivity of detection of vaccine derived antibodies, considering the possibility of a worst performing EIA having sensitivity to immunity induced by natural infection being 69% and a further reduction in sensitivity to vaccine-induced antibody of 76%. The base-case IgG test sensitivity of 88% was derived from the 2020 serosurvey. Children aged 1 to 4 years sampled in the 2020 serosurvey were UVV-eligible children born between 2016 and 2019. The latest immunisation coverage survey in 2021 showed that the varicella vaccination uptake for children born between 2015 and 2017 was 98.8% (158), which was similar to those born between 2013 and 2014 who were also eligible for universal vaccination [Table 4.2.1]. As the observed seroprevalence for these children was 82% and considering the assumption of a 5% primary vaccine failure, the sensitivity of the EIA in detecting vaccine-induced antibody would be nearly 88%. Hence, a sensitivity of 88% was assumed in the base-case scenario. A sensitivity of 100% (best-case scenario) assumed EIAs were fully sensitive in detecting vaccine-induced antibody, and that all the vaccinated responded and developed sufficient immunity.

Force of infection estimation

The annual force of infection (FOI), λ, is the proportion of susceptible individuals infected over a year. FOI was estimated for those aged between 1 to 4 years (mean age 2.5 years), those aged 5 to 9 years (mean age 7 years), those aged 10 to 14 years (mean age 12 years) and those aged 15 to 19 years (mean age 17 years). In each serosurvey, FOI of each age group i, λ_i, was estimated using the following equation (170):

$$\lambda_i = \frac{-\ln [x_{i+1}/x_i]}{\Delta a_i}$$

where x_{i+1} and x_i are the proportion seronegative in successive age groups and Δa_i is the difference in mean age of those age groups. In the post-vaccine era, the proportion immune (seropositive) is contributed by both infection (*PI*) and vaccination (*PV*). To avoid bias due to increasing vaccine uptake, the change in seropositivity/ susceptibility should remove seroconversion due to vaccination. Hence, the proportion susceptible in a certain age group i, x_i, was calculated from the estimated seroprevalence due to infection in that age group (PI_i):

$$x_i = 1 - PI_i$$

The FOI estimation was repeated for the three different assumptions of IgG test /EIA sensitivity to vaccine-induced immunity. Adults aged between 20 and 39 years were combined as those aged 20 years or above are largely seropositive (at least 88% before 2020) and stochasticity in sampling may affect seroprevalence in older ages. In addition, adults aged 40 years or above were excluded from the estimation as a reasonable mean

age is difficult to determine with a wide age range.

Results

Seroprevalence increased with age

For those under 20 years of age, the seroprevalence increased with age in early serosurveys [Figure 4.2.1 and Table 4.2.2]. In surveys between 1995 and 2010, seroprevalence patterns where similar and increased sharply from 45% and less for those aged 1 to 4 years (mean age 2.5 years), to 88% or above, for those aged 15 to 19 years (mean age 17 years). With increasing vaccine uptake these age differences became more subtle. For the 2015 survey, the seroprevalence increased moderately from 36% for those aged 1 to 4 years, to 76% among those aged 15 to 19 years [Table 4.2.2]. For the 2020 survey, 82% of those aged 1 to 4 were seropositive, higher than those aged 5 to 9 years (mean age 7 years, 53% seropositive), those aged 10 to 14 years (mean age 12 years, 52% seropositive), and those aged 15 to 19 years (mean age 17 years, 76% seropositive) [Table 4.2.2]. At least 88% of those aged 20 years or above were seropositive in all years, with the exception of only 82% of those aged 20 to 24 years in 2020 being seropositive.

Decreasing age-specific seroprevalence over the years

Between 1995 and 2020, there was substantial reduction in seroprevalence against varicella for those aged 5 to 25 years [Figure 4.2.1]. This reduction was 28% or above for those aged 5 to 9 years (28% reduction from 81% [95%CI: 72% to 88%] in 1995 to

53% [95%CI: 46% to 60%] in 2020) and those aged 10 to 14 years (33% reduction from 85% [95%CI: 76% to 91%] in 1995 to 52% [95%CI: 37% to 66%] in 2020). The extent of reduction was from 15% to 22% for adolescents and young adults (22% reduction for those aged 15 to 19 years from 98% [95%CI: 93% to 100%] in 1995 to 76% [95%CI: 62% to 87%] in 2020) and 15% reduction for those aged 20 to 24 years (from 97% [95%CI: 89% to 98%] in 1995 to 82% [95%CI: 68% to 91%] in 2020).

Observed seroprevalence lower than expected vaccine-induced seroprevalence in some ages and years

The expected vaccine-induced seroprevalence (*PV*) increased with rising vaccine uptake in young children in later surveys, as more children were eligible for UVV in 2015 and 2020 [Figure 4.2.2]. With the base-case assumption of an EIA sensitivity to vaccine-induced immunity being 88% [red triangle in Figure 4.2.2], those aged 1 to 4 years in 2010, 2015 and 2020, as well as those aged 5 to 9 years in 2020 had higher expected vaccine-induced seroprevalence than the observed seroprevalence, resulting in expected infection-induced seroprevalence below 0% [Table 4.2.2]. Under the worst-case assumption of an EIA sensitivity to vaccine-induced immunity being 50%, those aged 1 to 4 years in 2015 still had higher estimated seroprevalence by vaccination than the observed seroprevalence. Factors other than low EIA sensitivity to vaccine-induced immunity, such as residual sera collected from children not representative to the target age group, might lead to this observation.

Decreasing varicella force-of-infection for children aged 12 years or younger

With the base-case assumption of a reduced sensitivity to vaccine-induced immunity being 88%, the FOI estimated was highest for those aged 10 to 14 years (0.40), followed by those aged 1 to 4 years (0.23) in 1995, before the vaccine was available in the private market [Figure 4.2.3]. There was a general reduction in FOI for those aged 12 years or below. Comparing the FOI estimates in 1995 or 2000 (pre-vaccine or early vaccine era) with those in 2020 (6 years after UVV implementation), the FOI has been reduced from an estimated 0.16 in 2000 to 0.07 in 2020 for those aged 5 to 9 years, from 0.40 in 1995 to 0.12 in 2020 for those aged 10 to 14 years, and from 0.23 in 1995 to -0.03 in 2020 for those aged 1 to 4 years. The negative FOI among those aged 1 to 4 years in 2020 was a result of expected vaccine-induced seroprevalence being higher than the observed seroprevalence in those aged 5 to 9 years. Similar trends of decreasing FOI for these age groups were also observed under IgG test sensitivity assumption of 50% and 100% [Figure 4.2.4]. In contrast, the annual FOI for those aged 15 to 19 years was estimated to have increased between 2000 (0.00) and 2015 (0.14).

Table 4.2.2. Seroprevalence against varicella-zoster virus and expected vaccine- and infection-induced seroprevalence, 1995 to 2020, Hong Kong.

Year	Age	Cohort		Percent of cohorts under UVV (%)	Varicella vaccine uptake (%)	No. tested	Observed seroprevalence (%)			Expected vaccine- and infection-induced seroprevalence					
										IgG test sensitivity 88%		IgG test sensitivity 50%		IgG test sensitivity 100%	
		From	To				Value	95%CI		Vaccine (PV)	Infection (PI)	Vaccine (PV)	Infection (PI)	Vaccine (PV)	Infection (PI)
1995	1 to 4	1991	1994	0.0%	0.0%	100	**45.0%**	35.0%	55.3%	0.0%	45.0%	0.0%	45.0%	0.0%	45.0%
1995	5 to 9	1986	1990	0.0%	0.0%	100	**80.8%**	71.7%	88.0%	0.0%	80.8%	0.0%	80.8%	0.0%	80.8%
1995	10 to 14	1981	1985	0.0%	0.0%	100	**85.0%**	76.5%	91.4%	0.0%	85.0%	0.0%	85.0%	0.0%	85.0%
1995	15 to 19	1976	1980	0.0%	0.0%	100	**98.0%**	93.0%	99.8%	0.0%	98.0%	0.0%	98.0%	0.0%	98.0%
1995	20 to 24	1971	1975	0.0%	0.0%	100	**97.0%**	91.5%	99.4%	0.0%	97.0%	0.0%	97.0%	0.0%	97.0%
1995	25 to 29	1966	1970	0.0%	0.0%	100	**100.0%**	96.4%	100.0%	0.0%	100.0%	0.0%	100.0%	0.0%	100.0%
1995	30 to 34	1961	1965	0.0%	0.0%	100	**100.0%**	96.4%	100.0%	0.0%	100.0%	0.0%	100.0%	0.0%	100.0%
1995	35 to 39	1956	1960	0.0%	0.0%	100	**100.0%**	96.4%	100.0%	0.0%	100.0%	0.0%	100.0%	0.0%	100.0%
1995	40+	1896	1955	0.0%	0.0%	100	**100.0%**	96.4%	100.0%	0.0%	100.0%	0.0%	100.0%	0.0%	100.0%
2000	1 to 4	1996	1999	0.0%	9.3%	100	**25.0%**	16.9%	34.7%	7.8%	17.2%	4.4%	20.6%	8.8%	16.2%
2000	5 to 9	1991	1995	0.0%	1.1%	100	**65.0%**	54.8%	74.3%	0.9%	64.1%	0.5%	64.5%	1.0%	64.0%
2000	10 to 14	1986	1990	0.0%	0.0%	100	**84.0%**	75.3%	90.6%	0.0%	84.0%	0.0%	84.0%	0.0%	84.0%
2000	15 to 19	1981	1985	0.0%	0.0%	100	**97.0%**	91.5%	99.4%	0.0%	97.0%	0.0%	97.0%	0.0%	97.0%
2000	20 to 24	1976	1980	0.0%	0.0%	100	**95.0%**	88.7%	98.4%	0.0%	95.0%	0.0%	95.0%	0.0%	95.0%
2000	25 to 29	1971	1975	0.0%	0.0%	100	**99.0%**	94.6%	100.0%	0.0%	99.0%	0.0%	99.0%	0.0%	99.0%
2000	30 to 34	1966	1970	0.0%	0.0%	100	**94.0%**	87.4%	97.8%	0.0%	94.0%	0.0%	94.0%	0.0%	94.0%
2000	35 to 39	1961	1965	0.0%	0.0%	100	**99.0%**	94.6%	100.0%	0.0%	99.0%	0.0%	99.0%	0.0%	99.0%
2000	40+	1901	1960	0.0%	0.0%	100	**95.0%**	88.7%	98.4%	0.0%	95.0%	0.0%	95.0%	0.0%	95.0%
2005	1 to 4	2001	2004	0.0%	22.2%	200	**25.0%**	19.2%	31.6%	18.6%	6.4%	10.5%	14.5%	21.1%	3.9%
2005	5 to 9	1996	2000	0.0%	11.2%	200	**62.0%**	54.9%	68.8%	9.4%	52.6%	5.3%	56.7%	10.6%	51.4%
2005	10 to 14	1991	1995	0.0%	1.1%	100	**79.0%**	69.7%	86.5%	0.9%	78.1%	0.5%	78.5%	1.0%	78.0%
2005	15 to 19	1986	1990	0.0%	0.0%	100	**92.0%**	84.8%	96.5%	0.0%	92.0%	0.0%	92.0%	0.0%	92.0%
2005	20 to 24	1981	1985	0.0%	0.0%	50	**94.0%**	83.5%	98.7%	0.0%	94.0%	0.0%	94.0%	0.0%	94.0%
2005	25 to 29	1976	1980	0.0%	0.0%	50	**92.0%**	80.8%	97.8%	0.0%	92.0%	0.0%	92.0%	0.0%	92.0%
2005	30 to 34	1971	1975	0.0%	0.0%	50	**96.0%**	86.3%	99.5%	0.0%	96.0%	0.0%	96.0%	0.0%	96.0%
2005	35 to 39	1966	1970	0.0%	0.0%	50	**94.0%**	83.5%	98.7%	0.0%	94.0%	0.0%	94.0%	0.0%	94.0%
2005	40+	1906	1965	0.0%	0.0%	100	**98.0%**	93.0%	99.8%	0.0%	98.0%	0.0%	98.0%	0.0%	98.0%

Year	Age	Cohort		Percent of cohorts under UVV (%)	Varicella vaccine uptake (%)	No. tested	Observed seroprevalence (%)			Expected vaccine- and infection-induced seroprevalence					
										IgG test sensitivity 88%		IgG test sensitivity 50%		IgG test sensitivity 100%	
		From	To				Value	95%CI		Vaccine (PV)	Infection (PI)	Vaccine (PV)	Infection (PI)	Vaccine (PV)	Infection (PI)
2010	1 to 4	2006	2009	0.0%	34.9%	200	**26.0%**	20.1%	32.7%	29.2%	-3.2%	16.6%	9.4%	33.2%	-7.2%
2010	5 to 9	2001	2005	0.0%	24.5%	200	**56.0%**	48.8%	63.0%	20.5%	35.5%	11.6%	44.4%	23.3%	32.7%
2010	10 to 14	1996	2000	0.0%	11.2%	100	**77.0%**	67.5%	84.8%	9.4%	67.6%	5.3%	71.7%	10.6%	66.4%
2010	15 to 19	1991	1995	0.0%	1.1%	100	**88.0%**	80.0%	93.6%	0.9%	87.1%	0.5%	87.5%	1.0%	87.0%
2010	20 to 24	1986	1990	0.0%	0.0%	50	**94.0%**	83.5%	98.7%	0.0%	94.0%	0.0%	94.0%	0.0%	94.0%
2010	25 to 29	1981	1985	0.0%	0.0%	50	**90.0%**	78.2%	96.7%	0.0%	90.0%	0.0%	90.0%	0.0%	90.0%
2010	30 to 34	1976	1980	0.0%	0.0%	50	**96.0%**	86.3%	99.5%	0.0%	96.0%	0.0%	96.0%	0.0%	96.0%
2010	35 to 39	1971	1975	0.0%	0.0%	50	**96.0%**	86.3%	99.5%	0.0%	96.0%	0.0%	96.0%	0.0%	96.0%
2010	40+	1911	1970	0.0%	0.0%	100	**98.0%**	93.0%	99.8%	0.0%	98.0%	0.0%	98.0%	0.0%	98.0%
2015	1 to 4	2011	2014	50.0%	76.1%	200	**36.0%**	29.4%	43.1%	63.6%	-27.6%	36.1%	-0.1%	72.3%	-36.3%
2015	5 to 9	2006	2010	0.0%	37.7%	100	**50.0%**	39.8%	60.2%	31.5%	18.5%	17.9%	32.1%	35.8%	14.2%
2015	10 to 14	2001	2005	0.0%	24.5%	50	**62.0%**	47.2%	75.3%	20.5%	41.5%	11.6%	50.4%	23.3%	38.7%
2015	15 to 19	1996	2000	0.0%	11.2%	50	**76.0%**	61.8%	86.9%	9.4%	66.6%	5.3%	70.7%	10.6%	65.4%
2015	20 to 24	1991	1995	0.0%	1.1%	50	**92.0%**	80.8%	97.8%	0.9%	91.1%	0.5%	91.5%	1.0%	91.0%
2015	25 to 29	1986	1990	0.0%	0.0%	50	**94.0%**	83.5%	98.7%	0.0%	94.0%	0.0%	94.0%	0.0%	94.0%
2015	30 to 34	1981	1985	0.0%	0.0%	50	**100.0%**	92.9%	100.0%	0.0%	100.0%	0.0%	100.0%	0.0%	100.0%
2015	35 to 39	1976	1980	0.0%	0.0%	50	**92.0%**	80.8%	97.8%	0.0%	92.0%	0.0%	92.0%	0.0%	92.0%
2015	40+	1916	1975	0.0%	0.0%	50	**98.0%**	89.4%	99.9%	0.0%	98.0%	0.0%	98.0%	0.0%	98.0%
2020	1 to 4	2016	2019	100.0%	98.8%	195	**82.1%**	76.0%	87.2%	82.6%	-0.5%	46.9%	35.2%	93.9%	-11.8%
2020	5 to 9	2011	2015	60.0%	80.7%	200	**53.0%**	45.8%	60.1%	67.5%	-14.5%	38.3%	14.7%	76.7%	-23.7%
2020	10 to 14	2006	2010	0.0%	37.7%	50	**52.0%**	37.4%	66.3%	31.5%	20.5%	17.9%	34.1%	35.8%	16.2%
2020	15 to 19	2001	2005	0.0%	24.5%	50	**76.0%**	61.8%	86.9%	20.5%	55.5%	11.6%	64.4%	23.3%	52.7%
2020	20 to 24	1996	2000	0.0%	11.2%	50	**82.0%**	68.6%	91.4%	9.4%	72.6%	5.3%	76.7%	10.6%	71.4%
2020	25 to 29	1991	1995	0.0%	1.1%	50	**90.0%**	78.2%	96.7%	0.9%	89.1%	0.5%	89.5%	1.0%	89.0%
2020	30 to 34	1986	1990	0.0%	0.0%	50	**94.0%**	83.5%	98.7%	0.0%	94.0%	0.0%	94.0%	0.0%	94.0%
2020	35 to 39	1981	1985	0.0%	0.0%	50	**88.0%**	75.7%	95.5%	0.0%	88.0%	0.0%	88.0%	0.0%	88.0%
2020	40+	1921	1980	0.0%	0.0%	100	**97.0%**	91.5%	99.4%	0.0%	97.0%	0.0%	97.0%	0.0%	97.0%

Note: Expected seroprevalence by vaccine or infection below 0% is highlighted in red.

Figure 4.2.1. Observed seroprevalence against varicella in Hong Kong, 1995 to 2020.

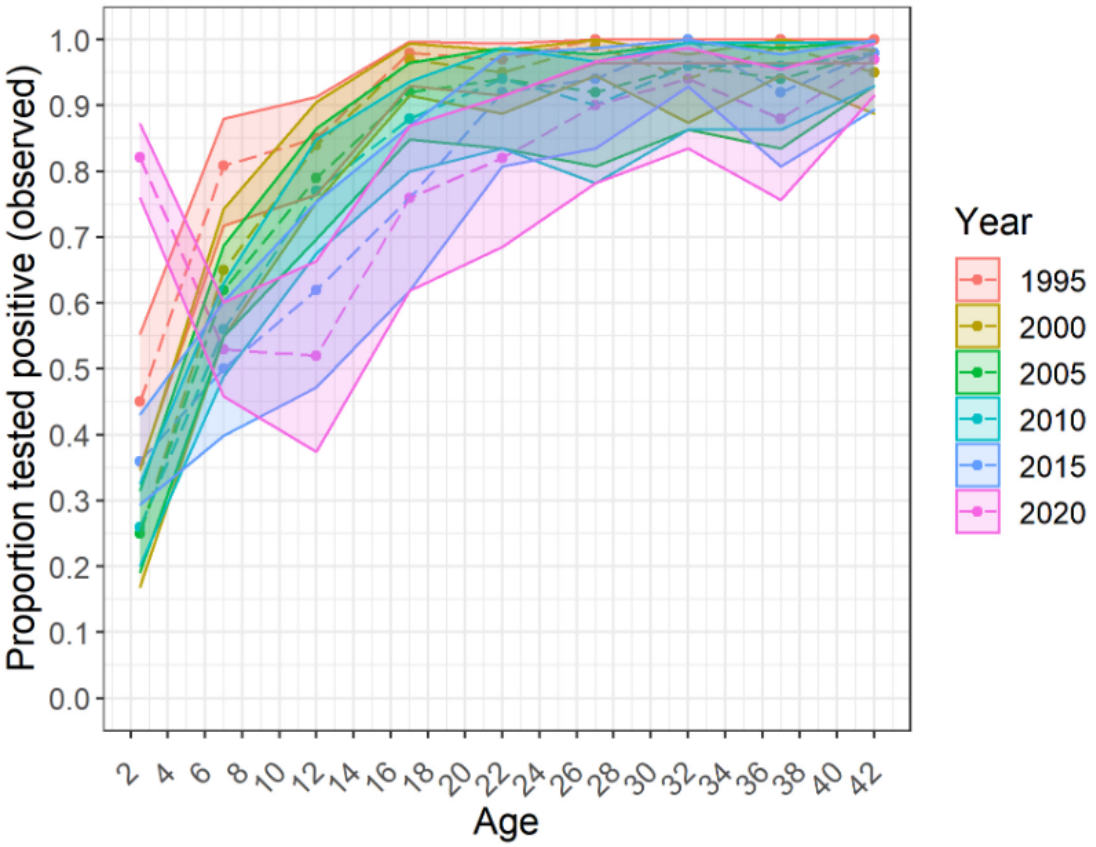
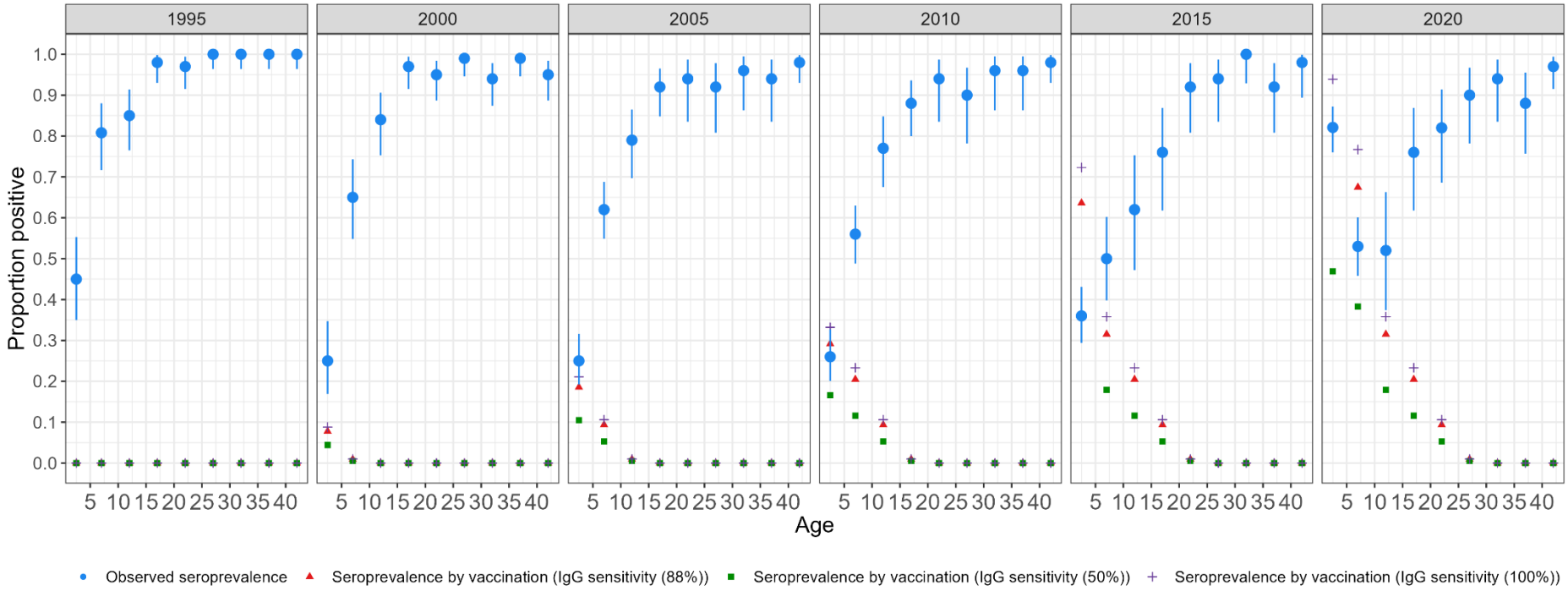
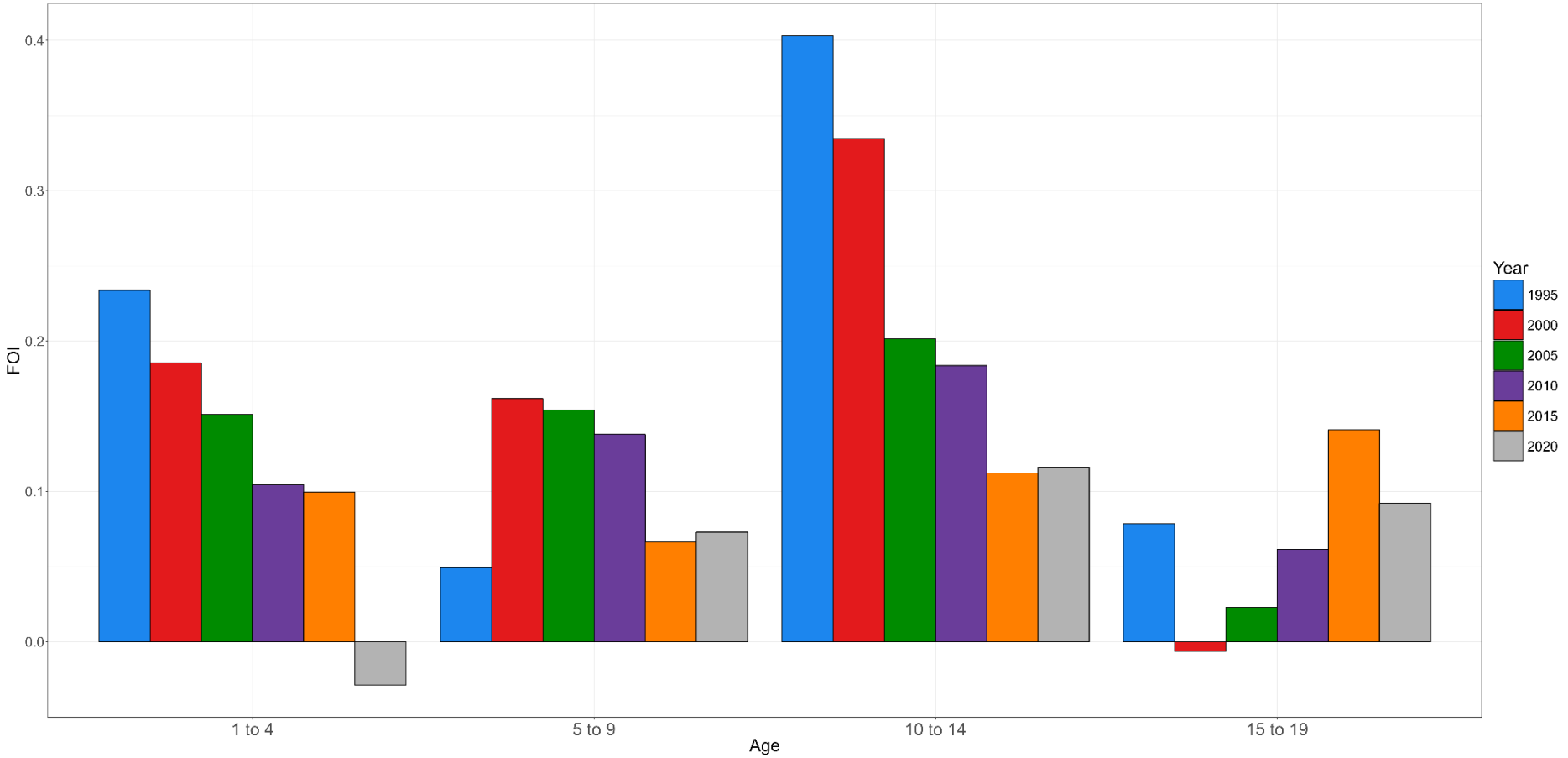


Figure 4.2.2. Observed seroprevalence against varicella and estimated seroprevalence due to vaccination in Hong Kong by age and year, 1995 to 2020.



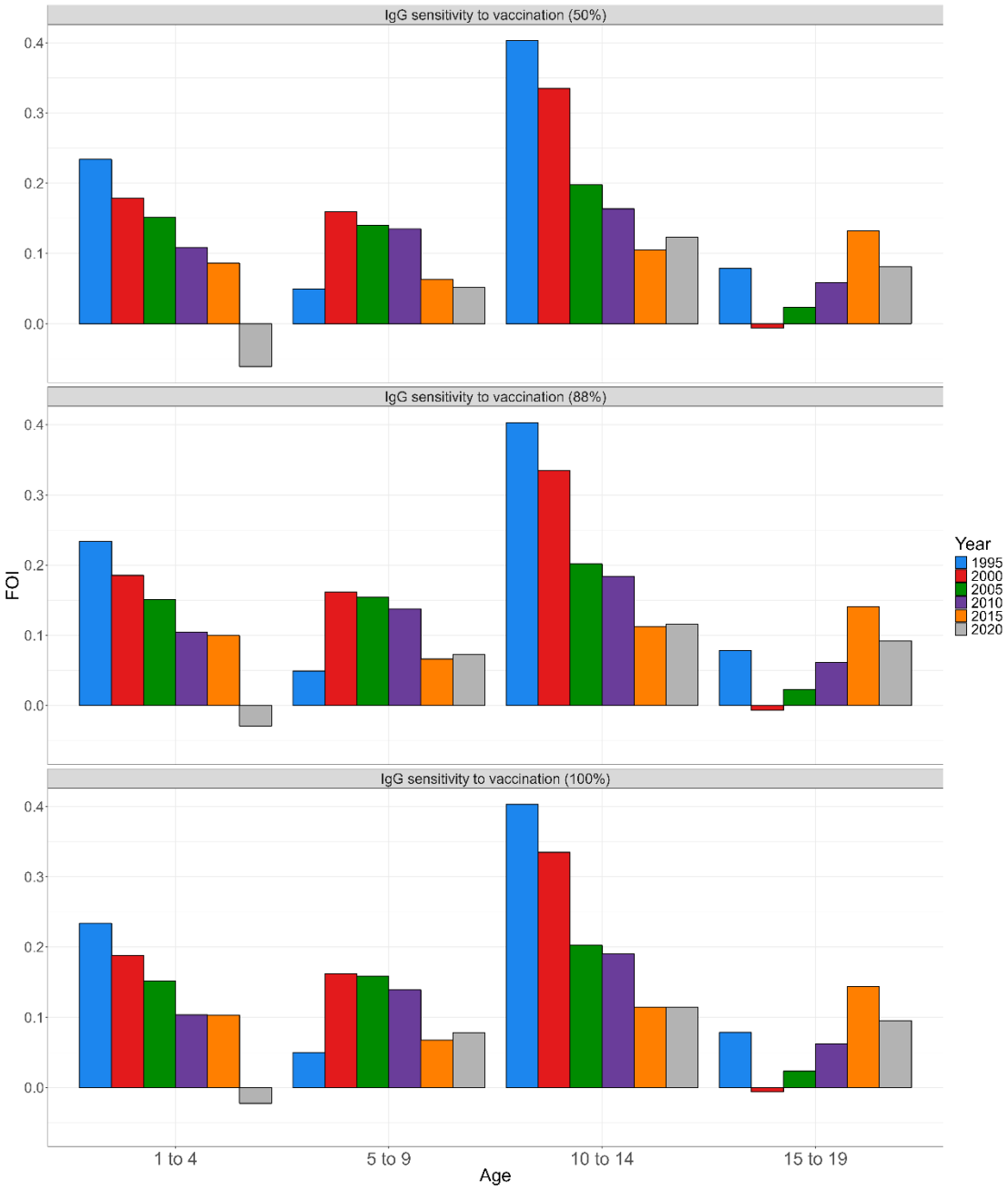
Note: Seroprevalence by vaccination was estimated based on vaccine uptake of respective cohorts, primary vaccine failure of 5% and IgG test sensitivity of 50%, 88% and 100%.

Figure 4.2.3. Estimation of age-specific force of infection (FOI) of varicella for individuals aged under 20 years in Hong Kong, 1995 to 2020.



Note: FOI was estimated based on the proportion seronegative of successive age groups, after taking into account the observed seroprevalence and expected seroprevalence by vaccination (based on vaccine uptake of respective cohorts, primary vaccine failure of 5% and IgG test sensitivity of 88%).

Figure 4.2.4. Sensitivity analysis on the estimation of age-specific force of infection (FOI) of varicella for individuals aged under 20 years in Hong Kong, 1995 to 2020.



Note: FOI was estimated based on the proportion seronegative of successive age groups, after taking into account the observed seroprevalence and expected vaccine-induced seroprevalence (based on vaccine uptake of respective cohorts, primary vaccine failure of 5% and IgG test sensitivity of 50%, 88% and 100%).

Discussion

Trend in seroprevalence and FOI over time and its implication on population immunity

These six 5-yearly seroprevalence surveys between 1995 and 2020 showed a substantial reduction in seroprevalence for those aged between 5 and 24 years. This reduction coincided with the increasing varicella vaccine uptake in preschool children. Before UVV, first-dose vaccine uptake increased from 10% or below between in 2001 and 2003, to between 18% and 30% from 2006 to 2012, and reached 48% in 2015 [Table 4.2.2]. The first-dose vaccine uptake for UVV eligible children was at least 98% in 2018 and 2021. The reduction in seroprevalence indicated a larger pool of susceptibles accumulated among older children, adolescents and young adults with low vaccine uptake [Table 4.2.2].

The 1995 serosurvey represented the transmission dynamics of varicella when it was still endemic in the pre-vaccine era. The FOI was estimated to be highest in young children and adolescents. The higher FOI in adolescents aged 10 to 14 years is comparable to higher reported contacts of this age group in the POLYMOD study (171). With the increase in vaccine uptake in young children before UVV, there was a reduction in FOI estimated for children aged 10 to 14 years or below between 1995 and 2010. The successful implementation of UVV led to nearly 100% of the eligible children to be vaccinated, which might further reduce VZV circulation in the community. This is evidenced by the lowest FOI for children aged 10 to 14 years or below in 2015 and 2020, one and six years after UVV started in 2014. Previous

modelling studies showed that natural infections in susceptible older children and adolescents are expected to remain low in the initial 'honeymoon' period of UVV, until a critical level of susceptibles is accumulated to lead to outbreaks (65, 76). Therefore, these susceptible individuals will be less likely to be infected until later in life and their risk of developing complications would be higher than if they were infected in early childhood. It should be noted that the FOI for those aged 15 to 19 years (mean age 17 years) was highest in 2015, indicating an increase in transmission in adolescents and young adults shortly after the UVV. The rate of varicella notification was from 113 to 169 per 100,000 for these age group between 2010 and 2014, which was relatively high compared to other periods when notification data was available (155). The dynamics of varicella transmission under both private and public vaccination should be studied by using a mathematical model while fitting both seroprevalence and notification data to help understand the effect of vaccination on population immunity and the potential for an upsurge in the future.

While the serosurveys provide valuable information to the changing sero-epidemiology of varicella in Hong Kong, the estimation of expected vaccine- and infection-induced seroprevalence indicated that the observed seroprevalence might under-estimate the immunity against VZV, especially in later surveys. After considering different scenarios of reduced EIA sensitivity to vaccine-induced seroconversion, the seroprevalence of children aged 1 to 4 years and 5 to 9 years observed in some of the 2010, 2015 and 2020 serosurveys were lower than the estimated seroprevalence due to vaccination, based on the vaccine uptake estimates of the immunisation coverage surveys. This indicated no or very low level of seroconversion due to natural infection, which seems unlikely considering that there were 278 to 1577 and 188 to 2290 varicella notifications per

100,000 for those aged under 5 years and 5 to 9 years between 2010 and 2019. Moreover, the FOI was estimated empirically to illustrate change in transmission over the years. Although vaccine-induced seroconversion was considered, the caveats and stochasticity of the data may lead to over- or under-estimation of the FOI. This method is more suitable to estimate FOI for children when there is a substantial difference in proportion susceptible/ immune between successive age groups. For adolescents or adults where the proportion immune approaches 100%, the fluctuation due to sampling may generate negative FOI estimates (e.g. those aged 1 to 4 years in 2020 and those aged 15 to 19 years in 2000) [Figure 4.2.3].

Potential issue in sampling

Sampling strategy and EIA sensitivity are two main potential sources of biases of the serosurveys. The sampling strategy may under- or over-estimate the seroprevalence. As samples of these serosurveys were residual clinical specimens collected until a target number of sera was fulfilled for the different age groups. Hence, the proportion tested positive might be over- or under-estimated in certain age groups if the age distribution of the actual samples were skewed towards the younger or older ends of the relevant age group. The effect of this sampling bias was likely to be particularly influential for young children, as their seroprevalence increases rapidly by age due to more intense infections and/ or vaccination under UVV. Those aged 1 to 4 years in 2010 and 2015, as well as those aged 5 to 9 years in 2020, had lower observed seroprevalence than the expected vaccine-induced seroprevalence [Table 4.2.2]. These were children who had varying vaccine uptake by birth cohorts and a skewed age distribution might have led to under-estimation of the seroprevalence. Second, individuals who seek medical

consultation and require blood testing may not be representative of the general population. This potential issue of representativeness is particularly important for young children, as blood sampling is a relatively invasive procedure. In addition, the COVID-19 pandemic led to avoidance of medical consultations in adults (172-174), which might also affect the health-seeking behaviour in children. For the 2020 serosurvey, children attending clinics or admitted to hospitals for infectious causes might be included due to difficulty in sampling during the pandemic. Also, those who had more severe medical conditions might be less likely to skip medical consultations or appointments during the pandemic. Hence the characteristics of the samples in 2020 may differ from those of previous surveys. Lastly, the residual samples collected by the Department of Health were more likely to be samples originally collected in the public medical sector. For cohorts not eligible for UVV, those who opted for private vaccination may be less likely to utilise public healthcare resources. Therefore, non-UVV eligible children sampled in the serosurvey might have lower vaccine uptake than those in the population.

Potential issue in serology tests

Sensitivity of the commercial EIAs may also affect the observed seroprevalence. At least four different whole-cell based (wc)-EIAs, Human Elisa, Siemens, Novalisa and VIDAS, were used in the six serosurveys in Hong Kong [Table 4.2.1]. Despite their scalability and relative availability, the sensitivity of different commercial EIAs vary and are affected by whether the 'borderline' (equivocal) samples are being regarded as positive or negative (175). Manufacturers' recommended cut-offs often lean towards specificity over sensitivity for diagnostic purposes, resulting in lower sensitivity for

detection of past infection/ vaccination at a population level (176). Although second EIAs were used to confirm samples yielding equivocal results in at least three serosurveys, their sensitivity was lower than the first EIA in 2010, or the same EIAs were used in 2015 and 2020 [Table 4.2.1]. Hence the overall sensitivity would be fairly similar to the first EIA kits. The three EIAs deployed were among the more sensitive assays in Maple *et al*'s evaluation, with the Siemens assay being the most sensitive at 97% (169). While these EIAs should be adequate in detecting humoral immunity after infection, their sensitivity to vaccine-induced seroconversion is expected to be lower. As the IgG titers after vaccination can be 10-30 times lower than those post-infection (2), the vaccinees will be less likely to be detected by EIAs. This is shown in Sauerbrei *et al*'s study as sensitivity to seroconversion by vaccination was only 76% for Siemens (35), which is one of the most sensitive EIAs. Similar to the potential issue of uneven age distribution, the reduced sensitivity to vaccine-induced immunity would lead to a more substantial under-estimation between 2010 and 2020, as vaccine uptake increased rapidly in young children [Table 4.2.2].

There have been few published studies validating different commercial EIAs' sensitivity and specificity to seroconversion due to vaccination. Of the available studies, they differ in the characteristics of the subjects and the serological tests used as references. For instance, Sauerbrei *et al* included vaccinees between 2 and 35 years of age in the vaccinee group and FAMA was regarded as the gold standard (35), while Maple *et al*'s study was conducted on healthcare workers using a time resolved fluorescence immunoassay (TRFIA) as the reference (177). Hence, no information on the comparative sensitivity of the EIAs used in the six Hong Kong serosurveys can be inferred from published studies. There is also no information on the quantitative

measurement of the EIA results for these serosurveys [Personal communication with the Department of Health Hong Kong SAR]. As such, alternative analytical techniques like mixture modelling to establish a more sensitive cut-off (175, 176) or standardisation of results from different assays cannot be applied (34). Therefore, a range of sensitivity was assumed in our analysis. This sensitivity can also be estimated when fitting a mathematical model to the serological data.

There are several potential improvements to the further serology studies in Hong Kong. First, characteristics such as age, place of birth/ residence and vaccination of individual samples should be collected to better understand the seroprevalence by cohort and vaccination status. Second, serology tests should be sufficiently sensitive to vaccine-induced seroconversion. This is an area where further research is needed as to date there is no commercially available serological test that is suitable for large-scale screening of varicella immunity in a population with high vaccine uptake (178). Third, availability of quantitative IgG titers allows alternative modelling strategies to be applied. Fourth, the use of less invasive specimens such as oral fluid to study prevalence of varicella IgG should be explored and could enable a more representative sample and/ or larger sample size to be achieved (179).

Other factors that may affect VZV seroprevalence

It should be noted that changes in VZV serology over an extended period may not be solely attributed to increasing vaccination uptake. Changes in demographics, such as decreasing number of new-borns (180) and/ or students can also lead to reduced viral transmission and lower population immunity due to infection. In the absence of

vaccination, Kudesia *et al*. reported an increase in VZV seroprevalence among those aged 1 to 4 years between 1966 and 1992 in the U.K., potentially linked to increased attendance of nurseries over time (181). It should be noted that there were a higher proportion of older children and adolescents having less time of residence in Hong Kong [Table 4.2 in (180)]. As these children were more likely to reside in mainland China in early childhood before attending kindergarten/ primary schools, their vaccine uptake and risk of varicella infection, as well as seroprevalence, likely differed from children residing in Hong Kong. There are other factors that may affect observed seroprevalence. Saiman L *et al*. reported fluctuations in seroprevalence over time among vaccinated health care workers (182). Ninety-three percent of participants tested by FAMA within 6 months of vaccination were sero-positive. The seroconversion rate decreased to 75% between six and 48 months post-vaccination, but it increased to 86% 49 months or later. It was postulated that circulating VZV boosted the vaccine-induced immunity. However, this boosting effect is likely to decrease with a reduced VZV transmission after UVV.

In summary, the six serosurveys between 1995 and 2020 showed a reduction in seroprevalence for those aged 5 to 25 years. There was also a decrease in varicella transmission in young children and adolescents, as evidenced by the progressively decreasing FOI. The reduction in VZV infections was likely driven by the increasing vaccine uptake in young children. Biases in sampling and sensitivity of serology tests needs to be considered when interpreting these data and should be minimised in future studies. In contrast there was evidence of an increase in the FOI in older adolescents (15 to 19 years) over time. As a higher proportion of the adolescents and young adults become prone to VZV infections, the risk of outbreaks should be carefully monitored

and studied in conjunction with other surveillance data.

4.3 Descriptive analysis of notification, AED attendance and hospital admission data up to 2020

Introduction

Before universal varicella vaccination (UVV) was implemented in Hong Kong in July 2014, vaccine uptake in the private market had increased to about 50% among preschool children. Previous analysis on data before UVV (private vaccine era between 1999 and 2014) showed a reduction in varicella notifications, varicella admission and herpes zoster Accident & Emergency Department (AED) attendance among young children aged less than 5 years (155) [Chapter 2]. In contrast, the rate of varicella notification, AED attendance and hospitalisation of both varicella and herpes zoster (HZ) increased in the same period for those aged 10 to 59 years. In addition to the increasing varicella vaccination uptake in the private market, other factors such as reduction in class size and potentially changes in contact patterns, might have contributed to these observed changes (155).

The successful implementation of UVV led to at least 98% first dose uptake for eligible children [Chapter 4.1]. The seroprevalence surveys conducted by the Department of Health (DH) of Hong Kong showed that the increase in seroprevalence among young children aged 5 to 9 years and adolescents aged 10 to 14 in 2015 was extremely small five years later [Chapter 4.2], despite the fact that most vaccinated children during this period received only one dose of vaccine [Chapter 4.1]. This sub-chapter will extend the previous analyses on surveillance data of varicella and HZ in the private vaccine era (155) to 2020 to examine their trends during the early UVV period. Varicella

surveillance data will be compared to the serology surveys to better understand varicella transmission in the first five years after UVV.

Methods

As in Chapter 2 (155), data included varicella notification, as well as AED attendance and inpatient admission for both varicella and HZ. Age stratified varicella notifications between 1999 and 2020 from healthcare workers in public and private sector, as well as schools, were available from the Department of Health, Hong Kong SAR (DH) for this PhD analysis. The DH also publishes aggregate varicella notification figures (without information on age) on a monthly basis on their website (183). This publicly available information was compiled to produce the annual notification data between 2021 and 2023 to understand the effect of the COVID-19 pandemic on varicella notifications. Although both confirmed and probable varicella were included in the analysis, nearly all notifications were probable (i.e. based on clinical symptoms alone) as laboratory confirmation of varicella is rare in Hong Kong (155). The AED attendance and hospital admission from public hospitals were available for this PhD between 2004 and 2020. The data were cleaned and processed similar to my previous analysis (155). In summary, attendance/ admission episodes with at least one ICD-9-CM code of varicella (052) and/ or herpes zoster (053) in any of the principal or secondary diagnoses were identified as related to varicella and/ or herpes zoster. Only the first record of varicella or herpes zoster was counted for each person, as reinfection of varicella and, to a lesser extent, herpes zoster is rare (2). Sensitivity analyses showed that different de-duplication methods/ counting of illness episode did not affect the trend for both diseases [Supplementary Figure S.4.3.1]. As a pay-for-performance

system was introduced in Hong Kong's public hospital in the 2009/10 financial year, there was a likely change in coding practice over the years (184). Therefore, the annual number of AED attendances and hospital admissions related to varicella and/ or herpes zoster were adjusted by the age- and time-specific coding rate (155) [Supplementary Figures S.4.3.2 and S.4.3.3]. Population estimates of the Census and Statistics Department of Hong Kong (185) were used to compute the incidence rates. There was a decreasing proportion of children aged under 10 years and an increasing proportion of adults 40 years or above over the study period [Supplementary Figures S.4.3.4 and S.4.3.5]. Hence both crude and age-standardised rates of notification, AED attendance and hospital admission were computed. I calculated annual age-standardised rates by applying the population estimates of the earliest available year for each data source (i.e. 1999 for notifications and 2004 for AED attendances and hospitalisations) to the age-specific rates. Annual age-specific rates were also computed using the corresponding population figures. Similar to my previous work (155), the trend of annual age-specific rates of varicella and herpes zoster was assessed by fitting a Poisson regression to age-specific cases for different disease endpoints:

$$\log(\mu_{a,i}) = \alpha + \beta x_i + \log(p_{a,i}) + \varepsilon$$

where,

$\mu_{a,i}$ is the age-specific number of notifications/ AED attendances/ hospitalisations in year *i*.

α is the intercept that represents the estimated (log) incidence rate in the baseline (first) year of the time-series.

x_i is the number of years before the last year of analysis and the coefficient (β)

corresponds to the (log) annual change in incidence rate (trend).

$p_{a,i}$ is the age-specific population as the offset.

ε is the error term.

In Hong Kong, various non-pharmaceutical interventions (NPI) were implemented against the COVID-19 pandemic between early 2020 and April 2023, affecting the circulation of various pathogens including VZV. Varicella notifications was at very low levels between 2020 and 2023 [Figure 4.3.2]. Hence, data from 2020 onwards was only included in the descriptive analysis but not in the regression of trend analysis. The regression was conducted for the whole period (up to 2019), the private vaccine era (up to 2014, similar to the previous analysis (155)) and early UVV era (2015 to 2019, first five years after UVV).

The Department of Health routinely investigated all notified varicella cases for potential outbreaks in schools and other institutions. An outbreak was defined as two or more cases in the same place with an overlapping incubation period. The number of outbreaks between 2007 and 2020 was described by school type and the outbreak size (defined as number of persons affected in each outbreak).

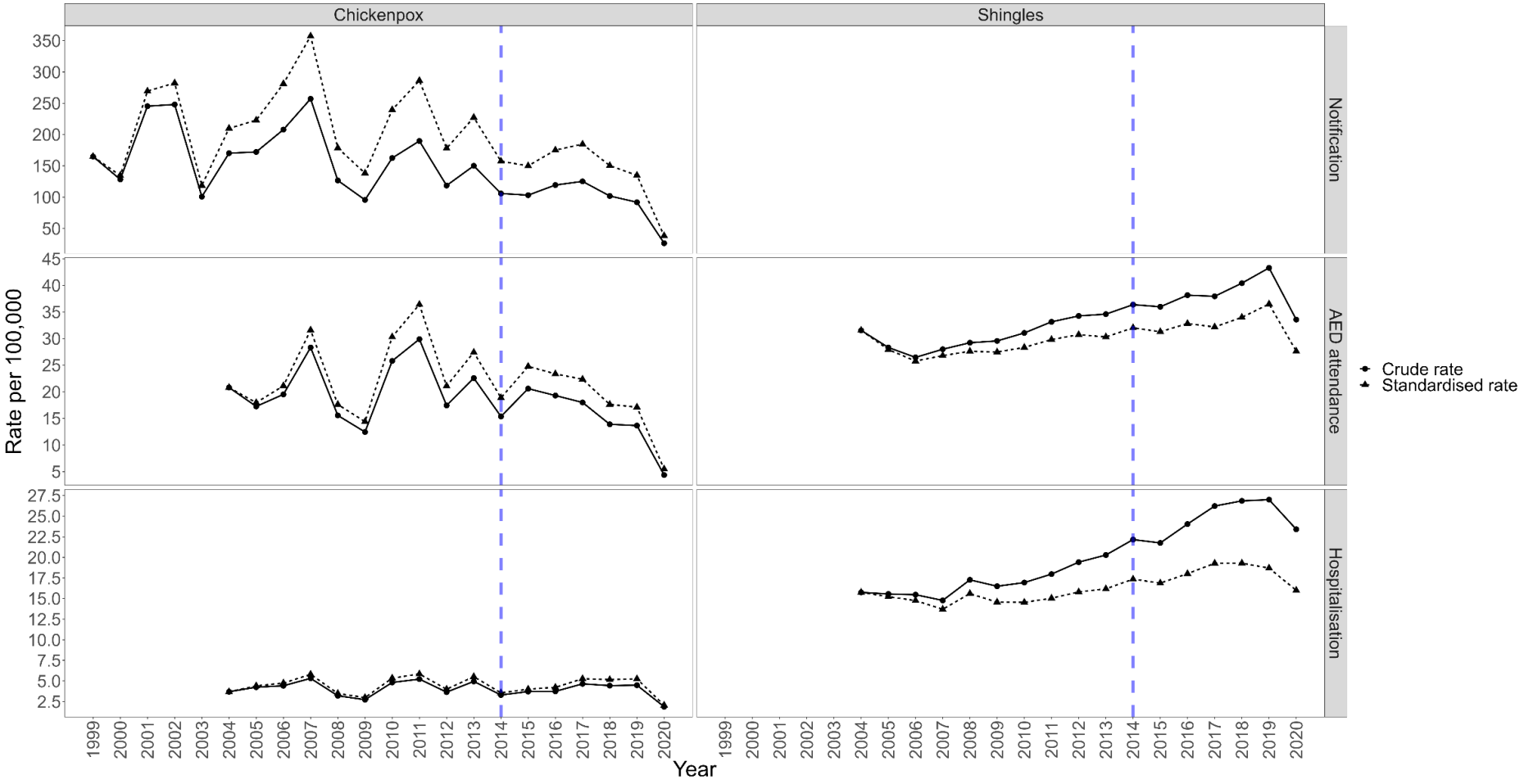
Results

Trends in varicella notifications, AED attendances and hospitalisations

Varicella notifications, AED attendances and hospitalisations exhibited cyclic patterns with peaks every four to five years before UVV (2001/02, 2007, 2011) [Figure 4.3.1].

This periodic fluctuation became less pronounced in the UVV era. The crude and age-standardised rate of varicella incidence showed similar trends, though the age-standardised rates were higher than the crude rates. With first dose varicella vaccine uptake increased to around 50% in the private market before 2014, the crude notification rate decreased slightly from an average of 177 per 100,000 between 1999 and 2003 and 187 between 2004 and 2008, to 143 between 2009 and 2013. Between 2015 and 2019, the crude notification rate per 100,000 reduced to 108 [Figure 4.3.1], and it further dropped to only 20 during the COVID-19 pandemic between 2020 and 2023 [Figure 4.3.2]. Both AED attendances and hospital admissions were largely stable before UVV implementation (crude AED attendance rate per 100,000: 20.4 from 2004 to 2008 and 21.7 from 2009 to 2013 respectively; crude hospitalisation rate per 100,000: 4.3 from both 2004 to 2008 and from 2009 to 2013 respectively), and only AED attendances showed a decreasing trend after UVV implementation (2015 to 2019: 17.2 for AED attendance and 4.2 for hospitalisation). Both AED attendances and hospitalisations dropped in 2020 as the COVID-19 pandemic started, with a bigger reduction for AED attendance (4.4 per 100,000) than hospital admission (1.9 per 100,000).

Figure 4.3.1. Crude and standardised rate of varicella notification, AED attendance and hospitalisation of varicella and herpes zoster per 100,000 population in Hong Kong, 1999 to 2020 (crude rate: solid line; standardised rate: dashed line).



Note:

(1) Notification of varicella started in 1999, but age-specific data were only available till 2020. There was no notification for herpes zoster in Hong Kong. Data on AED attendance and hospitalisation of public hospitals were only available between 2004 and 2020.

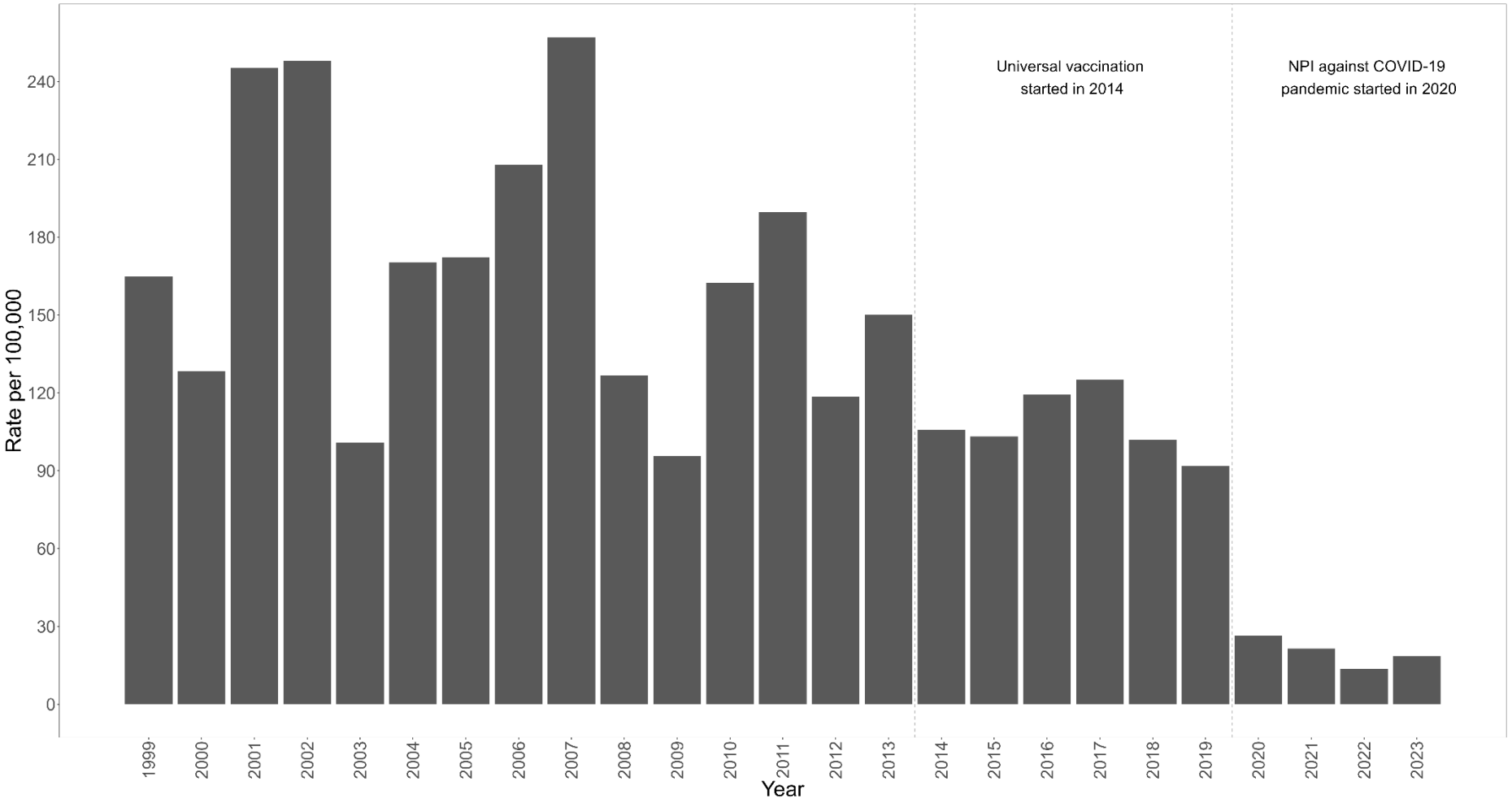
(2) Blue dashed line indicated universal varicella vaccination started in 2014.

(3) Various non-pharmaceutical interventions (NPI) against COVID-19 pandemic started in 2020 and all NPI ended in March 2023. Therefore, data in 2020 and beyond was affected by COVID-19 pandemic but was shown in the figure for completeness.

(4) The AED attendance and hospitalisation data was adjusted with coding rate. Only first records of the respective conditions for each individual were counted.

(5) Age-standardised rate was obtained by applying direct standardisation using population in the first available year i.e. 1999 for varicella notification and 2004 for AED attendance and hospitalisation data.

Figure 4.3.2. Crude rate of varicella notification per 100,000, 1999 to 2023, Hong Kong.



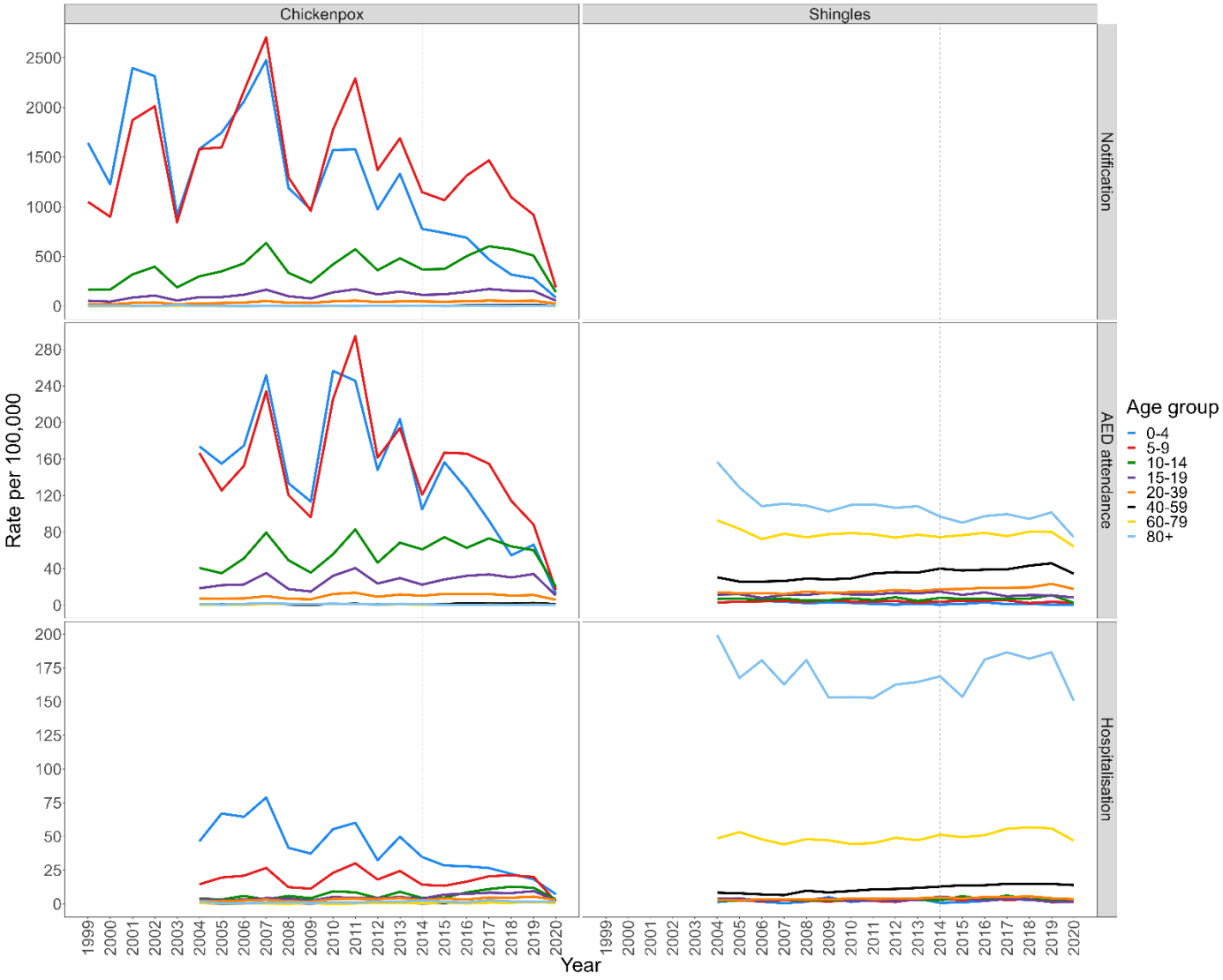
Age-specific varicella incidence

Throughout the study period (between 1999 and 2019 for notifications and between 2004 and 2019 for AED attendances and hospitalisations), the trends of varicella incidence differed by age [Figures 4.3.3 and 4.3.4]. Significant reductions in notifications were observed for both children aged 0 to 4 years and 5 to 9 years (annual changes (Poisson regression coefficient): -23.4% [95%CI: -22.0 to -24.7%] and -4.6% [95%CI: -3.6 to -5.6%], respectively) [Figure 4.3.4]. Compared to the changes in 2014 and before, the reduction for these young children was more substantial in the early UVV period (2015 to 2019) [Figures 4.3.3 and 4.3.4]. In contrast to the decreasing trend in young children, there was a significant rise in varicella notification rate for those between 10 and 79 years of age, and the increase became more marked with age [Figure 4.3.4]. The increase in notification rate was consistent irrespective of period (whole period, up to 2014, and between 2015 to 2019) for those aged 10 to 14 years to 60 to 79 years, though the increase was more substantial for those aged 60 to 79 years between 2015 and 2019. For those aged 80 years or above, there was a small reduction in notifications between 1999 and 2019 (annual changes: -6.5% [95%CI: -2.9% to -9.9%]) as well as between 1999 and 2014 (annual changes: -9.2% [95%CI: -4.0% to -14.2%]), contrary to an substantial but statistically insignificant increase between 2015 and 2019 (annual changes: 26.5% [95%CI: -8.6% to 79.5%]).

Across the entire period where data were available, the trend of age-specific varicella AED attendance was similar to that of notifications, with significant reductions among those aged 0 to 4 years and 5 to 9 years, as well as significant increases among 10 to 14 years and 40 to 59 years [Figure 4.3.4]. In comparison to the decrease in notification

and AED attendance among those aged 0 to 4 years and 5 to 9 years, only varicella hospitalisations in the youngest age group showed a significant reduction (annual changes: -10.0% [95%CI: -3.0 to -16.6%]) whilst increases were observed for those aged 5 to 9 years, 10 to 14 years, 20 to 39 years as well as those aged 40 to 59 years [Figure 4.3.4]. Like varicella notifications and AED attendances, the reduction in varicella hospitalisations among those aged 0 to 4 years became more substantial in the early UVV era.

Figure 4.3.3. Age-specific rate of varicella notification, AED attendance and hospitalisation of varicella and shingles per 100,000 population in Hong Kong, 1999 to 2020.



Note:

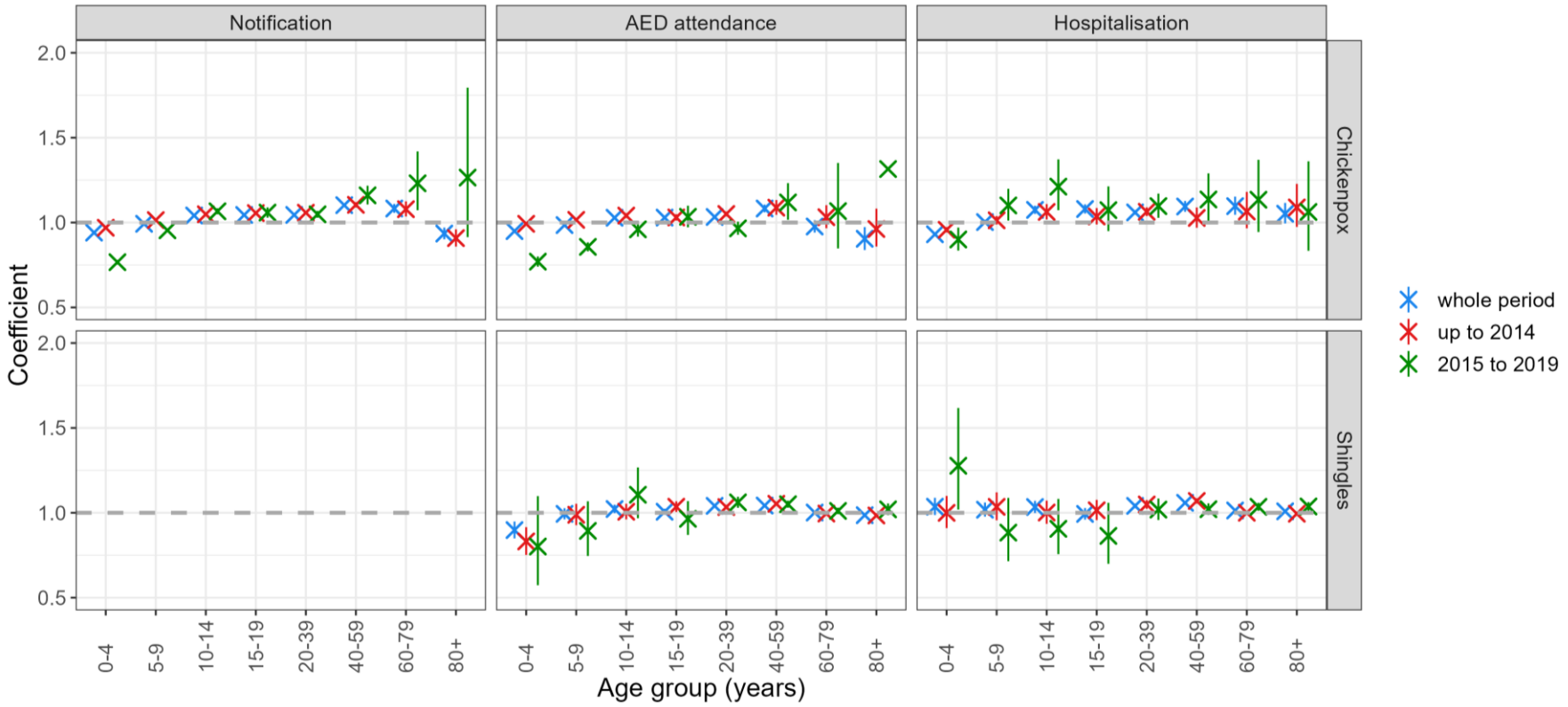
(1) Notification of varicella started in 1999, but age-specific data were only available till 2020. There was no notification for herpes zoster.

(2) Data on AED attendance and hospitalisation of public hospitals were only available between 2004 and 2020.

(3) The AED attendance and hospitalisation data was adjusted with coding rate. Only first records of the respective conditions for each individual were counted.

(4) Various non-pharmaceutical interventions (NPI) against COVID-19 pandemic started in 2020 and all NPI ended in March 2023. Therefore, data in 2020 and beyond was affected by COVID-19 pandemic but was shown in the figure for completeness.

Figure 4.3.4. Coefficients (trends) of the poisson regression on the annual rate of varicella notification, AED attendance and hospital admission of varicella and herpes zoster in Hong Kong, 1999 to 2019.

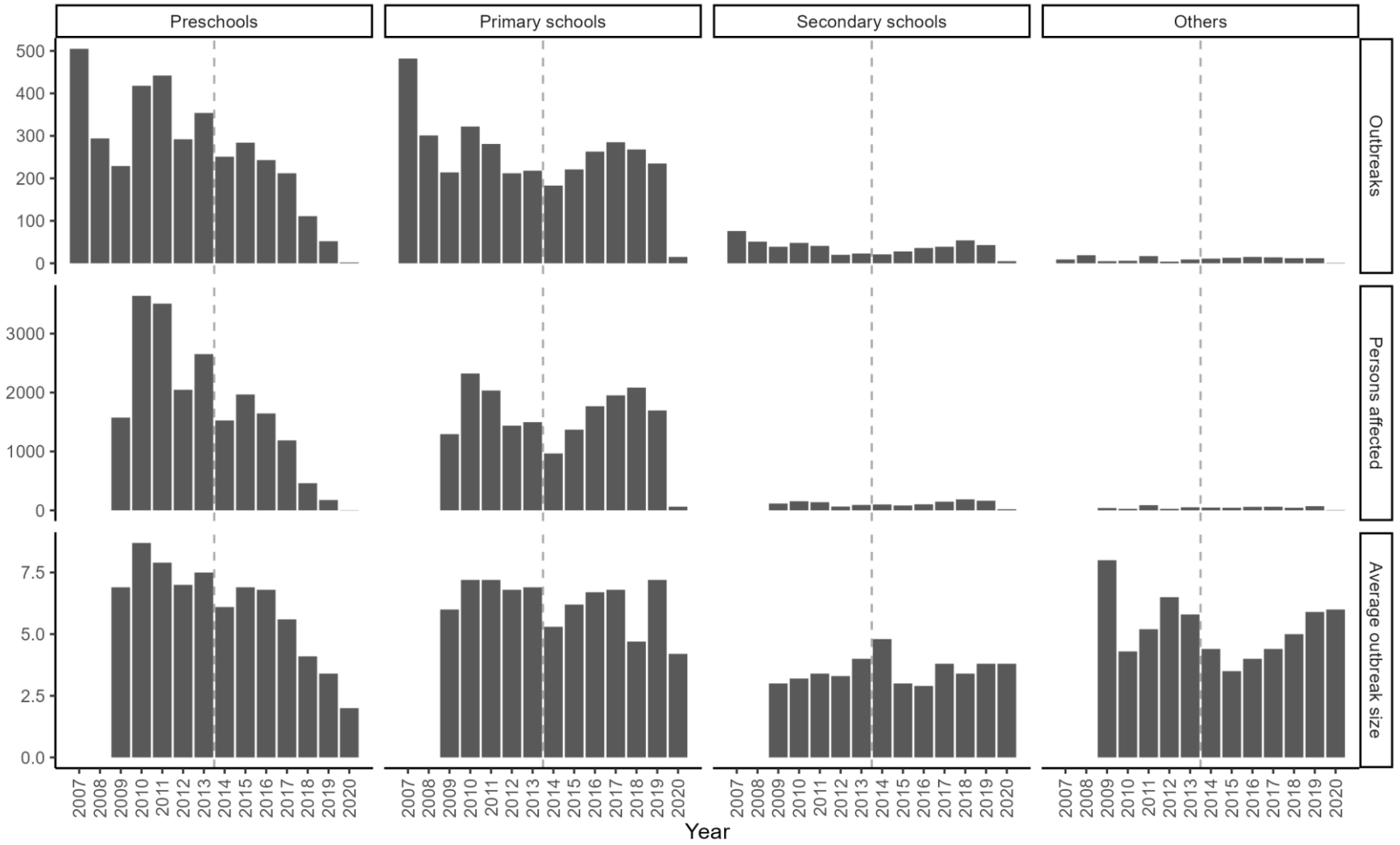


Note:

(1) Coefficient of 1 represents no change in annual rate.

(2) The 95% confidence intervals for the varicella AED attendance of those aged 80+ was 0.57 to 3.43. The error bar for this data point was not shown in the above figure to keep a smaller scale of the y-axis for a better overall visualisation.

Figure 4.3.5. Annual number of varicella outbreaks, number of persons affected and average outbreak size by outbreak settings, Hong Kong, 2007 to 2020.



Note:

(1) Dashed line refers to implementation of UVV in 2014.

(2) Data on persons affected per outbreak, and hence average outbreak size, was only available in 2009 and after.

(3) Various non-pharmaceutical interventions (NPI) against COVID-19 pandemic started in 2020 and all NPI ended in March 2023. Therefore, data in 2020 and beyond was affected by COVID-19 pandemic but was shown in the figure for completeness.

(4) Others include places such as tertiary institutions and correctional facilities.

Varicella outbreaks in schools

The highest number of varicella outbreaks for all school settings was recorded in 2007, which coincided with the peak in notifications [Figure 4.3.5]. Between 2007 and 2013, there was an average of 362 preschool, 290 primary school and 43 secondary school outbreaks every year. In the early UVV period between 2015 and 2019, the average number of preschool outbreaks was halved to 180 per year, with only 52 recorded in 2019. There was a 12% and 7% reduction in the average number of primary and secondary school outbreaks (254 and 40 per year) in the same period. The average outbreak size (number of persons affected in each outbreak) in preschools reduced from 7.6 between 2007 and 2013, to 5.3 between 2015 and 2019. There was only slight or no reduction for the average outbreak size in primary school outbreaks (6.8 and 6.3 before and after UVV) and secondary school outbreaks (3.4 both before and after UVV).

Trend of herpes zoster AED attendance and hospitalisation

There was an increase in the overall rate of AED attendances and hospitalisations related to herpes zoster, and the levels were highest in the early post-UVV era (2015 to 2019) [Figure 4.3.1]. The increase was less substantial for the age-standardised rates. Age-specific rates of AED attendance increased slightly between 2004 and 2019 for those 20 to 39 years (annual changes: 4.1% [95%CI: 3.4 to 4.7%]) and 40 to 59 years (annual changes: 4.3% [95%CI: 3.8 to 4.7%]) [Figures 4.3.3 and 4.3.4]. While there was an increase in the annual rate of hospitalisation for all age groups above 20 years for hospitalisation, the increase was less substantial for those aged 60 to 79 years (annual changes: 1.4% [95%CI: 0.3 to 1.4%]) and 80 years or above (annual changes:

0.8% [95%CI: 0.3 to 1.4%]), compared to those aged 20 to 39 years (annual changes: 4.1% [95%CI: 2.7 to 5.4%]) and those aged 40 to 59 years (annual changes: 5.9% [95%CI: 5.1 to 6.7%]) [Figure 4.3.4]. In contrast to the increasing trend in adults, there was no significant change in AED attendance and hospitalisation rate for herpes zoster among those aged under 20 years, with the exception of AED attendance among those aged 0 to 4 years (annual changes: -10.2% [95%CI: -15.1 to -5.2%]) [Figure 4.3.4]. These trends for herpes zoster AED attendances and hospitalisations were largely consistent in different periods (from 2004 to 2014 and from 2015 to 2019), except for a significant increase in hospitalisation for those aged 0 to 4 years between 2015 and 2019 [Figure 4.3.4].

Discussion

Overall varicella notifications and AED attendances dropped substantially in the early UVV period, in addition to what could have been expected under continued moderate vaccine uptake through the private sector only. However, I found no evidence for additional reduction among children hospitalised for varicella yet. With the initiation of various NPIs against COVID-19 in 2020, varicella notifications dropped sharply in 2020 and remained at very low levels in 2023, despite the lifting of all NPIs in Hong Kong in March 2023. A combination of the extended period of NPIs, very high varicella vaccine uptake among young children and some children voluntarily wearing of masks after the pandemic (186) might have sustained the interruption of varicella transmission, making it difficult to assess the contribution of UVV to the reduction during the period. In addition, a change in health-seeking behaviour and/ or reporting practice after the COVID-19 pandemic might also contribute to the very low levels of varicella

notifications. In contrast to the substantial decline of varicella incidence during the pandemic, herpes zoster AED attendance and hospitalisation only decreased slightly in 2020. This reduction was likely a result of reduced healthcare resource and/ or avoidance of consultation during the pandemic (172-174). Although less infectious than varicella, herpes zoster in the population might help sustain a low level of VZV circulation during the pandemic.

Impact of UVV on varicella incidence

For children aged 0 to 4 years and 5 to 9 years, there was substantial reduction in varicella notifications, AED attendances and hospitalisations (for 0 to 4 years only) during the study period, with a more marked decrease in the early UVV period. The force-of-infection (FOI) estimated from the seroprevalence data also reduced for those aged 1 to 4 years and 5 to 9 years, especially in 2015 and 2020 [Chapter 4.2]. By 2018 and 2019, almost all children aged one year and above were eligible for UVV and nearly all of them received at least one dose of varicella vaccine [Chapter 4.1]. The increasing one-dose uptake among children aged under five years coincided with a reduction in crude notifications from 736 per 100,000 in 2015 to 278 per 100,000 in 2019, which was the lowest level of notification since reporting started in 1999 and before the COVID-19 pandemic. In the previous analysis of varicella vaccine effectiveness in Hong Kong, one- and two-dose vaccination was shown to be 69% and 93% effective against all varicella notifications, indicating a substantial proportion of one-dose vaccinees did not develop sufficient immunity against mild varicella that were confirmed clinically [Chapter 3] (156). Vaccinees experiencing primary vaccine failure do not develop sufficient immunity against varicella infection, whilst those

experiencing secondary vaccine failure lose their initially mounted immunity over time (23, 54). Most varicella cases among one-dose vaccinees have been reported to develop breakthrough infections, a milder, modified varicella with less lesions compared to natural varicella in the unvaccinated (187). However, as detailed clinical symptoms such as number of skin lesions were not recorded during interviews of notified varicella cases, further analysis on the severity of notified varicella in post-UVV era Hong Kong was not feasible. Before the COVID-19 pandemic in 2020, all three sources of surveillance data showed varicella infections remained for children aged under 10 years with the inception of UVV, albeit at lower levels than the private vaccine era [Figure 4.3.3]. These infections should contribute to an increase in sero-immunity, which was different from the very low level of infections estimated from the seroprevalence studies in 2015 and 2020 [Chapter 4.2].

For young children aged 0 to 4 years, the reduction in varicella hospitalisations was less substantial those in notifications and AED attendances five years after UVV introduction [Figures 4.3.3 and 4.3.4]. On the other hand, post-UVV reductions were only observed for varicella notifications and AED attendances for children aged 5 to 9 years, in contrast to the increase in hospitalisations between 2015 and 2019. The varicella hospitalisation rate for children aged 5 to 9 years increased from 13 per 100,000 in 2015 to between 20 and 21 from 2017 to 2019, after fluctuating between 11 to 30 per 100,000 from 2004 to 2014. It should be noted that Hong Kong experienced an upsurge of scarlet fever in 2011 (188), with 1,526 notifications received, compared to an average of 142 notifications between 1997 to 2010 (range: 77 to 235) (183). The incidence of scarlet fever remained high after the 2011 upsurge (189), with an average of 1,571 notifications reported annually between 2012 and 2019 (183). The scarlet fever

notifications peaked at 2,353 and 2,098 in 2017 and 2018 with a median age at 6 years of age (190). As scarlet fever and Group A streptococcal infections are common complications following varicella, varicella might also be recorded in scarlet fever hospital admissions, contributing partly to the increased varicella hospitalisations in the post-UVV era. Scarlet fever notifications and public hospital admissions data were not available to this PhD. A joint investigation on the impact of varicella vaccination on both varicella and scarlet fever is warranted in future.

Increasing varicella incidence in teenagers and young adults under private vaccination and UVV

In contrast to the early impact of UVV in reducing varicella incidence in younger children, varying degrees of increase in varicella incidence were observed for older children aged 10 years or above and adults. Significant increases in notifications among teenagers and young adults between 10 and 19 years were observed, irrespective of analysis period [Figure 4.3.4]. In my earlier analysis of the seroprevalence data, the estimated FOI among those aged 15 to 19 years increased over the years, indicating an increasing proportion of these adolescents were infected [Chapter 4.2]. These individuals aged 10 to 19 years were not eligible for UVV, and their vaccine uptake in the private market was about 11% to 38% between 2015 and 2019 [Chapters 4.1 and 4.2]. With only low to moderate varicella vaccine uptake in the private market, a large pool of these teenagers and young adults remained susceptible to varicella. Although varicella vaccine uptake in young children increased from about 50% in the private vaccine era to nearly 100% in the early UVV era, the overall varicella transmission in the community was interrupted but not halted, as the majority of those vaccinated in

both the private market and under UVV received only one dose of vaccine. Hence, varicella infections are likely to have continued in adolescents and young adults with immunity gaps. Those vaccinated in the private market might have also experienced vaccine failures and developed breakthrough infections, contributing to the higher level of varicella notifications in the early UVV era. Data on the school outbreaks further affirmed the impact of UVV in very young children, as the preschool outbreak number and size decreased every year since 2015 with only 52 outbreaks recorded in 2019. Meanwhile, the reduction in average number of outbreaks for primary and secondary schools in the first five years after UVV was only 12% and 7%, indicating circulation of VZV persisted in older children and adolescents who were not eligible for UVV.

There was a reported rise in varicella notifications, AED attendance and hospitalisations in older adults. It is possible that these may not reflect a genuine increase in varicella incidence, although this is unclear. According to the seroprevalence studies in Hong Kong (155), nearly all adults over 40 years of age should be immune against varicella. As varicella re-infection is relatively rare, the apparent increase in varicella activity in these age groups may be a result of misdiagnosed (disseminated) herpes zoster (191) and/ or coding errors between varicella and herpes zoster in the discharge diagnoses. Considering the baseline rate of varicella in these age groups was low [Figure 4.3.3], it would be especially prone to reporting bias/ coding errors. With the introduction of UVV and the use of shingles vaccine in the private market, the awareness of varicella may have been enhanced for both parents and healthcare workers. This might lead to increased reporting sensitivity, which could contribute to part of the reported increases in adolescents and adults.

Impact of UVV on herpes zoster

In this analysis of the early UVV period in Hong Kong, there was a decline in herpes zoster AED attendance among children aged 0 to 4 years. By 2018, almost all children aged 1 to 4 years were vaccinated with at least 1 dose of varicella vaccine [Chapter 4.1]. Most of these children are expected to carry the vaccine-type (vt) VZV, with those experiencing breakthrough infections carrying both. Therefore, this reduction is likely the impact of successful implementation of UVV in Hong Kong. It has been shown that varicella vaccinees benefit directly from a lower risk of developing herpes zoster. A population study in the U.S. showed that the incidence of herpes zoster among vaccinated children was 79% lower than those of unvaccinated children (192), with similar reductions in vaccinated children reported in another study (193). An ecological study in the U.S. also showed a step-wise decline in herpes zoster incidence over nearly 20 years after UVV, starting with very young children eligible for varicella vaccination and persisted as the vaccine uptake among older children increased with time. The incidence of herpes zoster remained low for vaccinated cohorts entering young adulthood (194). A lower risk of herpes zoster among vaccinated children and a step-wise decline in herpes zoster with time was also reported in Alberta Canada, where UVV was introduced in July 2001 (195).

On the other hand, the increase in HZ hospital admission among children of the same ages between 2015 and 2019 cannot be readily explained. It should be noted that there was no change in herpes zoster hospitalisation for children aged 0 to 4 years between 2004 and 2014, and the incidence of herpes zoster AED attendance and hospitalisation is relatively low for these very young children (annually 5 per 100,000 or less between

2004 and 2019 for both outcomes). The short-term trend in shingles of the UVV cohorts is prone to changes in awareness/ diagnoses/ coding, which cannot be addressed by adjustment with the overall coding rate. The trend of herpes zoster among UVV-eligible children warrants further monitoring.

In addition to the direct effect of reducing the risk of varicella and herpes zoster among recipients of varicella vaccines, the reduction in varicella transmission may indirectly lead to an increase in herpes zoster. Hope-Simpson first postulated that immunity against VZV in those previously infected can be boosted both endogenously through periodic VZV re-activation, and exogenously through contact with infectious persons with varicella or herpes zoster (28). The boosting of cell-mediated immunity is believed to suppress re-activation of VZV and lower the risk of herpes zoster. Younger adults or those who have more frequent contact with children/ varicella have been shown to have reduced risk of herpes zoster, potentially because of repeated exogenous boosting (196). This boosting effect has also been investigated in different epidemiological and modelling studies. A systematic review by Ogunjimi B. *et al*. concluded that there was sufficient evidence on the existence of exogeneous boosting, yet the extent, duration and characteristics of those boosted remains largely uncertain (29). Early modelling work on the potential impact of universal varicella vaccination assumed the duration of protection from this exogenous boosting to be around 20 years, leading to a prediction of short- to medium-term increase of herpes zoster after UVV introduction (61). This indirect effect of varicella vaccination on herpes zoster was one of the concerns about UVV introduction in countries like the U.K (62). In this analysis of the combined effect of private and early publicly funded vaccination in Hong Kong, the rates of herpes zoster AED attendance and hospital admission increased for all adults aged 20 years or

above, with the exception of AED attendance for those aged 60+ years. The increase was more substantial in younger adults aged 20 to 39 years and 40 to 59 years, which may reflect a bigger reduction in contact with varicella and hence exogenous boosting. Although Zostavax was first registered in 2007, it was not publicly funded during the study period and the vaccine uptake is believed to be low [Personal communication – Drug Office, the Department of Health Hong Kong SAR]. Therefore, zoster vaccination in the private market would have limited impact on herpes zoster incidence. In the U.S., herpes zoster had been increasing even before the launch of their varicella vaccination programme in 1995. This increase persisted when varicella vaccine was first introduced to their childhood immunisation programme, and the increase eventually plateaued about 20 years after programme implementation (194).

In addition to the national study in the U.S., some countries also reported increases in incidence of herpes zoster prior to universal varicella vaccination. Increases in herpes zoster outpatient and inpatient incidence first started during the private vaccine period in British Columbia, Canada, but this increase did not accelerate with UVV in 2004, as the varicella vaccine uptake reached 90% (197). Similarly in Alberta, Canada, increases in medically-attended zoster was also reported before varicella vaccine introduction and the annual increase was not significantly different during the first eight years after UVV (198). In Australia, a national ecological study showed no increase in age-specific and age-standardised herpes zoster hospitalisation after UVV (199), but increase in zoster consultations was reported in Victoria for adults aged below 70 years (200). These diverse trends of herpes zoster incidence in different countries have shown that associations between varicella vaccine uptake and HZ incidence should be interpreted with cautions and other plausible factors should also be considered. Biological factors

such as advanced age, stress, immunosuppression and co-infections are known risk factors of herpes zoster (201, 202). Although age was often considered in studies of herpes zoster incidence, other factors such as prevalence of immunosuppression/ use of immune-suppressing drugs and stress are less often controlled due to data availability. In addition, varicella vaccination may not be the sole factor affecting exogenous boosting, if it is the main driver of changes in herpes zoster incidence. Temporal changes in demographics, such as reduction in the population of children, family size and contact pattern among different ages may also contribute to reduced exogenous boosting in adults. The population of Hong Kong has been rapidly aging in the past two decades and older persons contributed nearly one-fifth of the population by 2021 (203). Compared to 2011, the number of adults aged 65 years or above increased by 54% (from 510,202 to 1,451,514). More older persons are living alone or with their spouse but not with their children (36.3% in 2011 to 40.3% in 2021) (203). In addition, parents of young children may have become less inclined to involve grandparents in family issues (204), which may indicate less frequent contacts with children. The proportion of the labour force among adults aged 65 years or above also increased from 7.0% in 2011 to 14.6% in 2021, which may have adverse effect on stress or general health conditions that affects the risk of herpes zoster.

The uncertainty in the strength and durability of exogenous boosting is an area of research priority. Furthermore, there is also no known study on the potential relationship between exogenous and endogenous boosting. Lastly, there are potential limitations in the surveillance data that may affect our understanding in the epidemiology of herpes zoster. Evaluation of the impact of vaccination programmes often involves time-series data spanning over decades, of which there may be

unaccounted changes in health-seeking behaviour and/ or awareness in diagnosis. Changes in diagnosis can potentially be adjusted if data on other infection(s) or medical condition(s) of similar severity and clinical management were available as controls. In Hong Kong, only a pre-defined set of medical conditions for AED attendance and hospital admission from public hospitals were available for public health analysis, hence control by comparable infection(s) was not feasible in this analysis.

Future work

With the difficulty of accurately evaluating the post-UVV population immunity through seroprevalence [Chapter 4.2], it is important to have reliable and consistent surveillance data to monitor the impact of UVV on varicella and HZ. The Department of Health had been conducting universal varicella notifications for over 15 years before the UVV, which enabled the comparison of the pre-vaccine and private vaccine eras with the post-UVV era. However, there is no information on reporting behaviour and it is plausible that there has been changes in surveillance sensitivity over time as milder breakthrough infections increased with vaccine uptake. Evaluation of the notification system, in particular on reporting sensitivity should be carried out on a subset of clinical practitioners/ schools. Also, diagnosis of varicella is usually clinical, and laboratory testing based on less invasive specimens such as nucleic acid or antigen detection in lesions and/ or oral fluid will improve the accuracy of diagnosing atypical varicella (205, 206). An electronic immunisation record system is still under development in Hong Kong, a complete database on vaccination can enrich both notification and other health data such as AED attendance and hospital admission, allowing estimation and comparison of incidence by vaccination history. In addition, as varicella and herpes

zoster are generally mild, their health burden should be more accurately reflected by data from primary care, such as consultation rates in general practice in public and private sectors. These outpatient data are not currently available in Hong Kong. With a rapidly aging population in Hong Kong (203) [Supplementary Figure S.4.3.4], the health burden of herpes zoster will become more substantial and it is a priority to formulate herpes zoster vaccination policy, particularly with the availability of the more effective Shingrix vaccine.

Summary

Significant reductions in varicella among children aged under five years reflected the impact of the universal varicella vaccination programme on age eligible children. Despite the reduction, varicella was not eliminated and remained at a lower level in UVV-eligible cohorts, the majority of which were likely breakthrough infections. Increases in varicella in older children, adolescents and adults were observed in the private vaccine era and persisted five years after UVV, which is a concern as severity of varicella increases with age. The increase in herpes zoster among adults may not be solely attributed to increasing varicella vaccine uptake in children and could suggest generally increasing sensitivity of surveillance. Though the fact that the largest increase in herpes zoster incidence occurred in adults who are most likely to contact children (ages 20 to 39 years and 40 to 59 years) suggests that the childhood vaccination programme might have been one of the factors behind the increase. Prevention of herpes zoster through a shingles vaccination programme should be considered. As potential changes in surveillance sensitivity and issues in seroprevalence data identified may affect the interpretation of post-UVV varicella epidemiology, a modelling study is

warranted to jointly investigated these factors. A mathematical model should be developed to systematically explore different hypothesis and the implications on the interpretation of vaccination on varicella epidemiology.

Supplementary Materials

Supplementary Figure S.4.3.1. Sensitivity analysis on different de-duplication for (a) AED attendance and (b) hospital admission, public hospitals of Hong Kong, 2004 to 2020.

Supplementary Figure S.4.3.2. Proportion coded and average number of codes of AED attendance and hospitalisation, public hospitals of Hong Kong, 2004 to 2020.

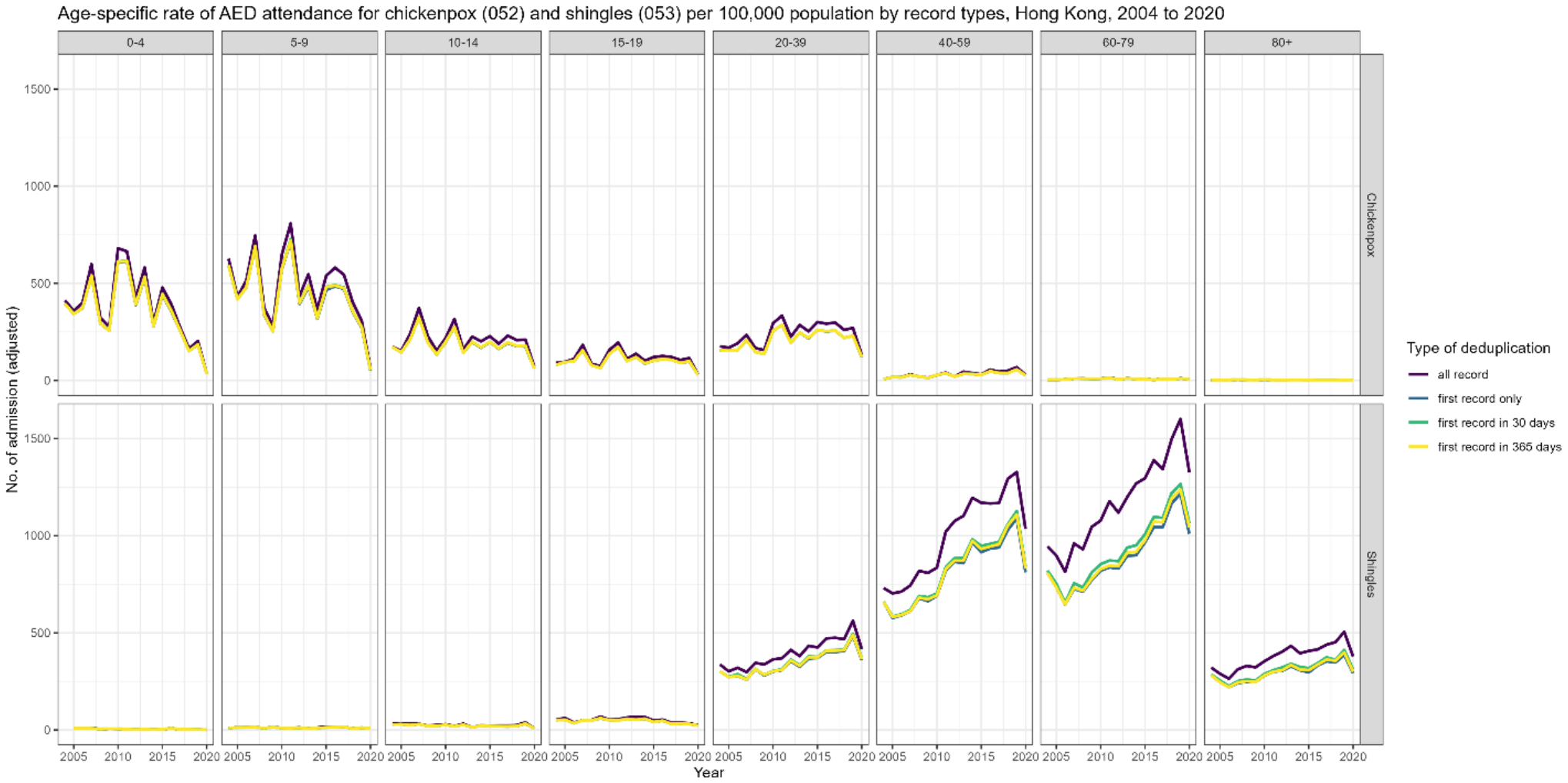
Supplementary Figure S.4.3.3. Comparison on the effect of adjusting AED attendance and hospital admission by coding rate, public hospitals of Hong Kong, 2004 to 2020.

Supplementary Figure S.4.3.4. Hong Kong population figures by age, 1999 to 2020.

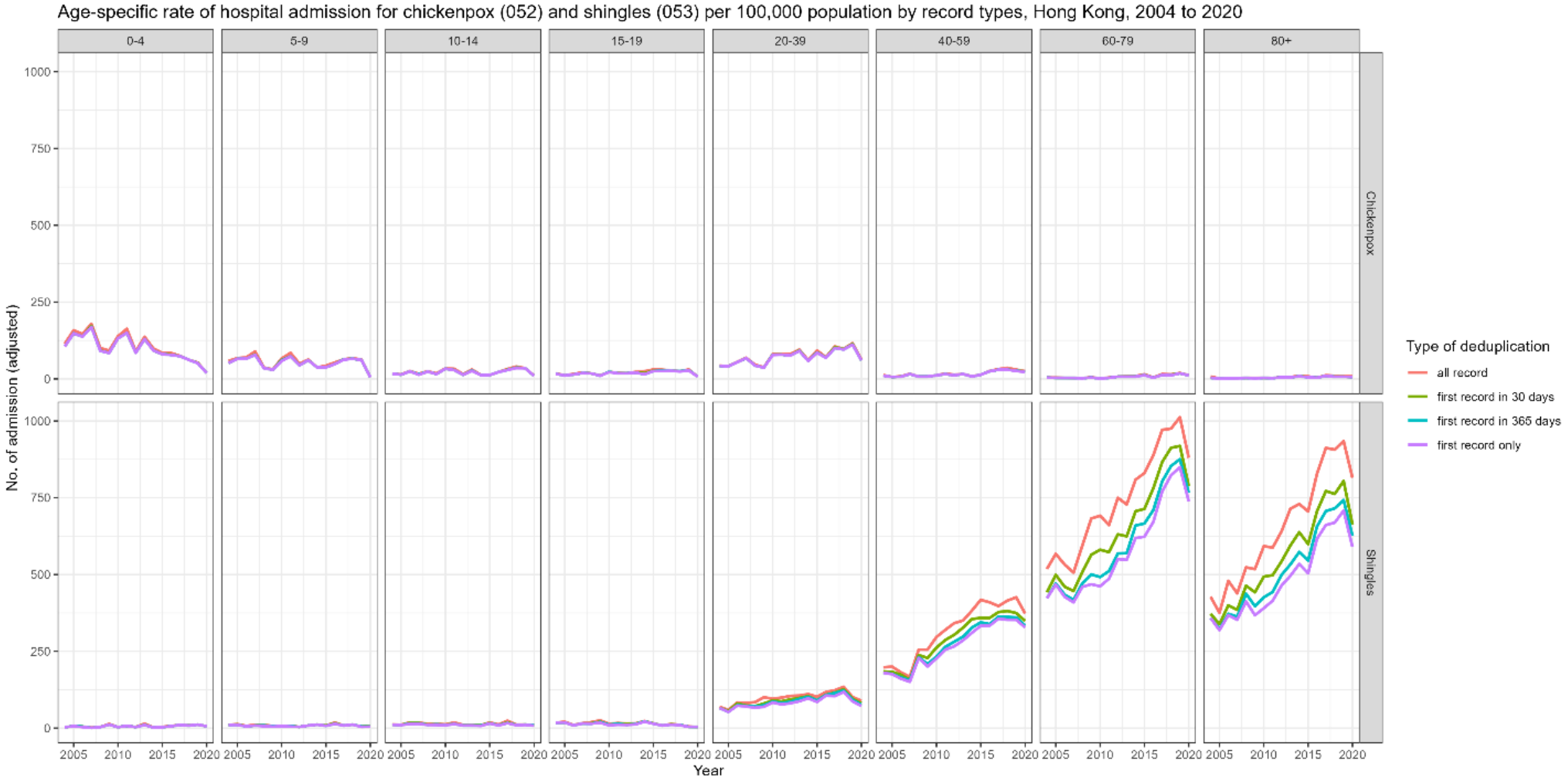
Supplementary Figure S.4.3.5. Proportion of Hong Kong population by age, 1999 to 2020.

Supplementary Figure S.4.3.1. Sensitivity analysis on different de-duplication for (a) AED attendance and (b) hospital admission, public hospitals of Hong Kong, 2004 to 2020.

(a)



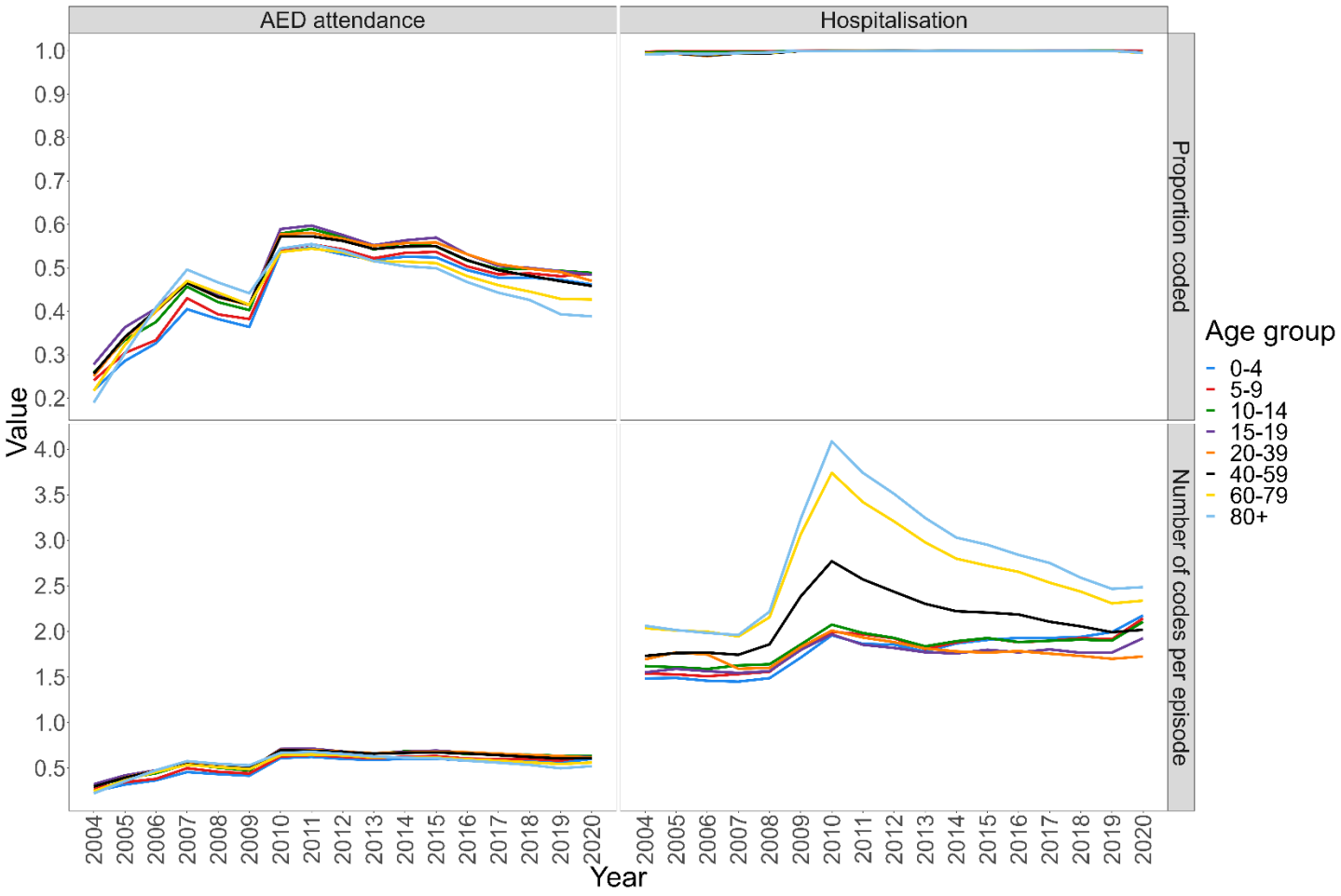
(b)



The trend of adjusted rate of AED attendance (a) and hospital admission (b) for varicella (upper panel) and herpes zoster (lower panel) were shown. The four different de-duplication method (represented by different color) included no de-duplication (counting all record), counting first record only, counting first record in 30 days and counting first record in 60 days. De-duplication resulted in similar number of varicella AED attendance and hospital admission, indicating most

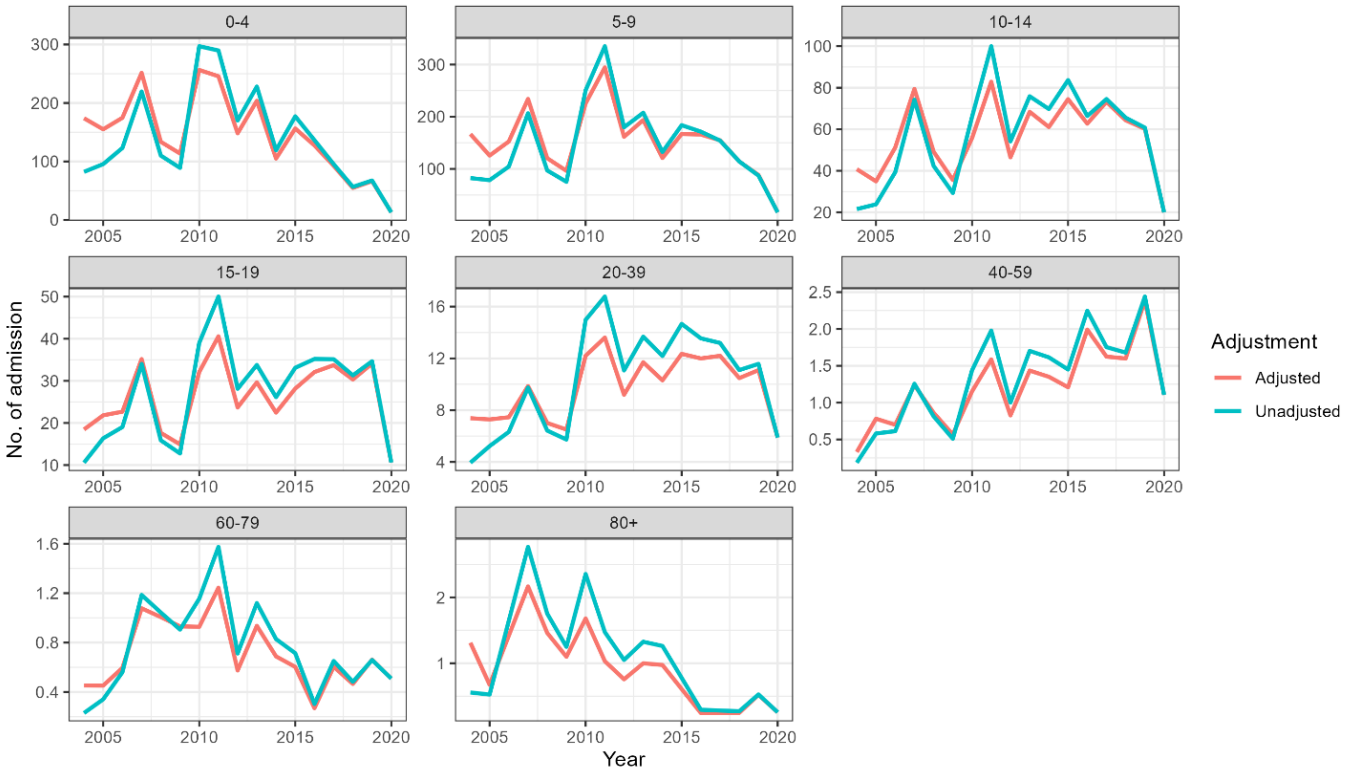
patients had only one such episode. On the other hand, counting all records for herpes zoster resulted in higher number of both AED attendance and hospitalisation for adults, indicating re-attendance and admission within one year with herpes zoster in at least one of the diagnosis codes was less rare. Regardless, the trend of herpes zoster was similar despite of the difference in absolute number of attendance/ admission episodes. Hence, counting only first record was chosen in the analysis as repeated attack is relatively rare for both diseases.

Supplementary Figure S.4.3.2. Proportion coded and average number of codes of AED attendance and hospitalisation, public hospitals of Hong Kong, 2004 to 2020.



Supplementary Figure S.4.3.3. Comparison on the effect of adjusting AED attendance and hospital admission by coding rate, public hospitals of Hong Kong, 2004 to 2020.

(a) AED attendance for varicella.



(b) AED attendance for shingles.

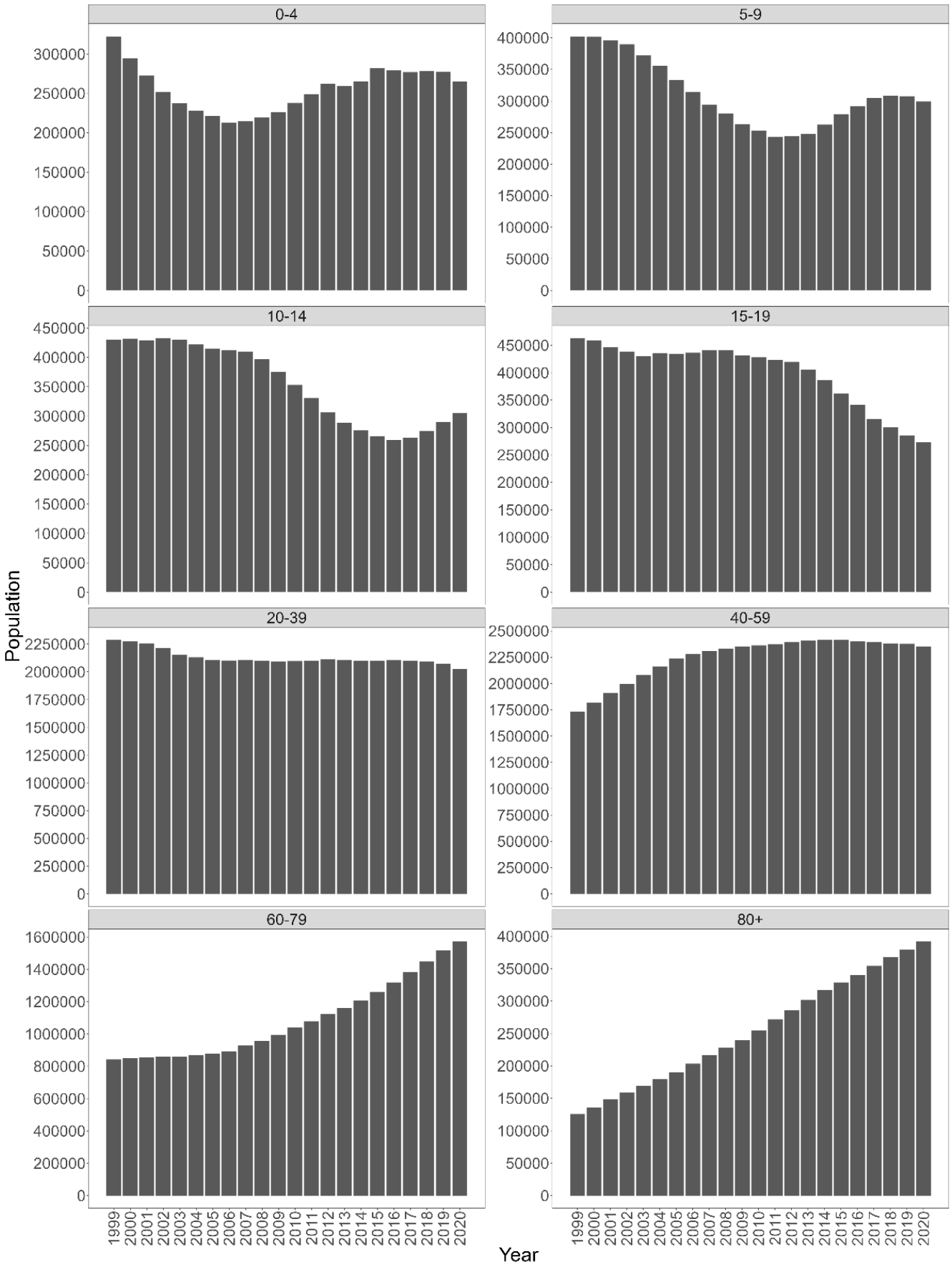
(c) Hospitalisation for varicella.

(d) Hospitalisation for herpes zoster

Comparison of the annual age-specific adjusted and unadjusted rate of AED attendance for varicella (a), herpes zoster (b) and hospital admission for varicella (c) and herpes zoster (d). Details of the adjustment can be found in Chapter 2 (155). Although the adjusted rate is generally lower in 2010 and after, the trend for AED

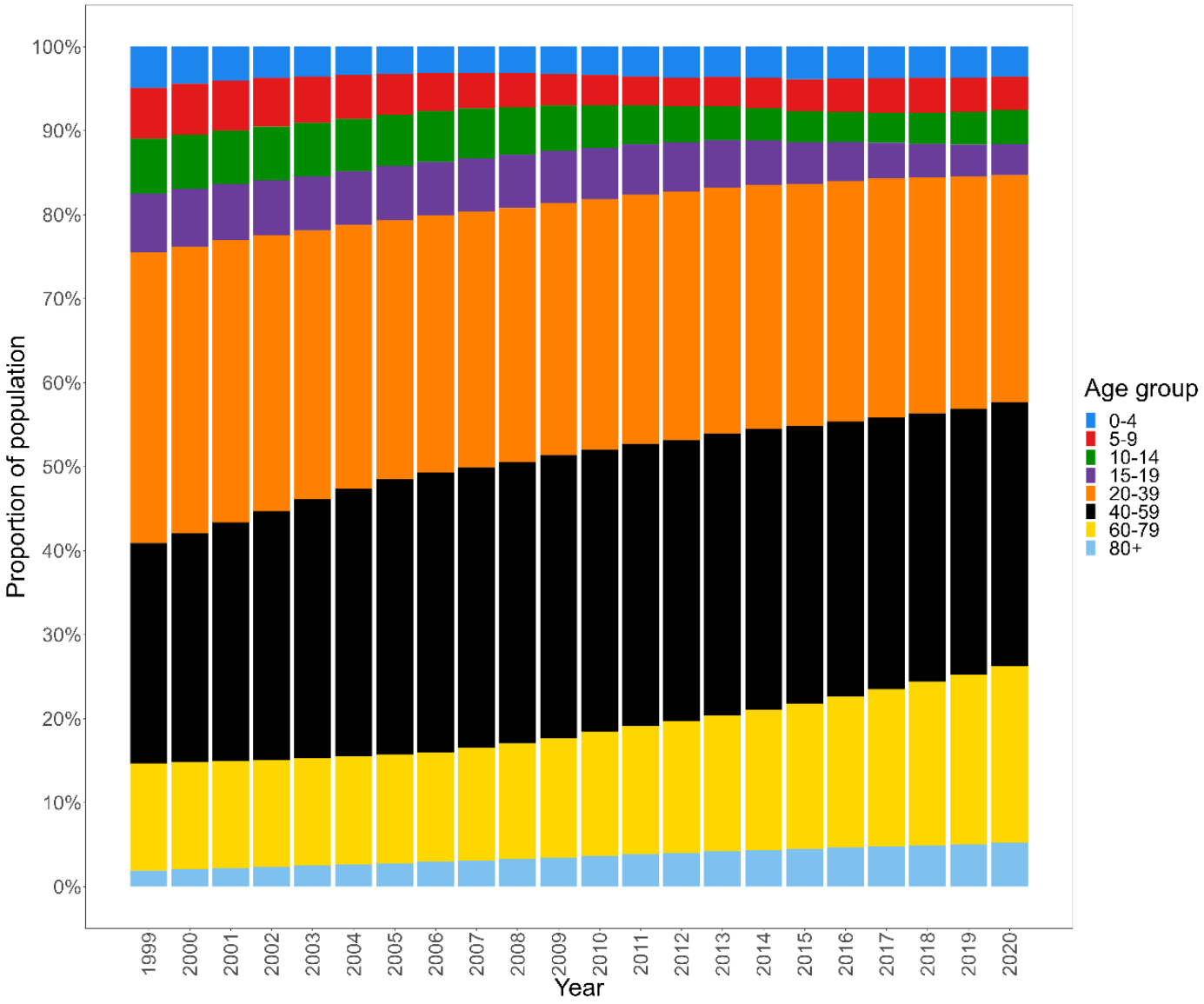
attendance and hospital admission for varicella is comparable, irrespective of the adjustment. On the other hand, the adjustment resulted in considerably lower rate for AED attendance and hospital admission of herpes zoster, especially for those aged 60 to 79 years and 80 years or above, for which the incidence was highest. To avoid the change in coding rate affecting the trend of both data, the adjusted rate was used in the analysis.

Supplementary Figure S.4.3.4. Hong Kong population figures by age, 1999 to 2020.



Source of information: Department of Census & Statistics, the Government of the Hong Kong Special Administrative Region (185).

Supplementary Figure S.4.3.5. Proportion of Hong Kong population by age, 1999 to 2020.



Source of information: Department of Census & Statistics, the Government of the Hong Kong Special Administrative Region (185).

Chapter 5. Modelling varicella vaccination in Hong Kong

Introduction

Varicella in Hong Kong, before and after the funded vaccination programme

Varicella was endemic in Hong Kong with infections predominantly occurring among children before ten years of age [Chapter 2]. In the 2000s, the Bureau of Health of the Hong Kong SAR assessed the benefits of universal varicella vaccination (UVV) for children in Hong Kong. The economic analysis suggested that childhood varicella vaccination would not be cost-beneficial, as considered by the Hong Kong Government (75). This economic analysis was based on the UK's varicella vaccination model, which predicted UVV leading to a reduction in wild-type (wt) varicella transmission, resulting in a shift of varicella burden to adolescents and an increase in herpes zoster (HZ) (76). It was assumed that there was no vaccine uptake in the community before UVV. However, in Hong Kong there had been an increase in varicella vaccine uptake to about 50% in the private market in 2015 and a reduction in births and school children since the 1990s, resulting in a shift of varicella burden to older children [Chapter 2]. As the risk for varicella complications increases with age, this change in disease burden and moderate vaccine uptake in the private market led to the recommendation of a 2-dose universal varicella vaccination programme by the Scientific Committee of Vaccine Preventable Diseases (SCVPD) (151). With the UVV launched in 2014, first dose varicella vaccine uptake in cohorts eligible for funded vaccination reached 98% among preschool children [Chapter 4.1].

Despite the success in the initial UVV implementation, there are remaining concerns with the varicella vaccination strategy in Hong Kong. First, funded vaccination is only available for those born in 2013 and after, with no catch-up vaccination provided for children of older cohorts. Unvaccinated children of non-UVV eligible cohorts had a reduced chance of acquiring immunity via natural infection [Chapter 4.2] and may remain susceptible to an older age. Second, most of the children vaccinated before UVV had only received one dose, and UVV-eligible children did not start to receive a second dose until 2020 [Chapter 4.1]. Therefore, a more complete 2-dose protection for children and young adults would not be achieved until 25 years after the launch of the programme i.e., in 2040. Although varicella notification incidence has reduced in the early post-UVV period among eligible children, the incidence has remained substantial even in cohorts with high 1-dose vaccination uptake [Chapter 4.3]. Furthermore, increases in varicella notifications among older children, adolescents and adults in the private vaccine era have persisted in early UVV era [Chapter 4.3], suggesting that a continuing shift in the burden of disease to older individuals might be possible. Given the difficulties of interpreting the complex patterns in notifications and seroprevalence over time [Chapter 4.2], and concerns about the future burden of disease, a mathematical model was formulated to assess these trends and project the impact of alternative vaccination strategies.

Use of mathematical model to understand the impact of UVV

Mathematical models and economic analyses have been frequently used to predict the effectiveness and cost-effectiveness of varicella vaccination programmes and have been central to the evaluation of different varicella vaccination strategies world-wide (61,

149-152). Most of these models used pre-vaccine era data to determine the endemic transmission intensity of varicella, with the majority of the vaccination parameters estimated from clinical trials of the varicella vaccine [Table 1.2 in Chapter 1]. Since the introduction of UVV in the U.S. in 1995, an increasing number of countries have incorporated varicella vaccine into their childhood vaccination programmes (46). There are numerous studies reflecting real-world evidence of the impact and direct effect of varicella vaccine, re-affirming the benefit of UVV (46, 57). It should be noted that despite the moderate effect of 1-dose varicella vaccine in preventing clinical diseases and relatively high rate of breakthrough infections (57), the reported impact (overall/ total effect) of reduction of notification is relatively substantial (50, 60, 67). Notable reductions in varicella hospitalisations have also been reported in countries with childhood varicella vaccination programmes (51, 58-60, 207, 208). Hence, observational studies on vaccine efficacy/ effectiveness alone might not provide sufficient insights to understand the mechanism of vaccine protection, which can be aided by the use of mathematical models (209). Using a mathematical model that fits both serology and surveillance data collected before and after UVV, this study jointly evaluates the efficacy of varicella vaccine against susceptibility to infection, transmission and development of disease, which are pivotal in assessing the overall varicella control strategy. The objectives of this study include:

(1) modelling the impact of the combined private and public varicella vaccination programme on varicella transmission,

(2) understanding the mechanism of varicella protection, the extent of vaccine failure,

(3) assessing the immunity gap in the population and the potential for an increase in varicella after UVV, and

(4) evaluation of alternative varicella vaccination strategies. Results of this varicella

transmission model should help inform public health officials and policy makers of countries that adopt similar varicella vaccination strategies.

Methods

A deterministic dynamic transmission model with realistic age-structure was developed, building on previously suggested model structures including by Brisson *et al* (65, 76), van Hoek *et al* (61) and Gao *et al* (118, 123).

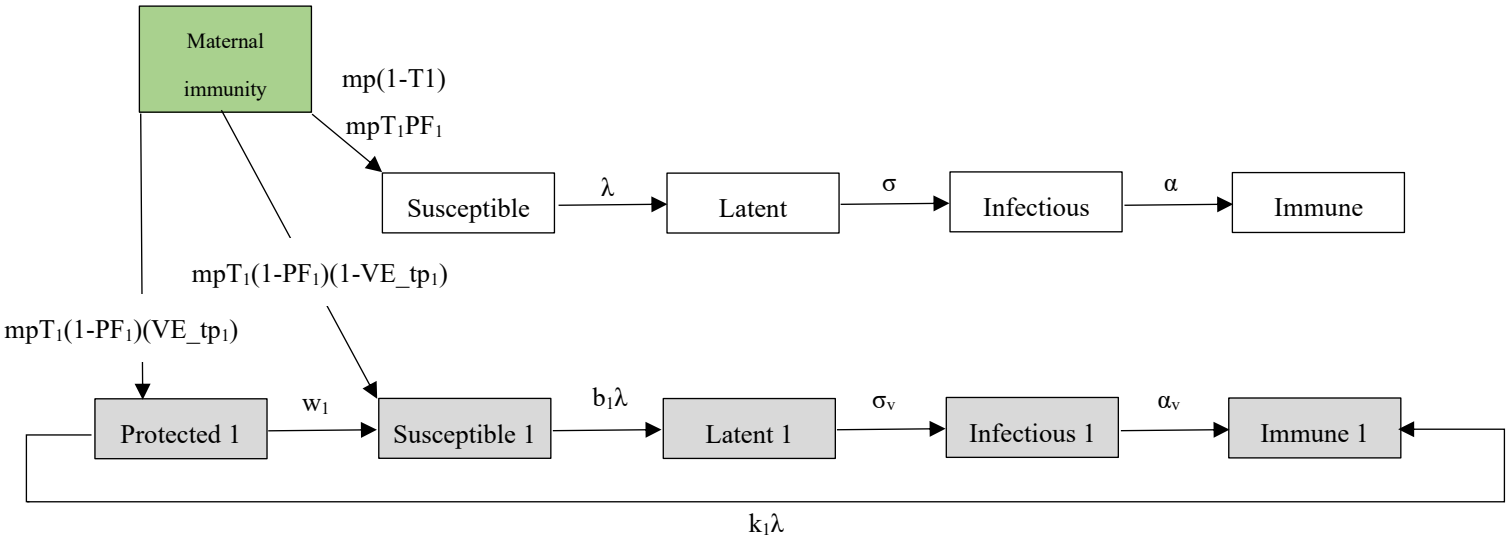
Model population

To model childhood varicella vaccination more precisely, I defined one-year cohorts for those aged 20 years or below, five-year cohorts for those aged 21 to 39 years and 10-year cohorts for those aged 40 years and above. In total, there are 32 age cohorts in the model, which mimics a population from the age of 0 to 100 years. Ageing occurs continuously in the model with respect to the corresponding age strata (i.e. at an average rate of one 365th per day for those aged 20 years and under (single age cohort), one 1825th per day for those aged 21 to 70 years (5-yearly cohort) and one 11,315th per day for those aged 71 to 100 years). The mortality rate was the rate of population leaving the last age group (71 to 100 years) due to ageing, which equaled the birth rate, the rate of population moving into 0 year of age. A stable model population was maintained with births and deaths being equal.

The annual new births and population in each 1- year age cohort was defined as 48,000, which approximates the average resident population of those aged under 1 year from

1997 to 2015 (46,744) (185). The population under 1 year was chosen over the number of newborns as a substantial proportion of newborns in Hong Kong during the study period do not reside locally and would therefore not contribute to VZV transmission. The number of new births to mothers from mainland China has been rising since 2001. This increasing trend stopped in 2013, when the Government required all public and private hospitals not to accept bookings for delivery by mainland women whose husbands are not Hong Kong permanent residents (210). Some of these babies were brought back to mainland China (211), but they may later move to Hong Kong for education or reside in mainland China with regular travel to Hong Kong as cross-border students (212). Varicella transmission and notification was assumed to be mainly contributed by the resident population and the contribution by these children not residing in Hong Kong was assumed to be negligible and hence not modelled.

Figure 5.1. Flow diagram of varicella and VZV vaccination in Hong Kong (Model 1a).



Compartments

B = birth; MI = Maternal immunity; S = Susceptible; E = Latent; I = Infectious; R = Immune

P_1 = Protected 1; S_1 = Susceptible 1; E_1 = Latent 1; I_1 = Infectious 1; R_1 = Immune 1

White boxes indicating unvaccinated compartments while grey boxes indicated vaccinated compartments.

Parameters

mp: duration of maternal immunity; **λ**: Force of varicella infection; **σ** and **σ_v**: duration of latent period for natural and breakthrough varicella; **α** and **α_v**: duration of infectiousness for natural and breakthrough varicella; **T1**: proportion received varicella vaccination; **PF_1**: proportion of vaccinated individuals experienced primary vaccine failure; **VE_tp_1**: proportion of individuals temporarily protected after vaccination; **w_1**: duration of temporary vaccine protection; **b_1**: Relative susceptibility to varicella infection for vaccine recipients who remain susceptible to breakthrough infection; **k1**: Proportion of temporarily protected individuals who become immune.

Model equations

$$dMI/dt = B - mp(1-T_1)MI - mpT_1PF_1MI - mpT_1(1-PF_1)(VE\_tp_1)MI - mpT_1(1-PF_1)(1-VE\_tp_1)MI - \mu MI$$

$$dS/dt = mp(1-T_1)MI + mpT_1PF_1MI - \lambda S - \mu S$$

$$dE/dt = \lambda S - \sigma E - \mu E$$

$$dI/dt = \sigma E - \alpha I - \mu I$$

$$dR/dt = \alpha I - \mu R$$

$$dP_1/dt = mpT_1(1-PF_1)(VE\_tp_1)MI - k_1\lambda P_1 - w_1P_1 - \mu P_1$$

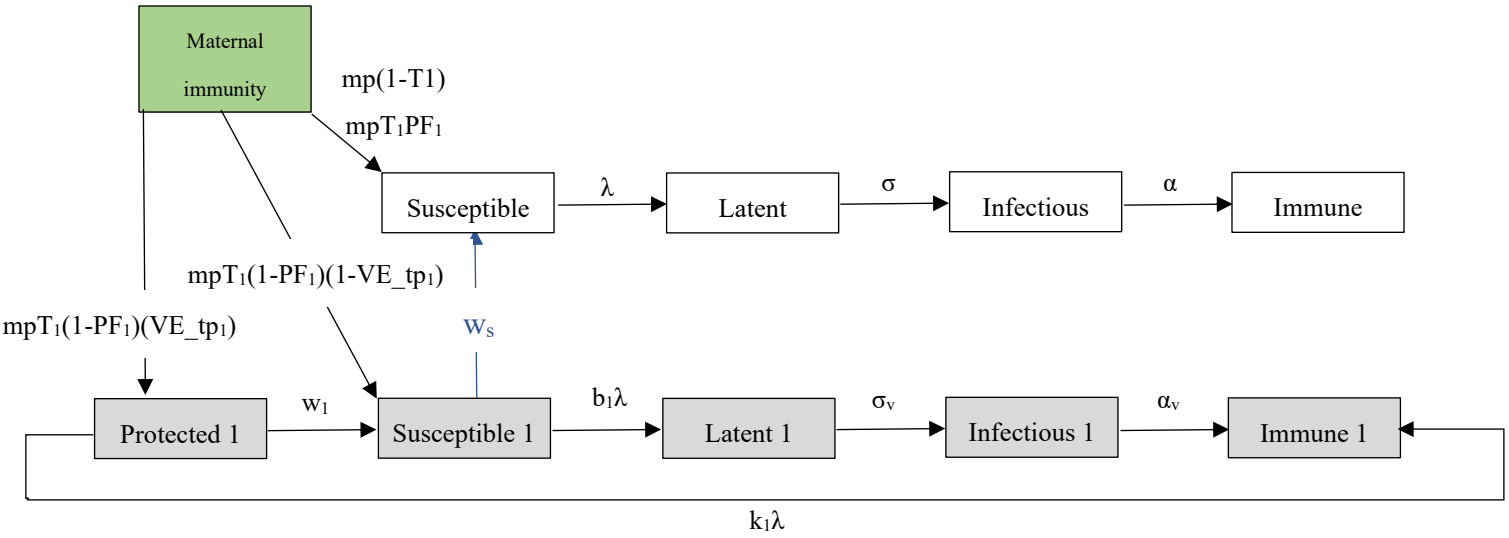
$$dS_1/dt = {}_{w1}P_1 + mpT_1(1-PF_1)(1-VE\_tp_1)MI - b_1\lambda S_1 - \mu S_1$$

$$dE_1/dt = b_1\lambda S_1 - \sigma_v E_1 - \mu E_1$$

$$dI_1/dt = \sigma_v E_1 - \alpha_v I_1 - \mu I_1$$

$$dR_1/dt = \alpha_v I_1 + k_1\lambda P_1 - \mu R_1$$

Figure 5.2. Flow diagram of varicella and VZV vaccination model in Hong Kong (Model 1b).



Compartments

B = birth; MI = Maternal immunity; S = Susceptible; E = Latent; I = Infectious; R = Immune

P_1 = Protected 1; S_1 = Susceptible 1; E_1 = Latent 1; I_1 = Infectious 1; R_1 = Immune 1

White boxes indicating unvaccinated compartments while grey boxes indicated vaccinated compartments.

Parameters

mp: duration of maternal immunity; **λ**: Force of varicella infection; **σ** and **σ_v**: duration of latent period for natural and breakthrough varicella; **α** and **α_v**: duration of infectiousness for natural and breakthrough varicella; **T1**: proportion received varicella vaccination; **PF1**: proportion of vaccinated individuals experienced primary vaccine failure; **VE_tp_1**: proportion of individuals temporarily protected after vaccination; **w1**: rate of waning from temporary protection to vaccine susceptible; **w_s**: rate of waning from vaccine susceptible to susceptible; **b1**: Relative susceptibility to varicella infection for those vaccine recipients who remain susceptible to breakthrough infection; **k1**: Proportion of temporarily protected individuals who become immune.

Model equations

$$dMI/dt = B - mp(1-T_1)MI - mpT_1PF_1MI - mpT_1(1-PF_1)(VE\_tp_1)MI - mpT_1(1-PF_1)(1-VE\_tp_1)MI - \mu MI$$

$$dS/dt = mp(1-T_1)MI + mpT_1PF_1MI + w_sS_1 - \lambda S - \mu S$$

$$dE/dt = \lambda S - \sigma E - \mu E$$

$$dI/dt = \sigma E - \alpha I - \mu I$$

$$dR/dt = \alpha I - \mu R$$

$$dP_1/dt = mpT_1(1-PF_1)(VE\_tp_1)MI - k_1\lambda P_1 - w_1P_1 - \mu P_1$$

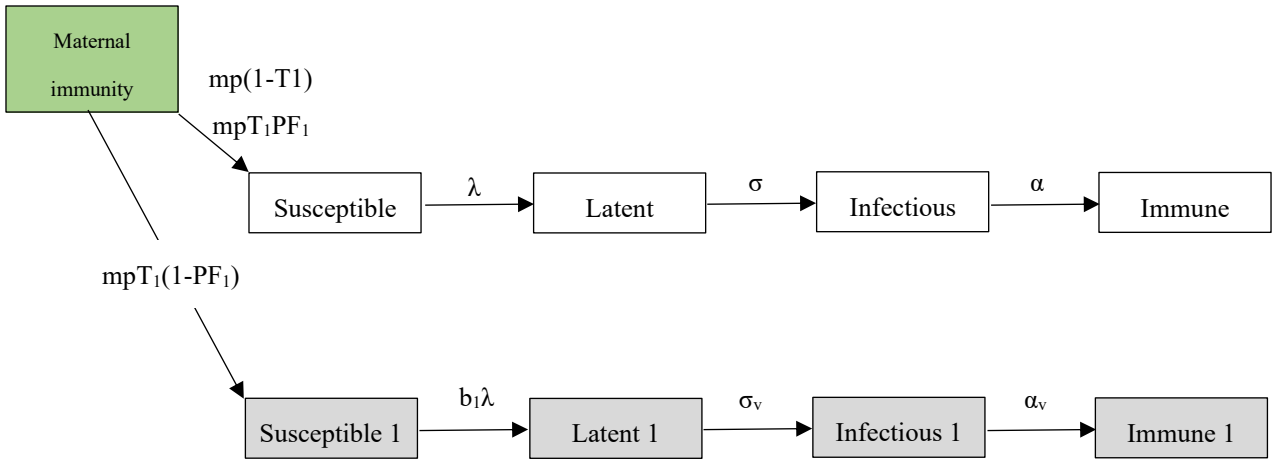
$$dS_1/dt = {}_{w1}P_1 + mpT_1(1-PF_1)(1-VE\_tp_1)MI - w_sS_1 - b_1\lambda S_1 - \mu S_1$$

$$dE_1/dt = b_1\lambda S_1 - \sigma_v E_1 - \mu E_1$$

$$dI_1/dt = \sigma_v E_1 - \alpha_v I_1 - \mu I_1$$

$$dR_1/dt = \alpha_v I_1 + k_1\lambda P_1 - \mu R_1$$

Figure 5.3. Flow diagram of varicella and VZV vaccination model in Hong Kong (Model 2a).



Compartments

B = birth; MI = Maternal immunity; S = Susceptible; E = Latent; I = Infectious; R = Immune

S_1 = Susceptible 1; E_1 = Latent 1; I_1 = Infectious 1; R_1 = Immune 1

White boxes indicating unvaccinated compartments while grey boxes indicated vaccinated compartments.

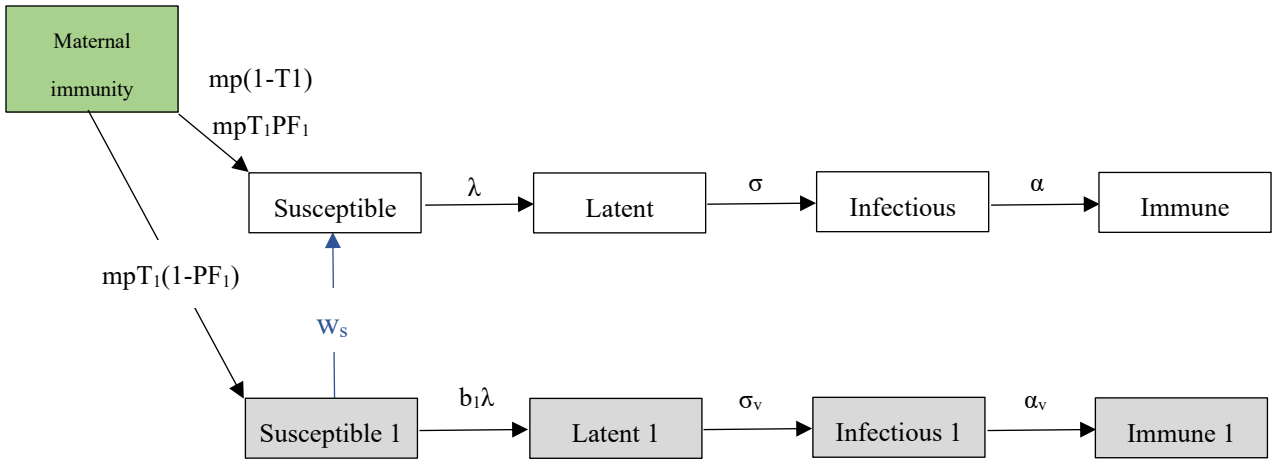
Parameters

mp: duration of maternal immunity; **λ**: Force of varicella infection; **σ** and $\boldsymbol{\sigma_v}$: duration of latent period for natural and breakthrough varicella; **α** and $\boldsymbol{\alpha_v}$: duration of infectiousness for natural and breakthrough varicella; **T1**: proportion received varicella vaccination; **PF1**: proportion of vaccinated individuals experienced primary vaccine failure; **b1**: Relative susceptibility to varicella infection for vaccine recipients who remain susceptible to breakthrough infection.

Model equations

$$
\begin{aligned}
dMI/dt &= B - mp(1-T_1)MI - mpT_1PF_1MI - mpT_1(1-PF_1)MI - \mu MI \\
dS/dt &= mp(1-T_1)MI + mpT_1PF_1MI - \lambda S - \mu S \\
dE/dt &= \lambda S - \sigma E - \mu E \\
dI/dt &= \sigma E - \alpha I - \mu I \\
dR/dt &= \alpha I - \mu R \\
dS_1/dt &= mpT_1(1-PF_1)MI - b_1\lambda S_1 - \mu S_1 \\
dE_1/dt &= b_1\lambda S_1 - \sigma_v E_1 - \mu E_1 \\
dI_1/dt &= \sigma_v E_1 - \alpha_v I_1 - \mu I_1 \\
dR_1/dt &= \alpha_v I_1 + k_1\lambda P_1 - \mu R_1
\end{aligned}
$$

Figure 5.4. Flow diagram of varicella and VZV vaccination model in Hong Kong (Model 2b).



Compartments

B = birth; MI = Maternal immunity; S = Susceptible; E = Latent; I = Infectious; R = Immune

S_1 = Susceptible 1; E_1 = Latent 1; I_1 = Infectious 1; R_1 = Immune 1

White boxes indicating unvaccinated compartments while grey boxes indicated vaccinated compartments.

Parameters

mp: duration of maternal immunity; **λ**: Force of varicella infection; **σ** and **σ_v**: duration of latent period for natural and breakthrough varicella; **α** and **α_v**: duration of infectiousness for natural and breakthrough varicella; **T1**: proportion received varicella vaccination; **PF1**: proportion of vaccinated individuals experienced primary vaccine failure; **w_s**: rate of waning from vaccine susceptible to susceptible; **b1**: Relative susceptibility to varicella infection for those vaccine recipients who remain susceptible to breakthrough infection;

Model equations

$$
\begin{aligned}
dMI/dt &= B - mp(1-T_1)MI - mpT_1PF_1MI - mpT_1(1-PF_1)\,MI - \mu MI \\
dS/dt &= mp(1-T_1)MI + mpT_1PF_1MI + \mathbf{w_sS_1} - \lambda S - \mu S \\
dE/dt &= \lambda S - \sigma E - \mu E \\
dI/dt &= \sigma E - \alpha I - \mu I \\
dR/dt &= \alpha I - \mu R \\
dS_1/dt &= mpT_1(1-PF_1)MI - \mathbf{w_sS_1} - b_1\lambda S_1 - \mu S_1 \\
dE_1/dt &= b_1\lambda S_1 - \sigma_v E_1 - \mu E_1 \\
dI_1/dt &= \sigma_v E_1 - \alpha_v I_1 - \mu I_1 \\
dR_1/dt &= \alpha_v I_1 + k_1\lambda P_1 - \mu R_1
\end{aligned}
$$

Table 5.1. Characteristics of different epidemiological states in the varicella vaccination model.

Compartment	Immunity against varicella infection	EIA sensitivity to humoral immunity (IgG)	Varicella disease if infected	Infectiousness
Maternal immunity (MI)	Full	Full	Not prone to varicella	Not infectious
Susceptible (S)	No	N/A (negative)	Natural varicella	Not infectious
Latent (E)				Not infectious
Infectious (I)				Full
Immune (R)	Full	Full	Not prone to varicella	Not infectious
Protected 1 (P1)	Full	Full	Not prone to varicella	Not infectious
Susceptible 1 (S_1)	Partial	Reduced/ adjusted (IgGsensVac)	Breakthrough varicella	Not infectious
Latent 1 (E_1)				Not infectious
Infectious 1 (I_1)				Reduced (RE)
Immune 1 (R_1)	Full	Full	Not prone to varicella	Not infectious

Note:
Individuals at compartments with full immunity were assumed to be fully detected by IgG assay. IgG antibodies start to develop several days after infection (213) and those unvaccinated who are infected (Latent (E) and Infectious (I)) are assumed yet to develop antibodies detectable by IgG assay before recovered;

Vaccinees avoiding primary vaccine failure develop partial immunity and they are susceptible to breakthrough varicella infections, which are generally milder than natural varicella. These individuals are expected to have lower antibody level and a lower proportion will be detected by the ELISA assay (reduced sensitivity, IgGsensVac).

Model structure

The model consists of a set of ordinary differential equations (ODE) that controls the flow of model populations in mutually exclusive compartments (in each age group), which represents different epidemiological states of varicella [Figures 5.1 to 5.4 and Table 5.1]. There are five compartments corresponding to the natural infection/ immune status of varicella [Figures 5.1 to 5.4, green and white boxes]. Newborns are fully immune to varicella infection (maternal protection (*mp*), green box). By the end of the maternal protection period, infants enter the susceptible class in the absence of vaccination (*Susceptible (S)*). Upon effective contact with an infectious individual, those susceptible will acquire natural varicella infection under an age- and time-specific force-of-infection (FOI) (to be described in detail), as they first become infected yet remain non-infectious (*Latent (E)*) and become infectious (*Infectious (I)*) after a latent period of 14 days (σ). After an infectious period of 7 days (α), individuals were assumed to recover from the acute illness and develop life-long immunity against varicella (*Immune (R)*).

The remaining compartments in the model correspond to different infection/ immune status for those who received varicella vaccine. [grey boxes in Figures 5.1 to 5.4 and rows highlighted in grey in Table 5.1]. Vaccination starts when infants lose their maternal protection, of which a proportion (T_I) will be vaccinated. In the model, *mp* was assumed to be 12 months which is the same as the scheduled age for receiving first dose of varicella vaccine. Most of the mathematical models of varicella vaccination assumed several pathways after vaccination (61, 65, 118) [Figure 5.1]. A small

proportion of the vaccinees experience primary vaccine failure (PF_1) and they will enter the *Susceptible* compartment. Similar to those unvaccinated, they do not develop any immunity against varicella and are fully susceptible to varicella infection. For vaccinees avoiding primary vaccine failure, existing models generally assume two possibilities [Figures 5.1 and 5.2]. First, a proportion of these vaccinees ($VE\_temp\_protection_1$ or VE_tp_1, referred as Take (T) in Brisson *et al*. (65) and van Hoek *et al.* (61)) enter a temporary protection compartment (*Protected 1 (P1)*). These vaccinees are assumed to develop sufficient immunity to protect them temporarily from breakthrough infections [Table 5.1]. After coming into effective contact with an infectious individual, a fraction of them (k) are boosted and become permanently immune from varicella without developing any disease (*Immune 1 (R1)*). In the absence of boosting to *Immune 1*, their immunity will wane after a period ($d\_temp\_protection_1$ or d_tp_1) to the partial protection status (*Susceptible 1 (S1)*). In addition, vaccinees escaping primary vaccine failure (1-$VE\_temp\_protection_1$) directly enter the vaccine-susceptible status (*Susceptible 1*) after vaccination. These vaccinated but partially susceptible individuals have only partial immunity against varicella and are prone to develop milder breakthrough varicella when they are infected (i.e. the vaccine is assumed to be 'leaky'). However, their risk of infection is reduced by a factor (1 - $VE\_infection_1$ (VE_i_1), referred as b_1 in previous varicella models) compared to those unvaccinated and those who failed to mount an immune response to the vaccine (*Susceptible*). Like natural varicella infections, those with breakthrough infections will be latent (*Latent 1*) for 14 days (σ_v), infectious (*Infectious 1*) for 7 days (α_v) and become fully immune to further varicella infections (*Immune 1*) subsequently. Those vaccinated infectious (*Infectious 1*) will have their infectivity/ infectiousness reduced by a factor (*RE* or $1\text{-}VE\_t_1$, to be discussed in detail in subsequent section "*force of varicella infection*"). In addition,

reinfection of chickenpox is ignored in the model as it is relatively uncommon (214).

Candidate models with alternative model structures

Although the temporary protection status (*Protected 1*) has been included in previous varicella vaccination models (61, 65, 118), its importance has rarely been examined. The varicella vaccination model used to inform the JCVI's recommendation of UVV in 2023 opted for a simpler model structure without this temporary protection status [Personal Communication, Caroline Trotter and Lauren Adams, University of Cambridge]. To determine the most appropriate model structure, I constructed and tested four candidate models (models 1a, 1b, 2a and 2b) and selected the main model by fitting them with seroprevalence and notification data collected before and after varicella vaccination in the private market and public sector. Model 1 [Figures 5.1 and 5.2] consists of the *Protected 1* compartment whilst model 2 [Figures 5.3 and 5.4] does not. To understand whether the partial immunity attained by those in *Susceptible 1* compartment will wane and become fully susceptible to natural varicella (*Susceptible*), I allowed an additional pathway in both models 1 and 2, as presented in candidate models 1b (Figure 5.2) and 2b (Figure 5.4).

There was further variation to the four candidate models that was explored when fitting to the data. The sensitivity of the enzyme-linked immunosorbent assay (ELISA)/ enzyme immunoassay (EIA) IgG assay to vaccine-induced immunity (*IgGsensVac*) is known to be lower than the immunity induced by natural infection [Chapter 4.2]. The seroprevalence survey in 2020 included children aged 1 to 4 years in 2020, who were born between 2016 and 2019 and were all eligible for UVV. Their first dose varicella

vaccination uptake was estimated to be 98% ($uptake_{uni}$) [Chapter 4.1]. Taking into account the observed seroprevalence for these children being 82% ($seropos_{uni}$) [Chapter 4.2] and assuming 5% of vaccinated children experienced primary vaccine failure (PF_1), the IgG test sensitivity to vaccine-induced immunity would be around 88%:

$$seropos\_vac = seropos_{uni}/(uptake_{uni} * 1 - PF_1)$$

However, assuming the IgG test sensitivity to vaccine-induced immunity to be as high as 88% or up to 100% yielded low to negative expected infection-induced seroprevalence between 2010 and 2020, a period when varicella vaccine uptake was increasing rapidly [Table 4.2.2 in Chapter 4.2]. Therefore, rather than fixing the *IgGsensVac* as 88%, it was alternatively included as a parameter to be estimated during calibration of all candidate models (described in detail in later section '*IgG test sensitivity to detect vaccine-induced immunity*'). Hence, the main model was selected from a total of 8 combinations of candidate models and parameter fitting [Table 5.9].

Contact patterns

Contact surveys are often used to inform the model on the contacts between different age groups for respiratory transmitted pathogens like chickenpox. POLYMOD is one of the most notable contact surveys conducted across eight European countries between 2005 and 2006 (171). To determine the appropriate mixing patterns, fitting of model 2a (simplest candidate model) was compared using the relative frequency of contacts between different ages from Hong Kong's contact survey conducted in 2015 (215) with those recorded in POLYMOD (171) [model calibration will be described in details in

later section]. To account for uncertainty, 100 bootstraps of contact matrices from all eight countries participating in the POLYMOD survey were sampled via the R package '*socialmixr*' (216). As varicella outbreaks spread by the airborne route have been reported (217-219), both physical and non-physical contacts were included. The mean contacts of these bootstraps were scaled with the population data of Hong Kong and adapted to the age structure of the model.

Force of varicella infection

The age- and time-dependent varicella force of infection (FOI), $\lambda(a, t)$, is contributed to by both varicella and herpes zoster exposure:

$$\lambda(a,t) = \lambda_{\mathrm{v}}(a,t) + \lambda_{\mathrm{HZ}}$$

where $\lambda_V(a, t)$ is the force-of-infection due to varicella, varying with age and time. λ_{HZ} is a constant force-of-infection of VZV due to herpes zoster.

The varicella force-of-infection consists of exposure to natural and breakthrough varicella infections:

$$\lambda_{\mathrm{v}}(a,t) = \sum \beta(a`,a)(I(a`,t) \ + (RE)\ I_1(a`,t))$$

where, $\beta(a`, a)$ was the effective contact rate between an infectious individual of age $a`$ and a susceptible individual a. $\beta(a`, a)$ depended on the average number of contacts between individuals at ages $a`$ and a, as informed by the POLYMOD contact matrix,

$C(a`, a)$, and the proportion of these contacts being effective and leading to infection (p) [Table 5.3]. p was an age-independent parameter used to scale the proportion of effective contacts leading to infections and was estimated during model calibration:

$$\lambda_v(a,t) = p\sum C(a`,a)(I(a`,t) + (RE)\, I_1(a`,t))$$

$I(a`, t)$ and $I_1(a`, t)$ were the number of infectious natural and breakthrough varicella aged $a`$ at time t among unvaccinated and vaccinated individuals. RE was the residual infectiousness in breakthrough varicella modified by vaccination, relative to natural varicella. Therefore, RE is a measure of the vaccine efficacy against onward transmission for those with breakthrough disease:

$$VE\_transmission = 1 - RE$$

Individuals with herpes zoster are believed to be infectious, though to a lesser extent than varicella. Since the model did not consist of compartments corresponding to herpes zoster, a stable force-of-infection due to herpes zoster (λ_{HZ}) was computed based on the estimates of annual herpes zoster incidence (ZI). Although data on AED attendance and hospital admission due to herpes zoster was available from the Hospital Authority [Chapter 4.3], there is no measure of cases that do not attend hospital services in Hong Kong (220). Therefore, the annual incidence of herpes zoster (ZI) in the model for those aged 50 years or above was estimated by multiplying the annual age-specific risk of herpes zoster reported in a Taiwan study (221) with the model population in the corresponding age groups [Table 5.3]. With reference from Chan PKS *et al*., the uptake of herpes zoster vaccine was assumed to be 5% as it has only been available in the

private market (220). In view of the low herpes zoster vaccine uptake and the fairly stable age-standardised hospitalisation rate of herpes zoster between 2004 and 2020 [Chapter 4.3], the annual incidence of herpes zoster (ZI) was assumed to be constant. As there is no clear seasonality of herpes zoster [Chapter 2], these herpes zoster cases were assumed to occur on average throughout the year. Following Brisson *et al*. (76), the annual force-of-infection by herpes zoster (λ_{HZ}) was computed as follow:

$$\lambda_{HZ} = \omega(ZI)$$

where $\omega = 5.4^{e-7}$ (76).

The λ_{HZ} estimated was very low (between 0.011 and 0.017) and was expected to contribute marginally to the overall force of varicella infection [Table 5.2]. As any changes in λ_{HZ} would only have a small effect on the overall varicella force-of-infection, λ_{HZ} was assumed to be unaffected by changes in varicella epidemiology. The mean λ_{HZ} estimated (0.014) was used as a constant contributing to the overall varicella force-of-infection ($\lambda(a, t)$).

Biological parameters

With the exception of fitting the proportion of effective contact (p), other biological parameters were adopted from previous studies of varicella epidemiology or modeling studies [Table 5.3]. Similar to van Hoek *et al* (61), the latent period (σ_v) and the infectious period (α_v) for vaccinees with breakthrough varicella are assumed to be the same as those with natural varicella [Table 5.3]. Previous studies showed that maternal

immunity of VZV may last between 3 and 6 months (222, 223) to between 6 and 12 months (224-230). 12 months of maternal immunity is adopted to cater for age of vaccination in Hong Kong's varicella vaccination schedule.

Table 5.2. Estimation of annual herpes zoster incidence and force of infection due to herpes zoster.

Age (years)	Population (model)	Annual risk of HZ from Taiwan study (221)			Annual incidence of herpes zoster estimated (ZI)			Force of infection contributed by herpes zoster (λ_{HZ})		
		Base	Lower limit	Upper limit	Base	Lower limit	Upper limit	Base	Lower limit	Upper limit
50-59	480,000	0.00830	0.00664	0.00996	3984.0	3187.2	4780.8	0.0021514	0.0017211	0.0025816
60-64	240,000	0.01094	0.00875	0.01313	2625.6	2100.0	3151.2	0.0014178	0.0011340	0.0017016
65-69	240,000	0.01094	0.00875	0.01313	2625.6	2100.0	3151.2	0.0014178	0.0011340	0.0017016
70-79	480,000	0.01217	0.00974	0.01461	5841.6	4675.2	7012.8	0.0031545	0.0025246	0.0037869
80+	1,008,000	0.01024	0.00820	0.01229	10321.9	8265.6	12388.32	0.0055738	0.0044634	0.0066897
50+	**2,448,000**	**0.05259**	**0.04208**	**0.06312**	**25398.7**	**20328.0**	**30484.32**	**0.0137150**	**0.0109770**	**0.0164620**

Note:

*Incidence of herpes zoster (ZI) was estimated by multiplying population and the annual risk of HZ from Taiwan study. On the other hand, force of infection due to herpes zoster (λ_{HZ}) was ω * ZI where $\omega = 5.4^{e-7}$ as assumed by Brisson et al. (76).*

Table 5.3. Model parameters.

Main model				
Biological parameters		**Symbol**	**Value**	**Reference/ Values adopted in other models**
Duration of latent period for natural varicella (days)		σ	14	Jumaan (231)
Duration of latent period for breakthrough varicella (days)		σ_v	14	Jumaan (231)
Duration of infectious period for natural varicella (days)		α	7	Jumaan (231)
Duration of infectious period for breakthrough varicella (days)		α_v	7	Jumaan (231), van Hoek (61)
Duration of maternal immunity (months)		*mp*	12	Kangro (228), Trlifajova (229), Gershon (230)
Force of infection due to herpes zoster (per year)		λ_{HZ}	0.014	Estimated based on age-specific risk of HZ and model population [Table 5.2]
Vaccination/ vaccine efficacy parameters	**Dose**	**Symbol**	**Value**	**Reference/ Values adopted in other models**
Varicella vaccination uptake at 1 year old	1	T_1	Varies by year	Immunisation surveys in preschool children [Chapter 4.1] (77, 232-236)
Proportion of vaccinees experiencing primary vaccine failure	1	PF_1	5.0%	Assumed to be 4% in previous studies (61, 65, 76, 118, 123)
	2	PF_2	2.5%	Gao 2010 (123) assumed to be half as 1-dose primary vaccine failure (4% vs 2%).

Proportion of temporarily protected individuals with immunity boosted after contacted by varicella cases[1]	1	k_1	100%		Brisson 2010 (237), van Hoek 2011 (61), Gao 2015 (118)		
	2	k_2	100%		Brisson 2010 (237), van Hoek 2011 (61), Gao 2015 (118)		
Parameters estimated (symbol)	**Dose**	**Short symbol**	**Estimated/ fixed**	**Prior for estimated parameter[3]/ Value for fixed parameter**	**Prior distribution (for estimated parameters)**	**Posterior distribution Median (95%CI) in main model (for estimated parameters)**	**Reference/ assumption**
Proportion of effective contact leading to infection (%) (*p*)	Not applicable	*p*	Estimated	5%	Uninformative	5.4% (5.0% to 5.7%)	No local reference.
Vaccine efficacy of temporary protection against breakthrough varicella infection[1] (%) (*VE_temp_protection*)	1	VE_tp_1 (Q_1)	Estimated	60%	Beta (left skewed)	Not included in main model	Hong Kong's VE study [Chapter 3] (156)
	2	VE_tp_2 (Q_2)	Fixed	97% (83%-100%)	Not applicable	Not applicable	Gao *et al*. (118)
Duration of temporary protection (year)[1] (*d_temp_protection*)	1	d_tp_1 ($1/w_1 * 365$)	Estimated	25.0 years	Gamma (left skewed)	Not included in main model	37.0 (11.8 to 47.6 years) by Gao 2015 (118); 25 (15 to 67 years) adopted by Brisson 2010 (237) and van Hoek 2011 (61).
	2	d_tp_2 ($1/w_2 * 365$)	Fixed	76.9 years	Not applicable	Not applicable	76.9 (38.5 to 200) by Brisson 2010 (237) and van Hoek 2011 (61); 100 (11.8 to Inf) by Gao 2015 (118).

Vaccine efficacy against acquisition of breakthrough varicella (%) (*VE_infection*)	1	VE_i_1 $(1-b_1)$	Estimated	50%	Beta (left skewed)	13.3% (5.1% to 28.2%)	Various assumption in previous models (0 by Brisson 2010 (237) and van Hoek 2011 (61); 0.1 (0.5 – 1.0) by Gao 2015 (118))
	2	VE_i_2 $(1-b_2)$	Fixed	66%	Not applicable	Not applicable	b2 assumed to be 0.34 by Gao 2015 (118)
Vaccine efficacy against onward transmission for breakthrough varicella (%) (*VE_transmission*)	1	VE_t_1 *(1-RE)*	Estimated	50%	Uninformative	98.2% (90.3% to 99.9%)	Assumed to be 50% for both dose 1 and 2 due to lack of data by Brisson 2010 (65) and Gao 2015 (118)
	2	VE_t_2	Same as VE_t_1	Same as VE_t_1	Uninformative	Not applicable	VE_t_2 was assumed to be 50% higher than VE_t_1 (Brisson 2010 (65) and Gao 2015 (93)). van Hoek assumed both 1- and 2- dose VE to be 50% (61).
Vaccine efficacy against disease after breakthrough varicella (disease severe enough to be notified) (%) (*VE_progression*)	1 & 2	*VE_p*	Estimated	50%	Uninformative	59.0% (20.3% to 82.2%)	Assumed, no relevant local reference
Duration of partial immunity (stay at S1 before waning to S) (year) $(d\_S1)^2$	1 & 2	*d_S1*	Estimated	25 years (0 to 100 years)	Uninformative	Not included in main model	This waning was not directly observed in vaccine studies. Prior of *d_S1* assumed to be the same as d_tp1.
Annual change in notification sensitivity (%) *(notiSens)*	NA	*notiSens*	Estimated	7.5%	Normal (symmetric)	6.0% (3.8 to 8.1%)	Annual change in varicella notification rate in adults [Chapter 4.3]
IgG test sensitivity to vaccine-induced immunity (%) (*IgGsensVac*)	1 & 2	*IgGsensVac*	Estimated	50%	Beta (symmetric)	52.9% (48.6% to 57.8%)	Prior assumed to be around 50%, based on analysis of seroprevalence data [Chapter 4.2]

Note:

1. *Only in candidate models 1a and 1b.*
2. *Only in candidate models 1b and 2b.*
3. *Parameter proposal for vaccine efficacy (VE_tp_1, VE_i_1, VE_t_1, VE_p) and IgG test sensitivity on vaccine-induced immunity (IgGsensVac) during MCMC were restricted from 0% to 100%. Parameters proposal related to duration of protection (d_tp_1 and d_S1) were restricted between 1 and 100 years.*

Table 5.4. Number of doses of varicella vaccines received by age and year in Hong Kong[1, 2].

Age[2]	Calendar Year										
	1996 to 2019	2020	2021	2022	2023	2024 to 2025	2026 to 2030	2031 to 2035	2036 to 2040	2041 to 2045	2046 to 2050
0	1	1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1	1	1
2	1	2	2	2	2	2	2	2	2	2	2
3	1	1	2	2	2	2	2	2	2	2	2
4	1	1	1	2	2	2	2	2	2	2	2
5	1	1	1	1	2	2	2	2	2	2	2
6	1	1	1	1	1	2	2	2	2	2	2
7	1	2	2	2	2	2	2	2	2	2	2
8	1	1	2	2	2	2	2	2	2	2	2
9	1	1	1	2	2	2	2	2	2	2	2
10	1	1	1	1	2	2	2	2	2	2	2
11	1	1	1	1	1	2	2	2	2	2	2
12	1	1	1	1	1	2	2	2	2	2	2
13	1	1	1	1	1	1	2	2	2	2	2
14	1	1	1	1	1	1	2	2	2	2	2
15	1	1	1	1	1	1	2	2	2	2	2
16	1	1	1	1	1	1	1	2	2	2	2
17	1	1	1	1	1	1	1	2	2	2	2
18	1	1	1	1	1	1	1	2	2	2	2
19	1	1	1	1	1	1	1	2	2	2	2
20	1	1	1	1	1	1	1	2	2	2	2
21 to 25	1	1	1	1	1	1	1	1	2	2	2
26 to 30	1	1	1	1	1	1	1	1	1	2	2
31 to 35	1	1	1	1	1	1	1	1	1	1	2
36 to 40	1	1	1	1	1	1	1	1	1	1	1

1) *Number of dose(s) for children in different year and age according to the vaccination statistics and vaccination schedule in Hong Kong. As the second dose uptake for majority of non-UVV eligible children was 10% or below, the vaccinated children in pre-UVV era are assumed to be one-dose.*

2) *Only those aged up to 40 years are shown. Those aged 40 years or above, even in 2050, should be born in 2010 or before and should have received only 1 dose of varicella vaccine in the private market.*

Varicella vaccination uptake and reflection of multiple doses in the model

The immunisation coverage surveys targeting preschool children in Hong Kong were conducted by the Department of Health every three years. The estimated proportion who received one dose of varicella vaccine estimated was used as the varicella vaccine uptake in the model (T_1) [Chapter 4.1].

There is limited data on second dose varicella vaccine uptake, as the first cohort of UVV-eligible children (born 2013) would only receive their second dose when they reach primary one (approximately 6 years of age). The administrative statistics of the School Immunisation Teams (SIT) in 2021 showed that second-dose uptake for the first cohort of UVV-eligible children was 91% [Chapter 4.1]. Both first and second dose varicella vaccines are given with MMR (first dose as separate MMR and mVV injections and second dose as combined MMRV). As first and second dose MMR uptake has been traditionally high at over 95%, second dose varicella vaccine uptake after the COVID-19 pandemic is expected to be similar to that of the first dose. Therefore, varicella vaccine uptake in the model (T_1) is assumed to be unchanged as UVV eligible cohorts advance to the age of receiving their second dose. To model the dose-depended effect of varicella vaccination, one-dose vaccine efficacy parameters were used before 2020, as second dose uptake was generally below 10% during this period. Starting in 2020, two-dose parameters were used for cohorts pre-dominantly receiving two doses [Table 5.4]. While a simplification, this one-dose model should sufficiently represent dose-depended varicella vaccination in Hong Kong and reduce computation time by including fewer compartments.

An overview of vaccine efficacy calibrated in the model

There are several vaccine efficacy parameters in the models which modify varicella infection and disease progression [Table 5.3]. Two of these parameters modify the risk of infection in vaccinees. As described earlier in the model structure, the vaccine efficacy of temporary protection (*VE_temp_protection*) represents the proportion of vaccinees with transient but complete protection from varicella infection following vaccination for the duration of temporary protection (*d_temp_protection*). These two parameters were only present in models 1a and 1b, which included the temporary protection (*Protected 1*) compartment. Another parameter reduces the risk of acquisition of breakthrough varicella infection (*VE_infection*) in vaccinees if exposed to varicella. The risk of infected vaccinees contributing to onward transmission was reduced by another vaccine efficacy parameter, *VE_transmission*. The last vaccine efficacy parameter in the model reduces the risk of infected vaccinees to progress from infection to symptoms severe enough to be notified, *VE_progression*. Both vaccine efficacy against onward transmission (*VE_transmission*) and against disease progression (*VE_progression*) depend on the vaccine efficacy against infection (*VE_temp_protection* in models 1a and 1b as well as *VE_infection* in all models). In models 1a and 1b, vaccine efficacy against acquisition of breakthrough varicella infection (*VE_infection*) depends on the vaccine efficacy of temporary protection (*VE_temp_protection)* and its duration (*d_temp_protection)*. *VE_progression* is an estimate of the degree of protection of the vaccine in alleviating disease severity after infection. Therefore, it does not correspond directly to the vaccine efficacy/ effectiveness estimated in pre-clinical trials or post-licensure studies, of which vaccine effect is a combination of protection against infection and disease severity.

To understand the mechanism of protective effect of varicella vaccination, these vaccination

related parameters were concurrently estimated with the proportion of effective contact (p) during model calibration. As the data available for model calibration covered a period predominated by single dose vaccination [Table 5.4], only one-dose vaccine efficacy parameters were estimated. Two-dose vaccine efficacy parameters were adopted from the literature [Table 5.3].

Vaccine efficacy against acquisition of breakthrough varicella (VE_infection)

Vaccination reduced the risk of acquiring breakthrough infections [Figure 5.1]. One- and two-dose vaccine efficacy against acquisition of breakthrough varicella infection (*VE_infection or VE_i*) was defined as $1 - b_1$ or $1 - b_2$, and was assumed to be very low in previous modelling studies [Figure 5.1 and Table 5.3]. The residual susceptibility for a one-dose vaccinee (b_1) was assumed by Brisson *et al*. to vary between 0.5 to 1.0 in earlier model (76), and was later perceived to be higher at 0.9 by Gao *et al.* (118, 123), and 1.0 by both Brisson *et al.* (65) and van Hoek *et al.* (61). b_1 (VE_i_1) was estimated during my model calibration. The residual susceptibility for two-dose vaccinees (b_2) was assumed to be 1.0 (i.e. $VE\_i_2 = 0$ or vaccine has no protective effect on acquiring infection) by Brisson *et al.* and van Hoek *et al.* (61, 65). In an Australian modelling study, Gao *et al* assumed b_2 to be lower at 0.340, implying second dose vaccination to be more effective at reducing the risk of acquiring breakthrough varicella than a single dose (118). As 2-dose varicella vaccine was substantially more effective than 1-dose vaccine against all varicella in Hong Kong's VE estimation (pooled VE: 81% (95%CI: 78%-84%) for 1-dose vs. 92% (95%CI: 88%-95%) for 2-dose) [Chapter 3] (57), I followed Gao's assumption with b_2 being 0.34 (i.e. $VE\_i_2 = 66\%$).

Vaccine efficacy against onward transmission for breakthrough varicella (VE_transmission$_1$)

Breakthrough varicella is less severe than natural varicella, which may affect its infectiousness as the number of lesions are usually 50 or less in vaccinees, compared to the typical 250 to 500 lesions in natural varicella among the unvaccinated (238). However, little is known about the level and duration of viral loads in upper respiratory secretions and skin lesions of breakthrough varicella, which would likely affect its infectiousness. *RE* is the residual infectiousness in breakthrough varicella (relative to natural varicella) (refer to earlier section `*Force of varicella infection*`). *RE* was assumed to be 0.5 in most other modelling studies (referred as *m*) [Table 5.3], after considering a household transmission study and the less severe symptoms of breakthrough infections (76). The vaccine efficacy against onward transmission (*VE_transmission$_1$ or VE_t$_1$*) is defined as 1 – *RE* and is estimated during model fitting. As there is no data to estimate the 2-dose VE against onward transmission (*VE_t$_2$*), a second dose of the vaccine was assumed to be the same as *VE_t$_1$*, referencing van Hoek *et al* (61).

Vaccine efficacy against disease progression after breakthrough varicella (disease severe enough to be notified) (VE_progression)

With breakthrough varicella being relatively mild compared to natural varicella, these cases are expected to be less likely to seek medical attention and hence be notified. There was no known study on the reporting sensitivity of breakthrough varicella in Hong Kong. Therefore, the vaccine effect at reducing breakthrough infection from progressing to disease severe enough to be reported (*VE_progression or VE_p*) was estimated in the model. During model calibration, the contribution of breakthrough varicella infections, *I$_1$(a`, t)*, to the force-of-infection is reduced by 1 – *VE_progression* to reflect this vaccine effect (refer to later section

'*Likelihood contribution of the observed varicella notification*').

Other vaccine parameters estimated in candidate models

In addition to the three vaccine efficacy parameters discussed above that are common in all candidate models, other parameters are included in models with additional compartments and pathways. The proportion of temporarily protected individuals boosted by contact with varicella cases who acquire permanent protection (k_1 and k_2, in candidate models 1a and 1b) is assumed to be 100%, similar to previous models (61, 118, 237). Three other parameters were included in the model calibration. In models 1a and 1b, the vaccine efficacy of temporary protection from breakthrough varicella (*VE_temp_protection* (*VE_tp*$_1$)) and the duration of this temporary protection (*d_temp_protection (d_tp)*) for first dose vaccinees were included in the model calibration whilst those for second dose were referenced from the literature [Table 5.3]. Another parameter, duration of partial immunity (i.e. vaccinees staying at compartment S_1 before waning to compartment *S*) (*d_S1*), was estimated in models 1b and 2b [Table 5.3].

In addition to the above vaccination-related parameters estimated during model calibration, the proportion of primary vaccine failures after one and two doses (PF_1 and PF_2) are assumed to be 5.0% and 2.5%, taking references from previous modelling studies (61, 65, 76, 118, 123).

IgG test sensitivity to detect vaccine-induced immunity (IgGsensVac)

Commercial EIAs against VZV IgG are less sensitive to vaccine-induced immunity (35). Those who are vaccinated but only have partial immunity are expected to have lower antibody levels, and hence a lower proportion (*IgGsensVac*) would have high enough IgG level to be detected

by EIA [Table 5.1]. My analysis of seroprevalence studies in Hong Kong between 1995 and 2020 showed that the EIA sensitivity to vaccine-induced immunity is likely around 50% and immunity due to infection would be under-estimated if this reduced sensitivity is not taken into account [Chapter 4.2]. Therefore, the IgG test sensitivity to detect vaccine-induced immunity (*IgGsensVac*) is included as a parameter during model calibration [Tables 5.3]. As described earlier, all models were also calibrated with *IgGsensVac* fixed at 88%, following an estimation from the observed seroprevalence of the UVV-eligible cohort in the 2020 survey.

Annual change in notification sensitivity (notiSens)

My previous analyses on varicella notifications between 1999 and 2019 showed an increase in notification rate per 100,000 for adults aged 40 to 59 years and those aged 60 to 79 years [Chapter 4.3]. Since adults aged 40 years or above are mostly seropositive against varicella [Chapter 4.2], the observed increase in notification was unlikely due to an increase in varicella incidence. Instead, an increase in notification sensitivity over the study period might account for these rises. Therefore, a parameter of annual change in notification sensitivity (*notiSens*) was included in the parameter estimation. The annual change in notification sensitivity was assumed to be independent of age.

Parameter adjustment due to COVID-19 pandemic

Since late January 2020, non-pharmaceutical interventions (NPIs) against COVID-19 such as mandatory masking, school closure and working-from-home were implemented in Hong Kong (162). All NPIs was lifted by the Hong Kong Government in March 2023 (239). Varicella transmission was impacted by these NPIs, with very low level of notification during the

pandemic restrictions and shortly afterwards [Chapter 4.3]. These NPIs would be expected to impact the transmission of a range of respiratory viruses, including varicella. Reduced varicella transmission is expected to have a relatively small impact on model calibration, as only seroprevalence data in 2020 would be affected. However, forward simulation of the model in 2021 and beyond involved multiple years of the COVID-19 pandemic during which varicella transmission was suppressed by the NPIs. Therefore, transmission parameters were adjusted to reflect the effect of reduced contacts and masking in the forward simulation in the period between 2020 and 2023.

Reduction in social contacts during COVID-19 pandemic

No contact survey was conducted in Hong Kong during the pandemic to capture the change in social contacts. Daily transactions of Octopus cards, a widely used payment method for public transport and retail payments in Hong Kong, has been used as proxies of mobility and social mixing to study COVID-19 transmission in Hong Kong (240). The data was stratified into children (aged 3 to 11 years), student (students aged <26 years old), adult (non-student adults aged under 65 years) and elderly (adults aged 65 years or above), which were used as age-stratified contact matrix (240). However, this data was only published between 1 Jan and 31 May 2020. On the other hand, Google mobility data, reflecting users of Google Locations in various settings, has been used to understand intra-city/ country mobility during the pandemic (241, 242). These data were percentage change relative to a five-week baseline of 3 January to 6 February 2020 and were available between 15 February 2020 and 15 October 2022. These covered most of the period where NPIs were implemented in Hong Kong. Correlation between the two data sets in the common period showed that Google mobility in the public transport and retail and recreation settings had the highest correlation with the Octopus transaction data

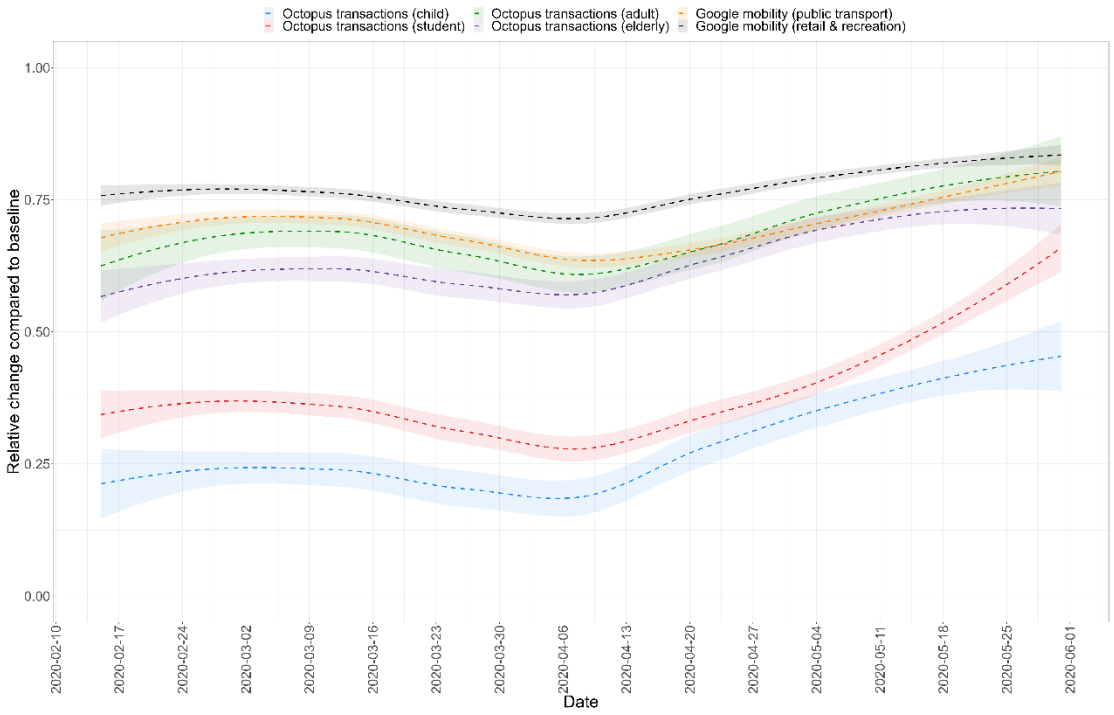
[Table 5.5].

A comparison of the two data sources in the common period showed that Google mobility (public transport as well as retail and recreation) had similar relative change with the Octopus transactions among adults and the elderly, and had lower relative changes compared to Octopus transactions among children and students [Figure 5.5]. This might be explained by the fact that school closure was in place intermittently since 23 January 2020, while there had never been lockdowns that affected the entire territory. Hence, the reduction in social contacts in Hong Kong during the pandemic should have disproportionally affected children and students. To cater for the reduction in social contacts during the pandemic, the annual change in contacts relative to pre-pandemic levels were computed between 2020 and 2022, based on the Google mobility (public transport) adjusted by the Octopus transactions. Between 1 January and 14 February 2020, the relative change in Octopus transactions was used as Google mobility data was not available. Between 15 February 2020 and 15 October 2022, Google mobility data (public transport) by age was computed by adjusting the data with the median ratio between the weekly Octopus transactions (children, students, adults and elderly) and Google mobility (public transport) in a common period (15 February 2020 and 31 May 2020). The annual change in contacts was computed by age and year [Table 5.6] and was used to account for the reduced contacts during the pandemic by multiplying the POLYMOD contact matrix with these reduced contacts between 2020 and 2022 [Table 5.7]. No further adjustment in social contacts was conducted in 2023 and beyond as face-to-face classes had been gradually resumed since late 2022 (243).

Table 5.5. Correlation between Octopus transaction and Google mobility data, 15 February to 31 May 2020, Hong Kong.

Google mobility	Octopus transaction	Pearson's correlation	p-value
Parks	Child	0.23	0.016
	Student	0.11	0.252
	Adult	0.06	0.540
	Elderly	0.19	0.045
Public transport	Child	0.54	<0.001
	Student	0.72	<0.001
	Adult	0.64	<0.001
	Elderly	0.66	<0.001
Residential	Child	-0.45	<0.001
	Student	-0.54	<0.001
	Adult	-0.40	<0.001
	Elderly	-0.42	<0.001
Retail & recreation	Child	0.72	<0.001
	Student	0.79	<0.001
	Adult	0.60	<0.001
	Elderly	0.72	<0.001
Supermarket & pharmacy	Child	0.63	<0.001
	Student	0.35	<0.001
	Adult	-0.07	0.495
	Elderly	0.18	0.066
Workplaces	Child	0.14	0.163
	Student	0.42	<0.001
	Adult	0.59	<0.001
	Elderly	0.52	<0.001

Figure 5.5. Octopus transactions and Google mobility, 15 February 2020 and 31 May 2020[1], Hong Kong.



1. Data included in the period where both Octopus transactions and Google mobility were available.

Effects of face masking on varicella transmission

A meta-analysis showed that wearing masks significantly reduced the risk of the wearers against infection of coronaviruses including SARS, SARS-CoV-2 or MERS (RR 0.34 [95%CI: 0.26 to 0.45]). In Hong Kong, face masking was made mandatory in public areas and transports between 23 Jan 2020 and 28 February 2023 (243). A survey in a secondary school conducted between May and June 2023 showed that more than 80% of students still voluntarily wore masks in schools despite lifting of the requirement (244). Hence, the relative susceptibility to varicella infection for vaccinees (b_1 and b_2) was adjusted by 0.34 between 2020 and 2023 to reflect the effect of masking in reducing infection risk [Table 5.7].

Table 5.6. Change in social contacts relative to before 2020 (pre-pandemic), based on Octopus transaction and Google mobility data, Hong Kong[1].

Age group Contact matrix	Adjusted Google mobility data	2020	2021	2022
0 to 5 6 to 10	Child	0.334	0.348	0.321
11 to 15 16 to 20	Student	0.440	0.483	0.446
21 to 25 26 to 30 31 to 35 36 to 40 41 to 45 46 to 50 51 to 55 56 to 60 61 to 65	Adult	0.741	0.888	0.819
66 to 70 >70	Elderly	0.683	0.811	0.747

1. *The table showed estimated changes in contacts during the pandemic. For instance, the contact for children in 2020 was 0.33, indicating a 67% reduction of contacts compared to pre-pandemic.*

Table 5.7. Reduction of contacts and masking effect in model simulation.

<table>
<tr><th rowspan="2">COVID-19 Pandemic</th><th rowspan="2">Year</th><th colspan="3">Model calibration</th><th colspan="3">Forward simulation</th></tr>
<tr><th>Reduced contact</th><th>Masking effect[3]</th><th>FOI_hz</th><th>Reduced contact</th><th>Masking effect[2]</th><th>FOI_hz</th></tr>
<tr><td>Pre-pandemic</td><td>1995 to 2019</td><td>N</td><td>N</td><td>Y</td><td colspan="3" rowspan="2">N/A</td></tr>
<tr><td rowspan="4">Pandemic</td><td>2020[1]</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td>2021</td><td colspan="3" rowspan="3">N/A</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td>2022</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td>2023[2]</td><td>N</td><td>Y</td><td>Y</td></tr>
<tr><td>Post-pandemic</td><td>2024 and beyond</td><td>N</td><td>N</td><td>Y</td></tr>
</table>

1. *Only serology data of 2020 was included in the model calibration. Notification data up to 2019 were included in the calibration.*
2. *All NPI lifted in Mar 2023 in Hong Kong.*
3. *Masking effect assumed to scaled down infection by 0.34.*

Model calibration

Model calibration was conducted using Monte Carlo Markov Chain (MCMC) methods with a Metropolis-Hastings (MH) algorithm applied to the likelihood of the varicella seroprevalence, notification and the proposed free parameters (θ) [Table 5.3]. Candidate parameters were sampled using a multivariate Gaussian (normal) distribution with adaptive MCMC to alter the variance and co-variance of the proposal distribution. The proposal distribution started with a symmetric variance, and its shape was altered according to the covariance matrix of the accepted values. The adaptive MCMC started after the 2,500th iteration, with the covariance matrix and scaling factor altering every 100 iterations. Pilot runs were conducted by running different proposal distributions for the initial scaling factor.

The model was simulated based on the proposed parameters and other fixed parameters by finding the numerical solutions to the ODEs using the *deSolve* package (245, 246). The model was initiated in the absence of vaccination and a totally susceptible population, with the exception of one pre-infectious individual. To mimic the pre-vaccine era (calendar year 1995), an equilibrium state was ensured to be reached using the *runsteady()* function. Once the steady state was reached, the post-vaccine era was simulated using the *ode()* function for 25 years (between 1996 and 2020) to obtain the daily age-specific population in different epidemiological states (compartments), based on the varicella vaccine uptake of each year (T_1). The posterior distribution of the parameters given the data is proportional to the likelihood of the observed data from the modelled outputs based on the (proposed) parameters (147). The likelihood of the model simulated data given the parameters was computed and evaluated by comparing with the previous likelihood using the Metropolis-Hastings algorithm. If the proposed parameters were rejected, the last accepted parameters were used to generate a new

set of candidate parameters. The process was repeated for 50,000 iterations with a burn-in period of 5,000 iterations. Median and 95% credible intervals of the accepted parameters were computed.

Likelihood computation

The log-likelihood of each set of proposed parameters was computed based on a combination of the binomial likelihood of the six VZV seroprevalence survey data between 1995 and 2020 [Chapter 4.2], the multivariate normal likelihood of the age-specific notifications between 1999 and 2019 [Chapter 4.3], as well as the likelihood of the proposed parameters compared to the priors [Table 5.3].

Likelihood contribution of the observed varicella seroprevalence

The Department of Health Hong Kong conducted six varicella seroprevalence surveys every five years between 1995 and 2020. Details of the seroprevalence surveys were given in Chapter 4.2. To compare the model simulation to the observed seroprevalence, the proportion of individuals in compartments having full (MI, R, R_1, P_1 (for models 1a and 1b)) and partial immunity (S_1, E_1, I_1) to varicella was computed [Table 5.1]. As commercial EIA are less sensitive in detecting varicella IgG induced by vaccination than those by natural infection, the proportion of individuals with partial immunity were discounted by the parameter $IgGsensVac$. The seroprevalence in the simulated model was computed for each age group and year (every five years between 1995 and 2020) corresponding to the observed data. The log-binomial likelihood of the observed age-specific seroprevalence in the six surveys given the proposed parameter θ (L_s) was calculated as follow:

$$L_S(x(a,y), t(a,y) \mid \theta) = log\binom{t}{x} + \sum (x(a,y)\, log(q(a,y) + (t(a,y) - x(a,y))\, log(1 - q(a,y))$$

where,

x(a,y) is the number of individuals tested positive in the serosurveys of age *a* and year *y*.

t(a,y) is the total number of individuals tested in the serosurveys of age *a* and year *y*.

q(a,y) is the proportion seropositive of age *a* and year *y* in the model simulated with the proposed set of parameter θ.

$log\binom{t}{x}$ is a constant term based only on the observed seroprevalence which does not change with different parameter proposals. Therefore, it is omitted when calculating the acceptance probability in the MCMC process.

Likelihood contribution of the observed varicella notification

Age-specific notifications of chickenpox between 1999 to 2020 are available and were analysed in Chapter 4.3. The focus of fitting notification data is on the changes in age-specific incidence (trend) over the study period when varicella vaccine uptake was rapidly increasing. Varicella notifications were greatly reduced due to the NPIs implemented during the COVID-19 pandemic. In addition, the sensitivity of varicella notification might vary during the pandemic. Potential factors affecting reporting sensitivity in the pandemic included closure of schools which contributed to reporting varicella outbreaks and notification, and children with mild varicella less likely to seek medical consultation during the pandemic. However, there was no relevant data to specifically adjust for these potential changes during the pandemic. Therefore, notification data for 2020 were not included in the model fitting. Several steps were taken to generate the modelled varicella notifications for model calibration. The number of

daily new varicella infections $NI_v(a, t)$ consisted of the natural infections for the unvaccinated ($NI_n(a, t)$) and breakthrough infections for those vaccinated ($NI_b(a, t)$). The daily new natural and breakthrough infections for each age group were extracted based on the force of varicella infection (λ_V), the number of susceptible (S and S_1) and the reduced susceptibility of vaccinees to infection (b_1 or $1\text{-}VE\_infection_1$).

$$NI_v(a,t) = \lambda_v(a,t)S(a,t) + \lambda_v(a,t)S_1(a,t)b_1$$
$$NI_v(a,t) = \lambda_v(a,t)S(a,t) + \lambda_v(a,t)S_1(a,t)(1 - VE\_infection_1)$$
$$NI_v(a,t) = NI_n(a,t) + NI_b(a,t)$$

The model-simulated infections were first scaled by the ratio between the actual and model population for different age groups between 1999 and 2019. The modelled infections were then adjusted by the parameter of annual change in notification sensitivity (*notiSens*) [described in earlier section '*Change in varicella notification sensitivity*']. As only a fraction of infections would be reported, the number of modelled notifications was obtained by adjusting the number of modelled infections with the ratio of notifications to infections, which represented disease progression from infections. Given the difference in health-seeking behaviour and clinical severity by age, the reporting sensitivity of varicella notification is likely age-dependent. To account for the age-varying varicella reporting sensitivity while avoiding estimation of multiple parameters, the age-specific rate of disease progression from infection, *rateDPI(a),* was computed by dividing the total number of observed notifications during the study period ($c(a)$) over the respective number of new infections ($NI_v(a)$) for every age group.

$$rateDPI(a) = c(a)/NI_v(a)$$

The *rateDPI(a)* was used to scale the number of modelled infections each year ($NI_v(a, t)$) to obtain the modelled varicella notifications ($N_v(a, t)$). As breakthrough varicella diseases are generally milder and hence less likely to be reported, the number of modelled notifications among vaccinees (breakthrough varicella) are also modified by the vaccine efficacy against disease progression (*VE_progression*), relative to natural varicella:

$$N_v(a,t) = (NI_n(a,t) + NI_b(a,t)(1 - VE\_progression))(rateDPI(a))$$
$$N_v(a,t) = N_n(a,t) + N_b(a,t)$$

The log-likelihood based on a multinomial distribution of the observed age-specific notifications compared with the modelled notifications given the proposed parameters θ (L_n) was computed for every age group between 1999 and 2019. This evaluated the relative distribution of notifications over the study period for each age group, fitting the trend of age-specific notifications over the year:

$$L_n(c(a,y) \mid \theta) = log(O!) - \sum log(c(a,y)!) + \sum (c(a,y) log(PN(a,y))$$

where *O* is the total number of observation and *c(a,y)* is the number of observed notifications in age *a* and year *y*. As the first two coefficient terms depend only on the observed data, they do not change with proposed parameters and hence are ignored during computation of the log-likelihood. *PN(a, y)* is the proportion of modelled notified cases in year *y* for age *a,* which represents the probability of cases in different age groups as predicted by the model.

Overall likelihood

The log-likelihood contribution of each sampled set of parameters, (L_θ) through their prior, was computed by evaluating the probability density function of the sampled values against their respective prior distributions [Table 5.3]. The shape and skewness of the distributions are based on prior belief, if available [Table 5.3]. The overall likelihood combined the likelihood of the observed serology, notifications and the sampled parameters. Due to the difference in the scales of serology and notification data, the likelihood of the notifications is scaled down (or penalised) so that both likelihoods of the observed serology and notification contributed similarly to the overall likelihood. This assumed that the value of information from each of the two is similar instead of being overwhelmingly driven by much larger sample size of notification data.

Model selection

The main model for this study was selected based mainly on the quality of the candidate models' fitting to the seroprevalence and notification data. Model fit to all seroprevalence and notification data was inspected while taking into account some potential limitations of the data identified in earlier analyses, such as the lower than expected seroprevalence in 2015 and 2020 for older children [Chapter 4.2] and the potential misclassification of shingles to chickenpox in older adults [Chapter 4.3]. These analyses were supplemented by comparing the deviance information criteria (DIC) of the model fits (147), as well as the quality and plausibility of parameters estimated.

To support model selection with a quantitative comparison of model fit, I calculated the DIC for MCMC chains using the following formula (147).

$$DIC = \overline{D} + pD$$

$$DIC = \overline{D} + (\overline{D} - \widehat{D})$$

Where $\overline{D}$ is the average deviance (D) of each set of proposed parameter values that were evaluated, pD is the penalty term (which represents the effective number of parameters), and $\widehat{D}$ is the deviance calculated at the median parameter values of the posterior distribution (147). Deviance is calculated as log-likelihood of the MCMC iterations, multiplied by -2.

After selecting the main model, the remaining candidate models were included as sensitivity analyses.

Data analysis

Model convergence was assessed by examining the mixing and density distribution of the posterior distribution. Medians and 95% credible intervals (CI) of the free parameters were computed based on the posterior distribution of the free parameters, after removing the samples in the burn-in period (5,000) of the MCMC chain. Analyses of the model were conducted based on 1,000 posterior draws (thinned every 50 iterations). Mean and 95%CI of the modelled seroprevalence and notifications were computed and compared to the observed data.

The model was programmed in R (247). To speed up model simulation, the functions of the ODE were compiled in C++ and was integrated into R using the *Rcpp* and *RcppArmadillo* packages (248, 249). All analyses of the model outputs were conducted in R (247).

Forward simulation

To project varicella transmission dynamics in 2021 and beyond, 100 parameter combinations were randomly sampled from the posterior to forward simulate the model till 2050. The main analysis for forward simulations focuses on the projections up to 2035, with the longer-term projections up to 2050 for illustrative purposes only as Supplementary materials, as major society changes such as demographics and social contact patterns are likely to occur over this time frame. Different catch-up vaccination programmes (CUP) were also simulated to understand their effect on varicella incidence [Table 5.8]. The aim of the CUP is to improve the immunity against varicella for cohorts with low seroprevalence. In Hong Kong, there are vaccination delivery strategies that can be adapted for varicella CUP. These include DH's School Immunisation Teams which routinely provide outreach vaccination to primary schools, Student Health Services with clinics located in different parts of the territory and a Vaccination Subsidy Scheme which provides allowance for certain funded vaccinations such as adult influenza and pneumococcal vaccination in the private sector (250). WHO recommends countries with UVV to sustain varicella vaccine coverage at 80% or above (251). Therefore, cohorts not eligible for UVV with a modelled seroprevalence lower than 80% in 2020 were included in the CUP. These consisted of seven non-UVV eligible cohorts born 2006 to 2012, who will turn 13 to 19 years in 2025 [Table 5.8].

Referencing the varicella catch-up vaccination for adolescents in the US (55), Canada (252) and Australia (253, 254), one or two doses of catch-up varicella vaccines will be offered to non-immune individuals of the CUP cohorts. CUP was assumed to start in 2025 and would last throughout the year. In Hong Kong, the first dose HPV vaccination uptake among Primary 5 and 6 girls (about 11 and 12 years old) delivered by the school outreach programme between

school years 2019/20 and 2022/23 was 87% to 91% (255). Considering the proposed varicella CUP cohorts will be older at the time of vaccination (13 to 19 years old) and outreach vaccination may not be available, a slightly lower CUP uptake of 80% was assumed by end of 2025.

Forward simulation was carried out for the main and candidate models. With the unknown effect of the COVID-19 pandemic on reporting sensitivity of varicella notifications and further maturation of UVV, the incidence of new infections was analysed. The incidence of varicella hospitalisation was also projected to understand the effect of CUP on reducing secondary care utilisation. Assuming only natural varicella would lead to hospitalisations, the age-specific ratios of modelled notifications to observed hospitalisations was computed [Supplementary Table S.5.1]. The age-specific incidence of varicella hospitalisations for different age groups was projected using these ratios with the simulated number of notifications. Median and 95% confidence intervals of the predicted new infections for different scenarios were summarised and compared. The effect of CUP was estimated by comparing the change in proportion susceptible and incidence of new infections. The incidence rate ratio (IRR) and its 95%CI of the overall and age-specific incidence of varicella infections and hospitalisations under different CUP scenarios was computed. As there is greater uncertainty for long-term projections, the IRR was computed based on projection up to 2035 (i.e. ten years after CUP). IRR up to 2050 was also calculated as a sensitivity analysis.

Table 5.8. Eligibility of proposed varicella catch-up vaccination (CUP) in 2025 and the corresponding modelled and observed seroprevalence in 2020 and varicella vaccine uptake.

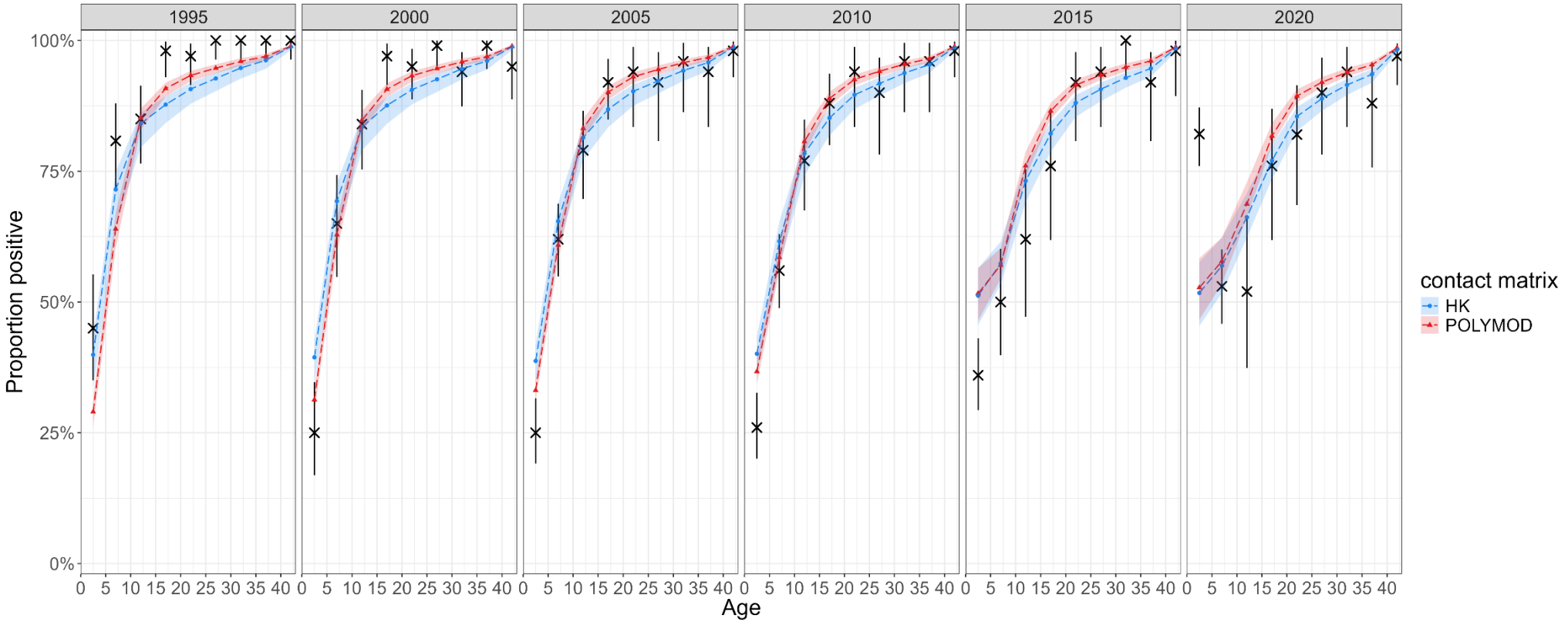
Birth cohorts	UVV eligible	Age (years) 2020	Observed seroprevalence 2020 (%)	Modelled seroprevalence 2020 (%)	Varicella vaccine uptake (%)	CUP inclusion (cohorts included)	Age (years) 2025
2016 to 2019	Y	1 to 4	82%	53%	99%	N	NA
2011 to 2015	2013 to 2015 only	5 to 9	83%	58%	81%	Y (2011 to 2012)	13 to 14
2006 to 2010	N	10 to 14	52%	69%	38%	Y (2006 to 2010)	15 to 19
2001 to 2005		15 to 19	76%	81%	25%	N	NA
1996 to 2000		20 to 24	82%	89%	11%		
1991 to 1995		25 to 29	90%	92%	0%		
1986 to 1990		30 to 34	94%	94%	0%		
1981 to 1985		35 to 39	88%	95%	0%		
≤1980		≥40	97%	98%	0%		

Results

Comparison of model fitting with POLYMOD and Hong Kong contact matrices

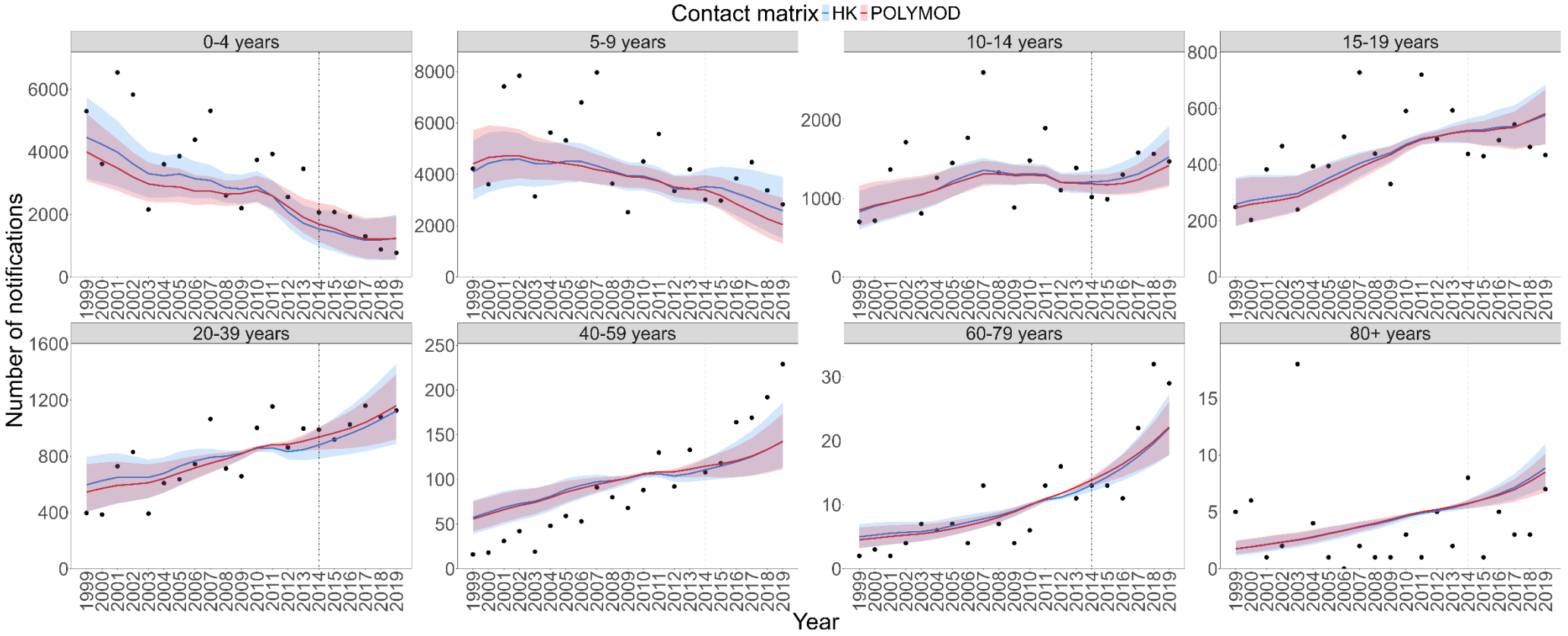
The POLYMOD contact matrix improved fitting of the model to seroprevalence data for adolescents and young adults, especially in year 1995, 2000 and 2005 [Figure 5.6]. Higher seropositivity was modelled in these age groups in all years when using the POLYMOD matrix. In contrast, lower seropositivity was modelled for young children. The fitting to notification data was similar [Figure 5.7]. The more frequent contacts among adolescence in POLYMOD is plausible with the higher FOI estimated in teenagers aged 10 to 14 years based on pre-vaccine era serological data in 1995 [Chapter 4.2] and the high level of secondary school attendance in Hong Kong. Due to the provision of free education through age 6 to 18 years in Hong Kong, the attendance of secondary schools for teenagers between 12 and 17 years was very high (≥96% surveyed in 2006 and 2016) (256). With this high school attendance rate, a higher contact rate should better reflect the mixing among the adolescents. Hence, the age-specific contact pattern from the POLYMOD study was used to inform the mixing of population in the model.

Figure 5.6. Fit to varicella seroprevalence data of model 2a using Hong Kong or POLYMOD contact matrices, Hong Kong, 1995 to 2020.



Note: IgG test sensitivity to detect vaccine-induced immunity was included in the model calibration.

Figure 5.7. Fit to varicella notification data of model 2a using Hong Kong or POLYMOD contact matrices, Hong Kong, 1995 to 2019.



Dots: observed notification; Line (ribbon): modelled notification.

IgG test sensitivity to detect vaccine-induced immunity was included in the model calibration. The vertical dashed line indicates the launch of UVV in 2014. Data fit included notifications of all ages between 1999 (first year of notification started) and 2019 (last year of age-specific notification data available before COVID-19 pandemic). Data of 2020 was not included in the model calibration.

Model convergence and mixing of MCMC chains

All MCMC chains for different candidate models mixed well and were stationary, as shown by traces of the posterior likelihood [Figure 5.8] and the posterior parameters after the burn-in period [Figure 5.9]. The acceptance of all models was between 27% and 34% [Table 5.9]. The effective sample size (ESS) for all parameters estimated in different models exceeded 200, except for the parameter *VE_progression* in model 2b – fix IgG test sensitivity (ESS: 188) [Table 5.10]. The majority of the parameters estimated had an ESS of 400 or above, indicating a good number of independent samples were tested during the model calibration.

Parameter calibration

Most of the free parameters converged well with identifiable posterior peaks when IgG test sensitivity was included in the parameterisation, except for the duration of partial immunity (stay in the vaccinated-susceptible compartment *S1*) (*d_S1*) [Figure 5.10a]. On the other hand, several of the free parameters did not converge well with poorly defined peaks or flat posteriors with IgG test sensitivity fixed [Figure 5.10b]. These included the duration of temporary protection (*VE_temp_protection*$_1$) (model 1b), VE against disease progression of breakthrough infection (*VE_progression*) (models 1b and 2b), and the duration of stay in the vaccinated-susceptible compartment (*d_S1*) for model 2b. The parameters calibrated by different models are reported and contrasted below.

Proportion of effective contact leading to infection (*p*)

There was no difference in this parameter estimated by different models as the median estimated *p* varied only slightly between 4.8% to 5.3% with narrow credible intervals [Table 5.9 and Figure 5.10].

Vaccine efficacy of temporary protection from breakthrough varicella (*VE_temp_protection*$_1$) and duration of temporary protection (*d_temp_protection*$_1$)

Estimation of these two parameters was included in fitting of models 1a and 1b, which consist of the temporary protection compartment (Protection *P1*). Posterior samples of *VE_temp_protection*$_1$ converged well for different model variations and were estimated to be moderate to high (median 66.6% to 83.7%), which was higher than the prior of 60% [Table 5.9 and Figure 5.10]. The duration of temporary protection (*d_temp_protection*$_1$) was estimated to be relatively short (median: 1.4 to 13.4 years), compared to the prior of 25.0 years referenced from other modelling studies (61, 237). There was a negative correlation between these two parameters [Table 5.9]. Fixing IgG test sensitivity yielded the most extreme estimation for both parameters, with the lowest *VE_temp_protection*$_1$ being 66.6% (95%CI 58.1% to 76.6%) and the longest *d_temp_protection*$_1$ being 13.4 years (95%CI 7.8 to 22.3 years) for model 1b, compared to the highest estimated *VE_temp_protection*$_1$ at 83.7% (95%CI 68.6 to 93.8%) with the shortest *d_temp_protection*$_1$ at 1.4 years (95%CI: 1.0 to 2.4 years) for model 1a. In contrast, when IgG test sensitivity was also included in the fitting, there was no difference in the distribution of the posterior samples for both *VE_temp_protection*$_1$

(model 1a: 71.3% [95%CI: 56.9 to 89.4%] and model 1b: 72.1% [95%CI: 57.1% to 88.1%]) and *d_temp_protection*$_1$ (model 1a: 5.7 years [95%CI: 2.8 to 12.0 years] and 5.8 years [95%CI: 7.8 to 22.3 years]) [Table 5.9 and Figure 5.10].

Vaccine efficacy against acquisition of breakthrough varicella (*VE_infection*$_1$)

VE_infection$_1$ converged well for all models [Figures 5.9 and 5.10]. One dose of varicella vaccine appeared to be not effective in protecting vaccinees against infections, as the median VE was estimated to be between 10.0% and 14.1% for various models [Table 5.9]. These estimates are lower than the prior of 50% but similar to the low level of protection assumed in some of the previous modelling studies [Table 5.3].

Vaccine efficacy against onward transmission for breakthrough varicella (*VE_transmission*$_1$)

The posterior sample distribution of *VE_transmission*$_1$ was concentrated at over 90% for most models [Figure 5.10], except for a more spread distribution for model 1b – IgG test sensitivity fixed with a lower estimate and wider credible intervals (median: 88.8% (95%CI: 40.2% to 99.6%)). These estimates are higher than the prior (50%) and assumptions from other modelling studies [Table 5.3].

Vaccine efficacy against disease progression after breakthrough varicella (disease severe enough to be notified) (*VE_progression*)

Compared to other VE estimation, the posterior distribution of *VE_progression* was

more diffuse with more variation between different models [Table 5.9 and Figure 5.10]. Peaks were identifiable for models with IgG test sensitivity fitted, ranging between 39.2% and 44.8% for models 1a and 1b, to 59.6% and 65.7% for models 2a and 2b [Table 5.9 and Figure 5.10a]. With IgG test sensitivity fixed, peaks of posterior samples were only clear for model 2a (median: 61.2%) and 2b (median: 88.0%) with wide credible intervals. The posterior sample distribution for models 1a and 1b were relatively flat [Figure 5.10b].

Duration of partial immunity (stay at compartment *S1* before waning to compartment *S*) (year) (*d_S1*)

d_S1 was only available for models 1b and 2b. The distribution of posterior samples for this parameter widely spread between 20 to 100 years without a clear peak identified for models 1b and 2b when IgG test sensitivity was fitted [Figure 5.10a]. When IgG test sensitivity was fixed, the higher duration of partial immunity was quickly rejected during the burn-out period. The peaks were more identifiable with a mostly lower parameter space explored (mostly below 10 years) [Figure 5.10b].

Annual change in notification sensitivity (*notiSens*)

The parameter converged well with similar posterior distribution when IgG test sensitivity was fitted [Figure 5.10a], ranging from 5.5% (95%CI: 3.3% to 7.6%) for model 2b to 6.1% (95%CI: 3.7% to 8.3%) for model 2a [Table 5.9]. These were lower than the 7.5% assumed based on the per year increase in notification for adults in the previous analyses, indicating a potentially lower annual increase in children. With IgG

test sensitivity fixed, the posterior distribution was still relatively sharp except for model 1a [Figure 5.10b]. For models 1a and 2a, the median *notiSens* estimated was similar, regardless of whether IgG test sensitivity was fitted or fixed [Table 5.9]. On the other hand, fixing the IgG test sensitivity at 88% for models 1b and 2b resulted in a significantly lower per year change in notification sensitivity (model 1b: 2.8% [95%CI: 1.3% to 4.2%] and model 2b: 2.1% [95%CI: 0.6% to 3.7%]).

IgG test sensitivity to vaccine-induced immunity (*IgGsensVac*)

The posterior samples of *IgGsensVac* of all models showed sharp peaks for IgG test sensitivity to vaccine-indued antibody [Figure 5.10a]. The estimated sensitivity was moderate for models without temporary protection and was similar to the prior of 50% (model 2a: 53.2% [95%CI: 48.5% to 58.2%] and model 2b: 55.2% [95%CI: 50.2% to 60.1%]). For models 1a and 1b with a temporary protection compartment which allowed a certain proportion of vaccinees to have a higher level of detectable antibody [Table 5.1], the *IgGsensVac* estimates were significantly lower (model 1a: 31.0% [95%CI: 23.0% to 39.4%] and model 2b: 31.1% [95%CI: 22.9% to 40.1%]). All estimates were substantially lower than the 88% that were assumed when the parameter was fixed.

Table 5.9. Comparison of candidate models and parameters estimated.

Model – IgGsensVac	1a – fit	1a – fix	1b – fit	1b – fix	2a – fit	2a – fix	2b – fit	2b - fix
Model structure								
Temporary protection (P_1)	Y				N			
Waning of partial immunity (from S1 to S)	N		Y		N		Y	
Number of parameters fitted	8	7	9	8	6	5	7	6
MCMC								
Acceptance (%)	30%	30%	27%	28%	29%	33%	27%	34%
DIC	8128	8418	8124	8175	8081	8311	8078	8143
Parameter estimation^								
Median parameters estimated (95% CI)								
Proportion of effective contact leading to infection (%) (*p*)	5.3 (5.0 – 5.6)	4.9 (4.6 – 5.2)	5.2 (4.9 – 5.6)	4.8 (4.5 – 5.0)	5.3 (5.0 – 5.7)	4.9 (4.6 – 5.7)	5.3 (4.9 – 5.6)	4.9 (4.6 – 5.1)
IgG test sensitivity to detect vaccine-induced immunity (%) (*IgGsensVac*)	31.0 (23.0 – 39.4)	Fixed at 88%	31.1 (22.9 - 40.1)	Fixed at 88%	53.2 (48.5 - 58.2)	Fixed at 88%	55.2 (50.2 - 60.1)	Fixed at 88%
VE of temporary protection from breakthrough varicella (%) (*VE_temp_protection*$_1$)	71.3 (56.9 - 89.4)	83.7 (68.6 - 93.8)	72.1 (57.1 - 88.1)	66.6 (58.1 - 76.6)	Not applicable (Fixed at 0%)			
Duration of temporary protection (year) (*d_temp_protection*$_1$)	5.7 (2.8 - 12.0)	1.4 (1.0 - 2.4)	5.8 (3.1 - 11.9)	13.4 (7.8 – 22.3)	Not applicable			

Model – IgGsensVac	1a – fit	1a – fix	1b – fit	1b – fix	2a – fit	2a – fix	2b – fit	2b - fix
Duration of partial immunity (stay at S1 before waning to S) (year) (*d_S1*)	NA	NA	54.7 (18.5 - 96.6)	1.1 (1.0 - 1.4)	NA	NA	69.6 (33.0 - 98.5)	6.7 (4.9-9.3)
Vaccine efficacy against acquisition of breakthrough varicella (%) (*VE_infection*$_1$)	13.0 (4.9 - 24.7)	12.2 (4.8 – 24.8)	12.3 (4.6 - 24.4)	10.0 (3.6 - 21.1)	14.1 (5.1-27.9)	13.9 (5.3-27.8)	13.7 (5.0 – 28.4)	10.7 (4.0-21.9)
Vaccine efficacy against onward transmission for breakthrough varicella (%) (*VE_transmission*$_1$)	97.2 (85.6 - 99.9)	99.2 (95.5 – 100.0)	97.2 (85.9 - 99.9)	88.8 (40.2 - 99.6)	98.1 (89.8-99.9)	99.2 (95.4-100.0)	98.3 (91.2 - 99.9)	98.3 (91.2-99.9)
Vaccine efficacy against disease after breakthrough varicella (disease severe enough to be notified) (%) (*VE_progression*)	39.2 (3.5 – 71.6)	56.0 (15.5 - 80.7)	44.8 (4.4 - 81.6)	52.5 (2.3 – 96.8)	59.6 (19.3-84.4)	61.2 (15.3-84.6)	65.7 (22.8 - 89.0)	88.0 (53.9-99.5)
Annual change in notification sensitivity (*notiSens*) (%)	6.0 (4.2 – 8.1)	6.2 (3.9 – 8.3)	5.7 (3.8 – 7.8)	2.8 (1.3 – 4.2)	6.1 (3.7-8.3)	6.2 (3.8 – 8.6)	5.5 (3.3 – 7.6)	2.1 (0.6-3.7)

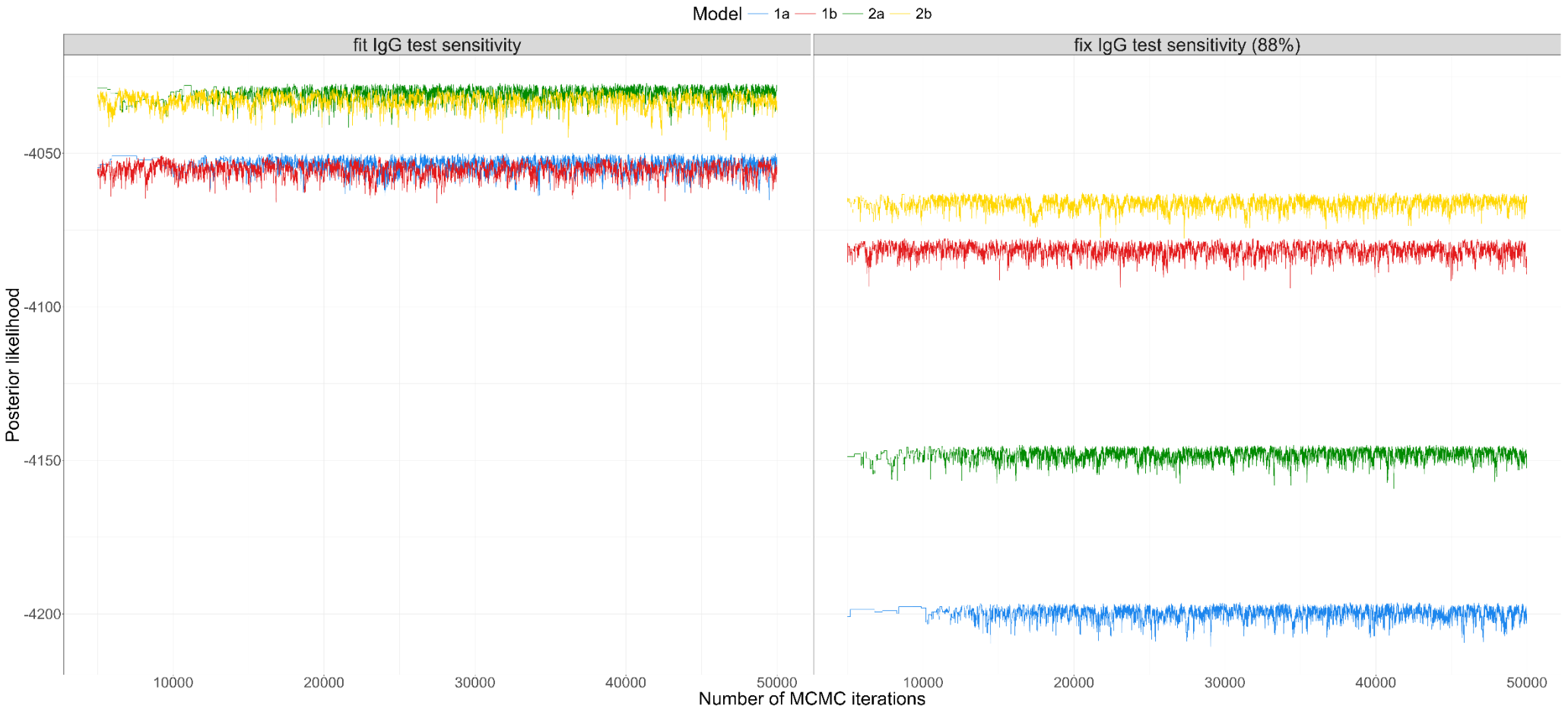
^Parameters on vaccine efficacy and IgG test sensitivity estimated in the model are bound between 0 and 100%, whilst parameters related to duration of protection and immunity (d_temp_protection$_1$ and d_S1) are bound between 1 and 100 years.

Table 5.10. Effective sample sizes (ESS) of free parameters included in model calibration.

Model	IgG test sensitivity to vaccine-induced immunity	Proportion of effective contact (p)	VE_temp_protection	d_temp_protection	VE_infection$_1$	VE_Transmission$_1$	VE_progression	Duration of partial immunity	Annual change in notification sensitivity	IgG test sensitivity to vaccine-induced immunity
1a	Fit	447	427	554	435	1250	363	NA	399	427
	Fixed (88%)	370	317	402	407	1633	308		324	NA
1b	Fit	411	303	362	389	1492	388	507	450	525
	Fixed (88%)	684	784	861	1791	697	509	684	820	NA
2a	Fit	643	NA	NA	576	758	459	NA	642	668
	Fixed (88%)	441			506	1419	323		404	NA
2b	Fit	318			378	2272	229	410	283	331
	Fixed (88%)	249			292	2193	188	333	266	NA
Minimum		**249**	**303**	**362**	**292**	**697**	**188**	**333**	**266**	**331**
Mean		**445**	**458**	**545**	**597**	**1464**	**346**	**484**	**448**	**488**

Note: Parameters not included in a particular model – IgG test sensitivity variation is highlighted in grey and labelled as NA.

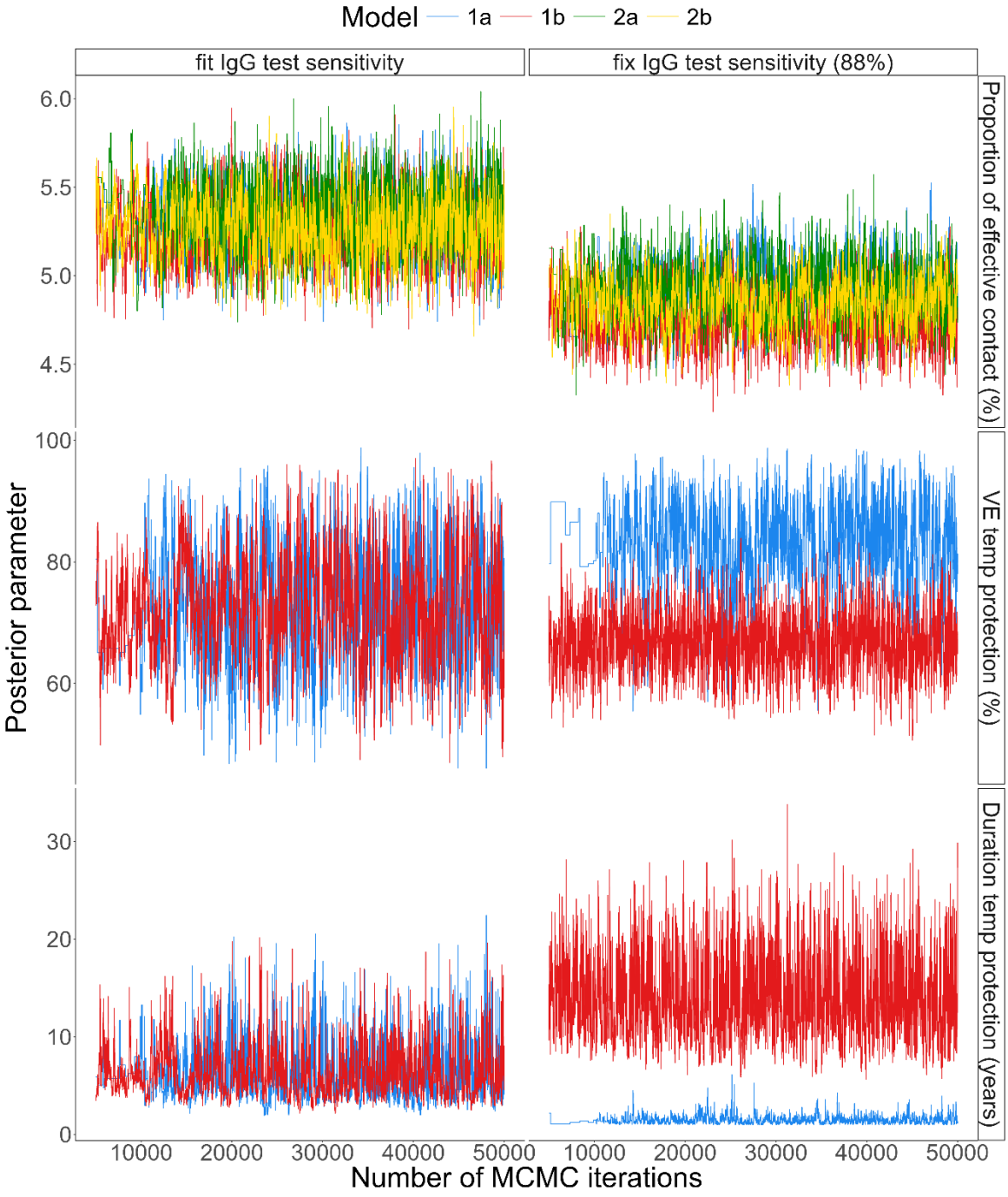
Figure 5.8. Posterior log-likelihood for different candidate models.



Note: Burn-in period of first 5,000 iterations was removed from the above plot.

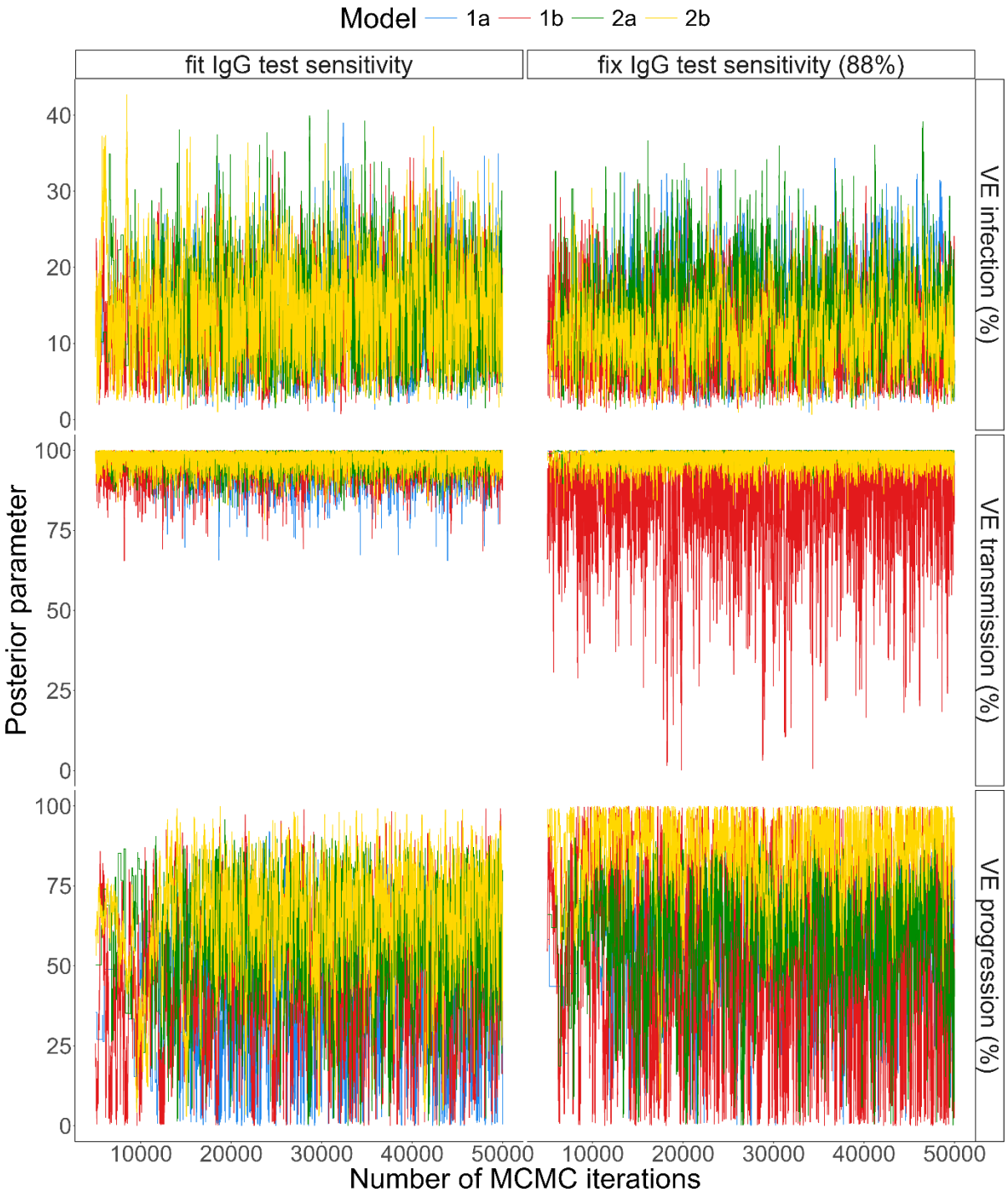
Figure 5.9. Trace plots of sampled values of free parameters for different candidate models (a) proportion of effective contact, VE against temporary protection and duration of temporary protection; (b) VE against breakthrough infection, VE against onward transmission and VE against progression of breakthrough varicella and (c) duration of partial immunity for vaccinees, annual change in notification sensitivity and IgG test sensitivity to vaccine-induced immunity.

(a)



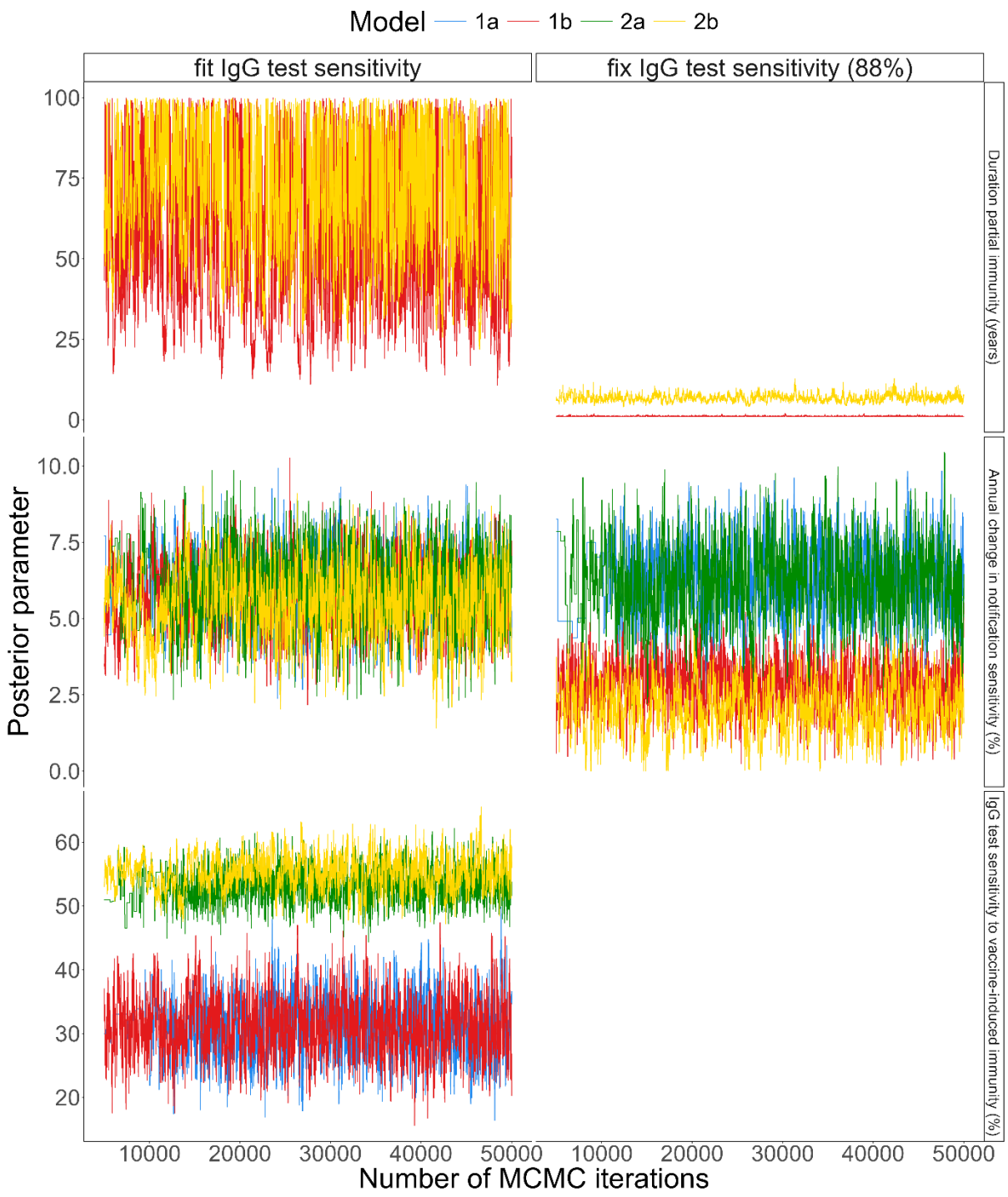
Note: Burn-in period of first 5,000 iterations was removed from the above plot.

(b)



Note: Burn-in period of first 5,000 iterations was removed from the above plot.

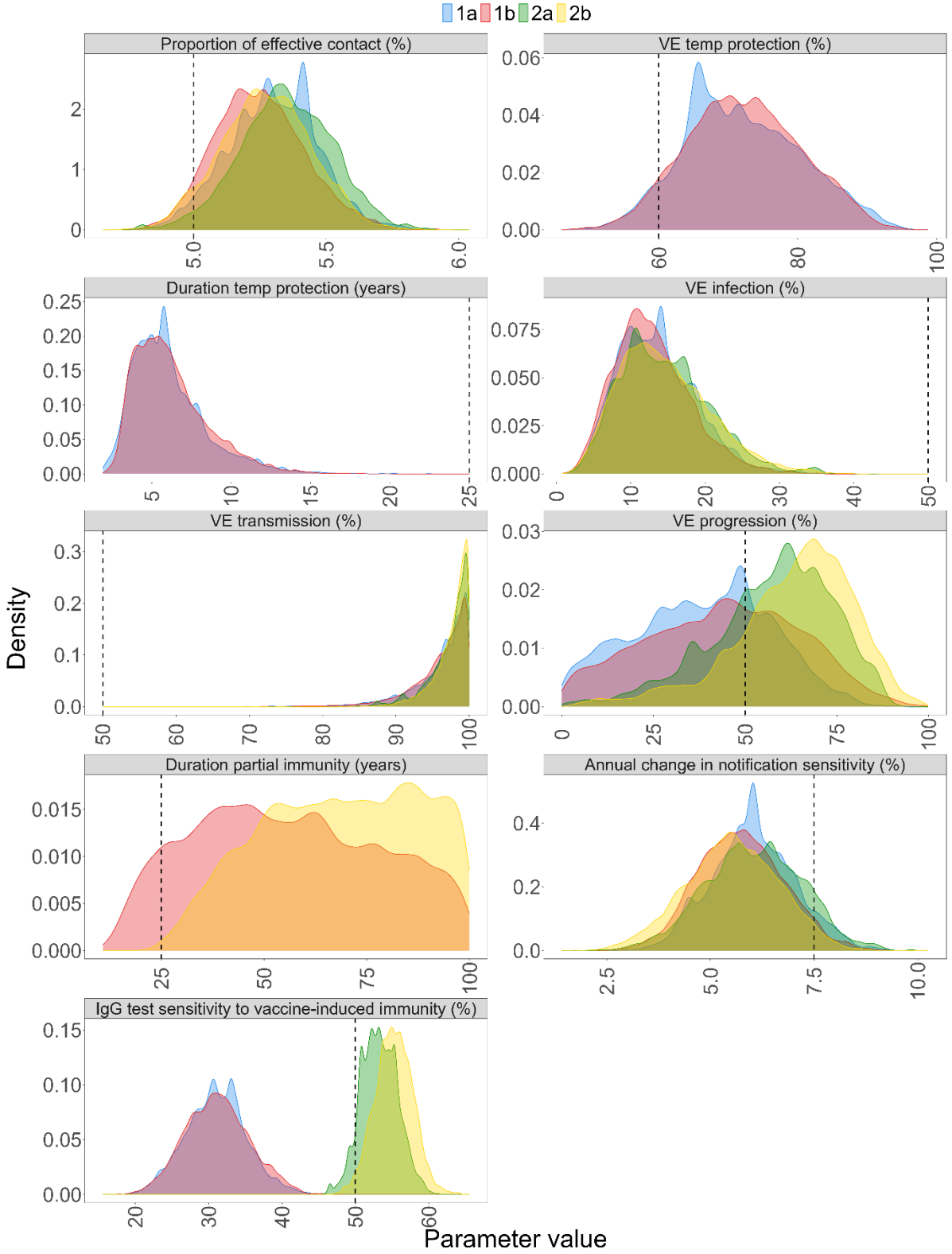
(c)



Note: Burn-in period of first 5,000 iterations was removed from the above plot.

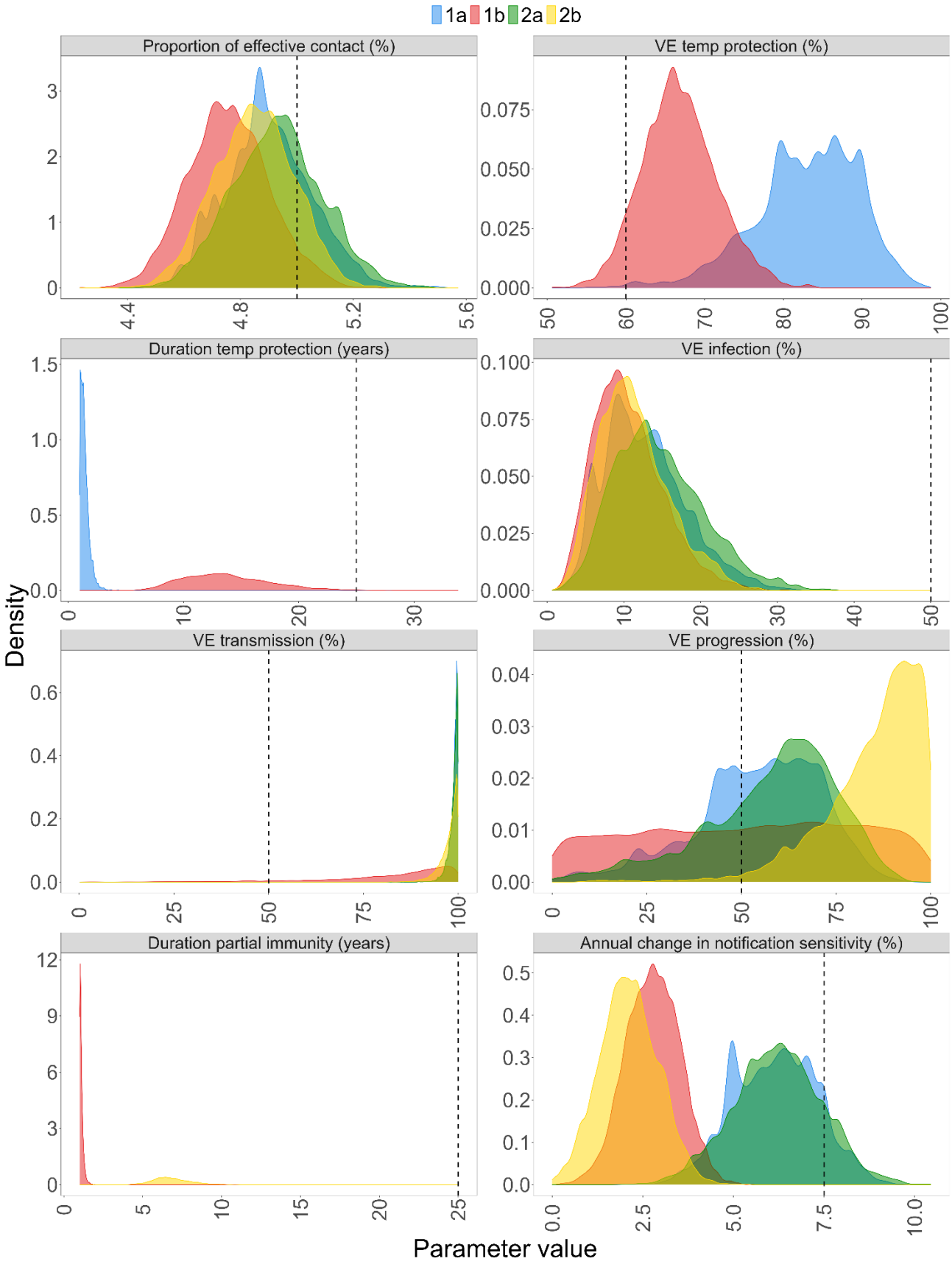
Figure 5.10. Posterior distribution of sampled parameters for candidate models with (a) IgG test sensitivity fitted and (b) IgG test sensitivity fixed at 88%.

(a) IgG test sensitivity fitted



Note: Burn-in period of first 5,000 iterations was removed from the above plot. Vertical dashed lines represent priors of each parameter.

(b) IgG test sensitivity fixed at 88%



Note: Burn-in period of first 5,000 iterations was removed from the above plot. Vertical dashed lines represent priors of each parameter.

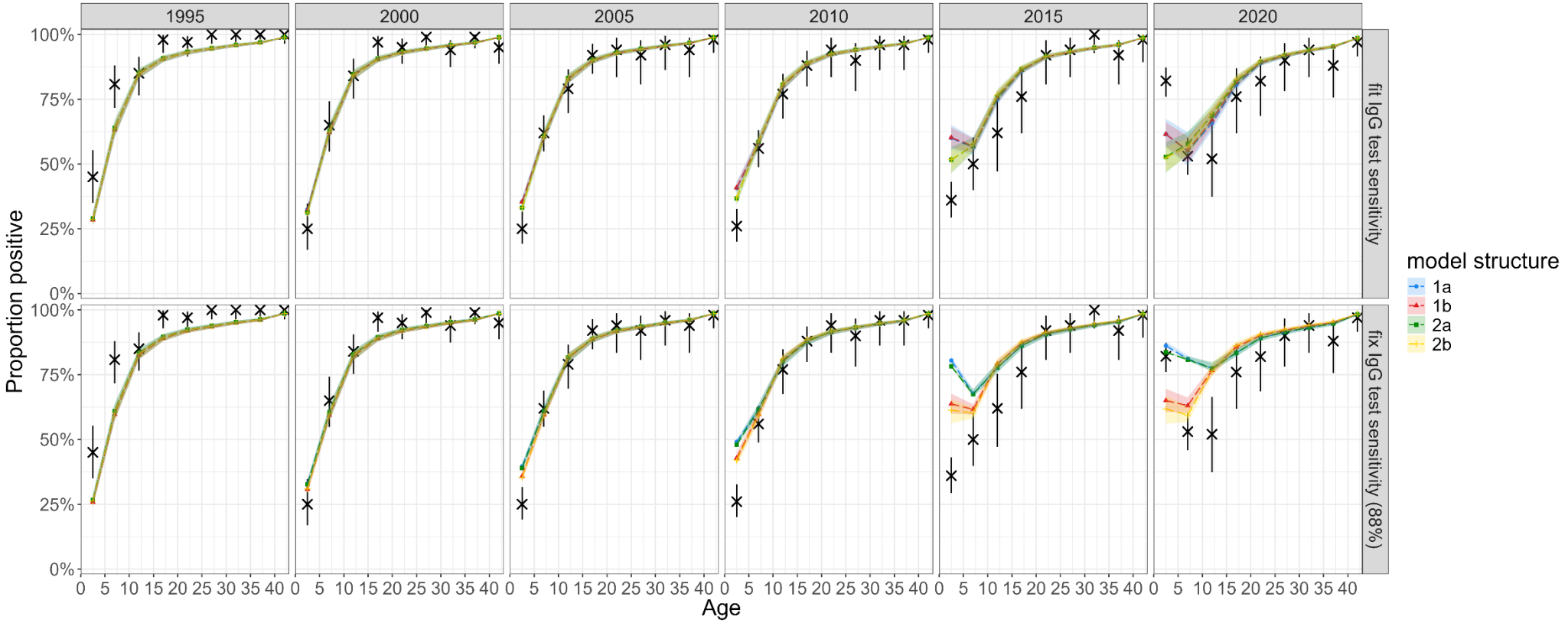
Model fit to seroprevalence against varicella

All models fitted the seroprevalence data well between 1995 and 2010, when the varicella vaccination uptake was 0% to 34% [Figure 5.11]. Both modelled and observed seroprevalence increased sharply with age for children aged under 15 years during this period. The median modelled seroprevalences were higher than the observed for children aged 1 to 4 years in 2005 and 2010 (8 to 15% higher for 2005 and 11 to 23% higher for 2010).

With the launch of UVV in 2014 and the varicella vaccine uptake reaching 98% or more for eligible children, there were more notable differences in the fitting to the seroprevalence in young children for the 2015 and 2020 surveys [Figure 5.11]. A better overall fit was achieved for models when IgG test sensitivity to vaccine-induced immunity was estimated rather than being fixed at 88%. The modelled and observed seroprevalence were largely comparable for those aged 20 years or above. For the 2015 survey, the median modelled seroprevalences were higher than those observed for those aged under 20 years for all models. For those aged 1 to 4 years, the median modelled seroprevalence when IgG test sensitivity was fitted (52% to 60% for all four models) and when it was fixed (64% and 61% for model 1b and 2b; 80% and 78% for model 1a and 2a) were significantly higher than the observed seroprevalence (36%). For the 2020 survey, a good fit to the data was largely achieved for all models when the IgG test sensitivity was fitted [Figure 5.11 (upper row)], except for those aged 1 to 4 years as the modelled seroprevalence was 21% (for models 1a and 1b) to 29% (models 2a and 2b) lower than the observed (82%). In contrast, fixing the IgG test sensitivity at 88% to match the seroprevalence of those aged 1 to 4 years resulted in inferior fitting for those aged 5 to 9 years and 10 to 14 years as their modelled seroprevalence were significantly higher than the observed [Figure 5.11 (lower row)].

A reduction in observed and modelled age-specific seroprevalence between 5 and 25 years of age was observed over the years, but the reduction was less substantial for the model [Figure 5.12].

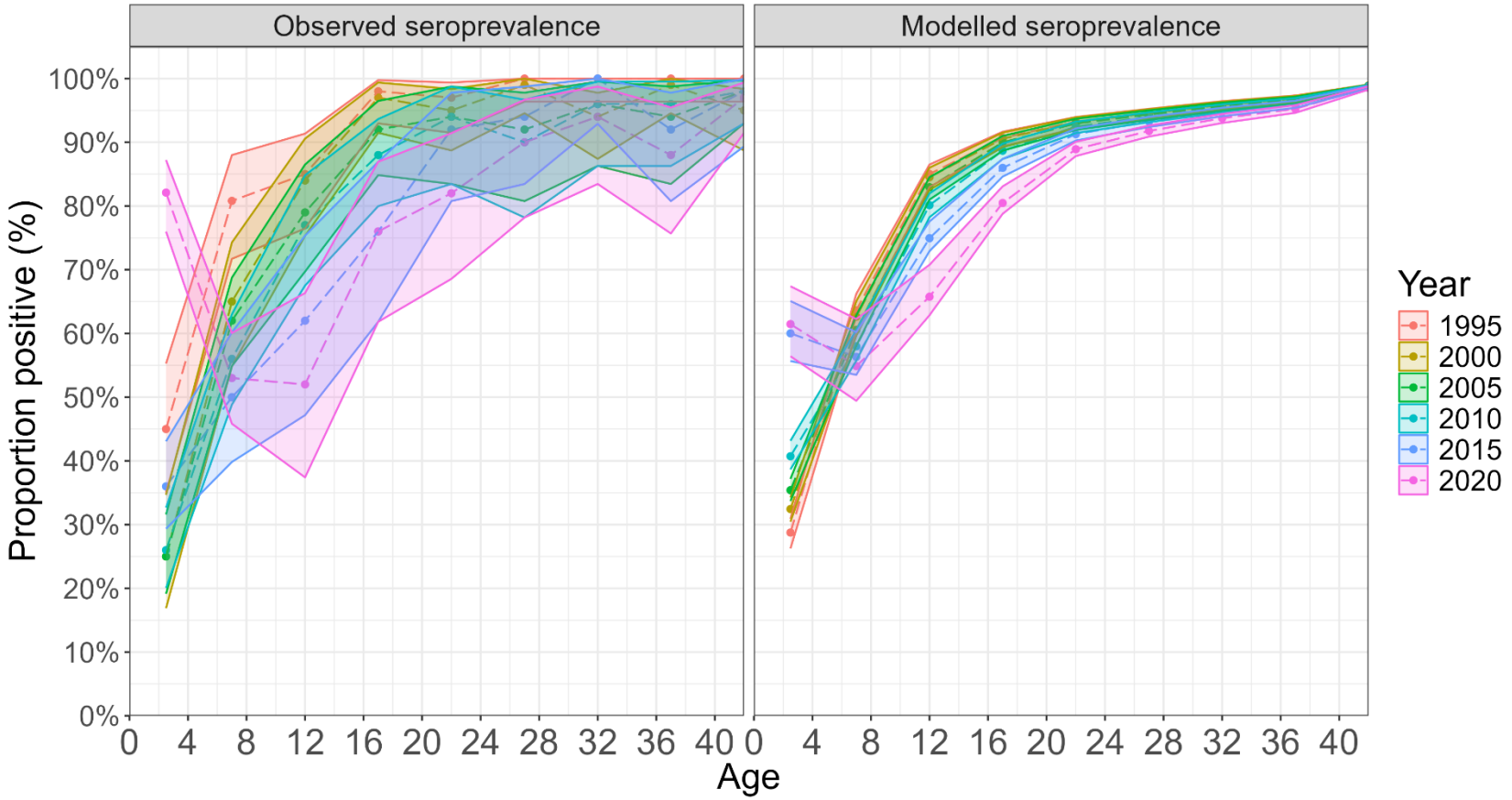
Figure 5.11. Model fit to varicella seroprevalence data by model structure and fitting/ fixing IgG test sensitivity towards vaccine-induced immunity, Hong Kong, 1995 to 2020.



Note:

Cross and error bars - observed seroprevalence and its 95% CI; Dashed line and shadow - median modelled seroprevalence and its 95%CI. The upper row shows the results of different models with IgG test sensitivity to vaccine-induced immunity estimated during model calibration; The lower row shows the results of different models with IgG test sensitivity to vaccine-induced immunity fixed at 88%.

Figure 5.12. Observed and modelled seroprevalence by year for model 2a - IgG test sensitivity fitted, Hong Kong, 1995 to 2020.



Model fit to varicella notification data

The model fit to notification data is shown in Figure 5.13a for those aged 0 to 19 years and Figure 5.13b for those aged 20 years and above. All models achieved a decent fit to the trend in age-specific notifications, especially when IgG test sensitivity was estimated [Figure 13a and b (upper rows)]. For young children aged 0 to 4 years and 5 to 9 years, both the data and modelled notifications showed a decreasing trend between 1999 and 2019, with a more rapid decrease after the implementation of UVV in 2014. Models 1b and 2b with IgG test sensitivity fixed at 88% showed an increase in notifications for 0 to 4 years between 2017 and 2019 and a small increase for 5 to 9 years between 2012 and 2019, which differed from the decreasing trends in the observed notifications.

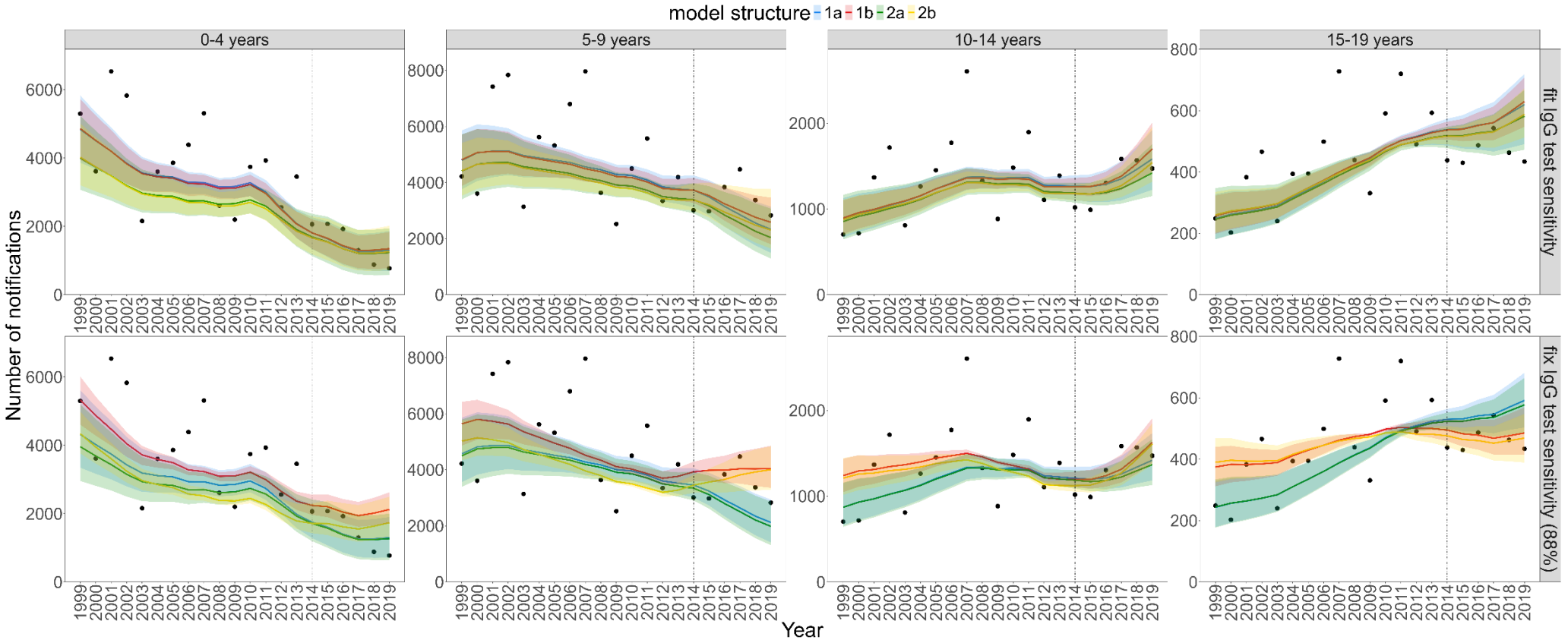
All model variations fitted the increasing trend of data for those aged 10 to 14 years to those aged 60 to 79 years reasonably well. For those aged 40 to 59 years, the modelled notifications were higher than the observed data between 1999 and 2006 but were lower than the data between 2016 and 2019 [Figure 5.13b]. For those aged 80 years or above, all models struggled to fit the initial reduction which was signified by higher than usual notifications in 2003. Nevertheless, the increase shown in the data in later years was captured by all models [Figure 5.13b].

Although the 2020 notification data was not included in the model calibration due to NPIs implemented against COVID-19, adjustments on reduced contacts and the effect of face masking in public areas were included in simulating the varicella infections and notifications between 2020 and 2023 [Supplementary Figure S.5.1]. The modelled notifications in 2020 were similar to the observed for those aged 0 to 4 years, 5 to 9 years and 10-14 years, as both

showed a sharp drop compared to the 2019 level [Figure S.5.1a]. The modelled notifications for those aged 15 years or above also showed substantial reductions, but the modelled estimates were higher than the observed notifications in corresponding age groups [Figure S.5.1b].

Figure 5.13. Model fit to varicella notification data by model structure and fitting or fixing IgG test sensitivity towards vaccine-induced antibody, Hong Kong, 1999 to 2019 for (a) 0 to 19 years or below and (b) 20 years or above.

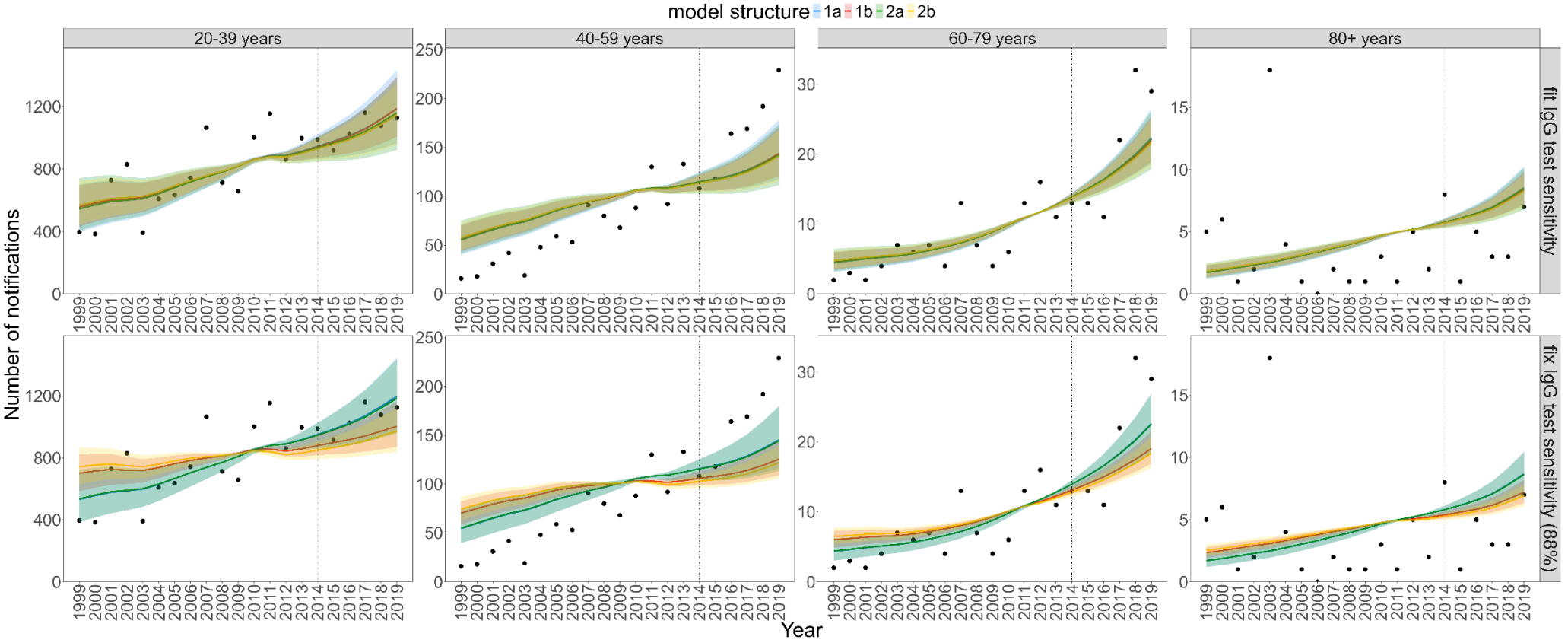
(a) 0 to 19 years or below



Dots: observed notification; Line (ribbon): modelled notification.

The upper row shows the observed and modelled notifications of different models with IgG test sensitivity to vaccine-induced immunity estimated. The lower row shows the observed and modelled notifications of different models with IgG test sensitivity to vaccine-induced immunity fixed at 88%. The vertical dashed line indicates the launch of UVV in 2014. Data fit included notifications of all ages between 1999 (first year of notification started) and 2019 (last year of age-specific notification data available before COVID-19 pandemic). Data of 2020 were not included in model calibration due to the effects of NPIs on varicella transmission.

(b) 20 years or above.



Dots: observed notification; Line (ribbon): modelled notification.

The upper row shows the observed and modelled notifications of different models with IgG test sensitivity to vaccine-induced immunity estimated. The lower row shows the observed and modelled notifications of different models with IgG test sensitivity to vaccine-induced immunity fixed at 88%. The vertical dashed line indicates the launch of UVV in 2014. Data fit included notifications of all ages between 1999 (first year of notification started) and 2019 (last year of age-specific notification data available before COVID-19 pandemic). Data of 2020 were not included in model calibration due to the effects of NPIs on varicella transmission.

Selection of main model

All models fitted the observed notification data reasonably well. Although there were some variations between models for different ages and time periods, those differences were relatively small. On the other hand, the fit to serology data in 2015 and 2020 was inferior when IgG test sensitivity was fixed at 88% compared to the fit when the parameter was included in the calibration (sensitivity estimated to be between 31% and 55% for different models). Therefore, only models with IgG test sensitivity fitted were considered further.

When comparing the remaining models with IgG test sensitivity fitted, the plausibility of parameters estimated was considered. The estimated IgG test sensitivity for models 1a and 1b was only 31% but was higher at 53 to 55% for models 2a and 2b, which is closer to the reported sensitivity to vaccine-induced immunity in previous studies comparing different ELISA assays (35, 169). In addition, the relatively short duration of temporary full protection against infection ($d\_temp\_protection_1$) indicated this may not be a significant pathway of protection for one-dose varicella vaccination. Regarding the additional pathway of waning from partial immunity (i.e. from *Susceptible 1* (S1) compartment to non-immune Susceptible (*S*) compartment), the diffused posterior distribution indicated a lack of evidence from the available data to support convergence to narrow posterior samples [Figure 5.10a].

Considering the quality and plausibility of parameters estimated, and the lower DIC of models 2a and 2b (8,081 and 8,078 respectively) when compared to models 1a and 1b (8,128 and 8,124) [Table 5.9], model 2a (i.e. the simple model assuming the absence of temporary full protection and no waning of partial immunity) was selected as the main model. Models 1a, 1b and 2b were retained as sensitivity analyses to project the future trajectory of varicella transmission.

Change in population susceptibility against varicella and varicella infections before the pandemic

The proportion of the population with no immunity / the immune naive (susceptible to natural infections) and those with partial immunity (susceptible to breakthrough infections) trended differently under the increasing vaccine uptake in young children, when private vaccine uptake increased to 50% by 2013 and UVV uptake reached 98% after 2014. The overall proportion of the population with no immunity is estimated to have decreased from around 8% in the late 1990s to around 5% after UVV (2015 to 2019) [Figure 5.14]. In contrast, the proportion of the population with partial immunity increased from less than 1% in 1999, to 5% in 2013 and to 10% in 2020. Before the COVID-19 pandemic, the rate of reduction in infections simulated were greater than the notifications between 1999 and 2019 for all models, likely due to an increase in notification sensitivity over the same period [Figure 5.16a]. The reduction in infections was driven by a consistent decrease in natural infections, offset only to a small part by a relatively small increase in breakthrough infections among the vaccinated [Figure 5.17].

The proportion of children aged 0 to 4 years with no immunity dropped from an estimated 62% in 1999 to 20% in 2013 [Figure 5.15a]. Following the UVV launch in 2014, this dropped further to an estimated 5% by 2019 and remained at this level afterwards. There were differences in the pre-pandemic trends between the modelled infections and observed notifications for some age groups [Figure 5.16b]. The reduction of modelled infections was more substantial than that of the notifications for these children, with natural infections declining sharply from 6,630 (95%CI: 6,111 to 7,199) per 100,000 in 1999 to only 128 (95%CI: 122 to 200) per 100,000 in 2019 [Figure 5.16b, model 2a]. On the other hand, the proportion of partially immune children

in this age group gradually increased to an estimated 77% in 2019, and the incidence of breakthrough infections peaked at 2,100 (95%CI: 1,617 to 2,517) per 100,000 in 2013 and declined afterwards [Figures 5.15a and 5.18a]. For those aged 5 to 9 years, there was an increase in the modelled and observed notification between 1999 and 2012, in contrast with the gradual reduction in modelled infections in the same period [Figure 5.16b]. The reductions in modelled infections were more substantial than the modelled notifications between 2013 and 2019, partly due to the increase in notification sensitivity over the years. Like children aged 0 to 4 years, natural infections decreased substantially while breakthrough infections increased for these children before the pandemic [Figure 5.18a].

In contrast to the decreasing proportion of non-immune children aged under 10 years between 1999 and 2019, an increasing proportion of those aged 10 to 14 years and 15 to 19 years were estimated to have remained susceptible to both natural and breakthrough infections because of a reduction in the force of infection in those not age-eligible for the national vaccination programme from 2014 and not privately vaccinated before 2014 [Figure 5.15a]. The proportion with no immunity was estimated to slightly increase from 15% in 1999 to 19% between 2015 and 2019 for those aged 10 to 14 years. In addition, the proportion with partial immunity is estimated to have increased to 24% for those aged 10 to 14 years and 8% for those aged 15 to 19 years by 2019. For those aged 10 to 14 years, both modelled infections and notifications increased at comparable paces before the pandemic [Figure 5.16b]. In contrast to a reduction in natural infections, there was an estimated increase in breakthrough infections [Figure 5.18a]. For those aged 15 to 19 years, the annual incidence of natural infections simulated by the main model was stable before the pandemic (range of median infections: 585 to 652 per 100,000), but the incidence of breakthrough infections rose from 0 in 1999 to an estimated 292 per 100,000 in 2019 [Figure 5.18a]. For adults aged 20 years or above, less than 2% and 1% were

modelled to be susceptible to natural and breakthrough infections [Figure 5.15a]. The modelled infections for adults decreased over the years before the pandemic, in contrast to the increase in notifications during the same period, likely driven by an increase in notification sensitivity [Figure 5.16b]. The incidence of natural infections dropped for all adults before the pandemic, with a slight increase in breakthrough infections only in those aged 20 to 39 years as the early cohorts receiving varicella vaccine in the private market aged into this age group [Figure 5.18a and 5.19].

Before UVV, the FOI was estimated to be highest for those aged 6 to 10 years, followed by those aged 11 to 15 years and those aged 0 to 5 years [Figure 5.20]. The FOI for all age groups declined before UVV introduction in 2014, but the reduction was most prominent for very young children aged under 5 years (from 11% in 1999 to 4% in 2013) and older children aged 6 to 10 years (from 22% in 1999 to 12% in 2013).

Post-pandemic model predictions of varicella resurgence

Due to the public health measures introduced, marked reductions in both natural and breakthrough varicella infections for all age groups were projected during the pandemic [Figures 5.17 and 5.18a]. The decline in the FOI between 1999 and 2019 continued and reached very low levels at 4% or below for all age groups between 2020 and 2022 [Figure 5.20]. The overall proportion of the population with no immunity was estimated to remain low at 4 to 5% between 2020 and 2035, but a small increase was predicted for those aged 15 years or above shortly after the pandemic, potentially due to a lack of VZV circulation leaving those non-immune persons unexposed [Figures 5.14 and 5.15a]. On the other hand, with an increasing number of UVV eligible cohorts and UVV uptake assumed to remain high at 98%, the overall

proportion with partial immunity was estimated to increase from 10% in 2020, to 22% in 2035. This proportion is expected to continue to increase gradually, eventually plateauing [Supplementary Figure S.5.3a].

The changes in population susceptibility affected projections of varicella infections. As NPIs were gradually phased out in 2023, both natural and breakthrough varicella infections were predicted to resurge and remain largely stable [Figure 5.17 and 5.18]. For children aged under 10 years, both natural and breakthrough varicella infections were predicted to remain low after the pandemic [Figure 5.18a], echoing the stable trend of non-immune and partially immune in the corresponding age groups [Figure 5.15a]. The predicted resurgence of varicella among those aged 10 to 14 years and 15 to 19 years was estimated to be mainly attributed to breakthrough infections, with a longer period of high incidence of breakthrough infections estimated to start to subside in the 2030s [Figure 5.18a]. Both natural and breakthrough infections for those aged 10 to 19 years were predicted to decrease and remain stable towards 2030s. Increase in breakthrough infections in these children overlapped with the rise of partially immune individuals in these age groups [Figure 5.15a]. The increase in immune naïve individuals aged 10 to 19 years started before the pandemic and was predicted to drop gradually and would maintain at 4 to 5% after the predicted natural infections upsurge [Figure 5.15a]. Varicella infections for those aged under 20 years were predicted to be roughly stable [Figure 5.18a].

For adults aged 20 years or older, varicella infections were projected to be higher than the pre-pandemic levels [Figure 5.16b]. There were modelled changes in susceptibility to natural and breakthrough infections for adults. For adults over 20 years or above, only 2% or fewer were projected to be susceptible to natural varicella before 2020, but this proportion increased and

remain higher than pre-pandemic levels following a general reduction in FOI among all age groups [Figure 5.15a]. For instance, only up to 2% of young adults aged 20 to 39 years would be completely non-immune in 2020, but this proportion was expected to have increased to 8% during the pandemic, reaching 9% afterwards and gradually decreasing thereafter. Similar increases in susceptibility to natural infections were also predicted for older adults, leading to peaks in natural infections [Figure 5.18a]. Resurgences of natural infections were also predicted for adults 40 years or above after the decline during the pandemic. As with all these long-term projections, they are very uncertain and can be influenced by other factors, such as if the demographic structure and contact patterns remain the same (which is highly unlikely over a long period).

Very few adults acquired partial immunity through vaccination before 2020 [Figure 5.15a]. A steady increase in the proportion being partially immune was projected as vaccinated cohorts age [Figure 5.15a]. The model projected that the incidence of breakthrough infections will continue to increase for all adults [Figure 5.18a]. As one dose varicella vaccine was estimated to be not effective against acquisition of breakthrough varicella (median $VE\_infection_1$ estimated with IgG test sensitivity fitted: 12.3% to 14.1%) and an increasing proportion of young adults will become partially immune, the incidence of breakthrough infections is expected to remain high [Figures 5.15a and 5.18a].

Due to the COVID-19 pandemic likely changing reporting and health-seeking behaviour and unavailability of age-specific notification data beyond 2021, data beyond 2020 was not included in model calibration. It should be noted that the predicted notifications from different models were similar to those observed in 2020 and 2021 [Figure 5.16a]. The observed notifications in 2023 and 2024 remained low and were significantly lower than the predicted

notifications.

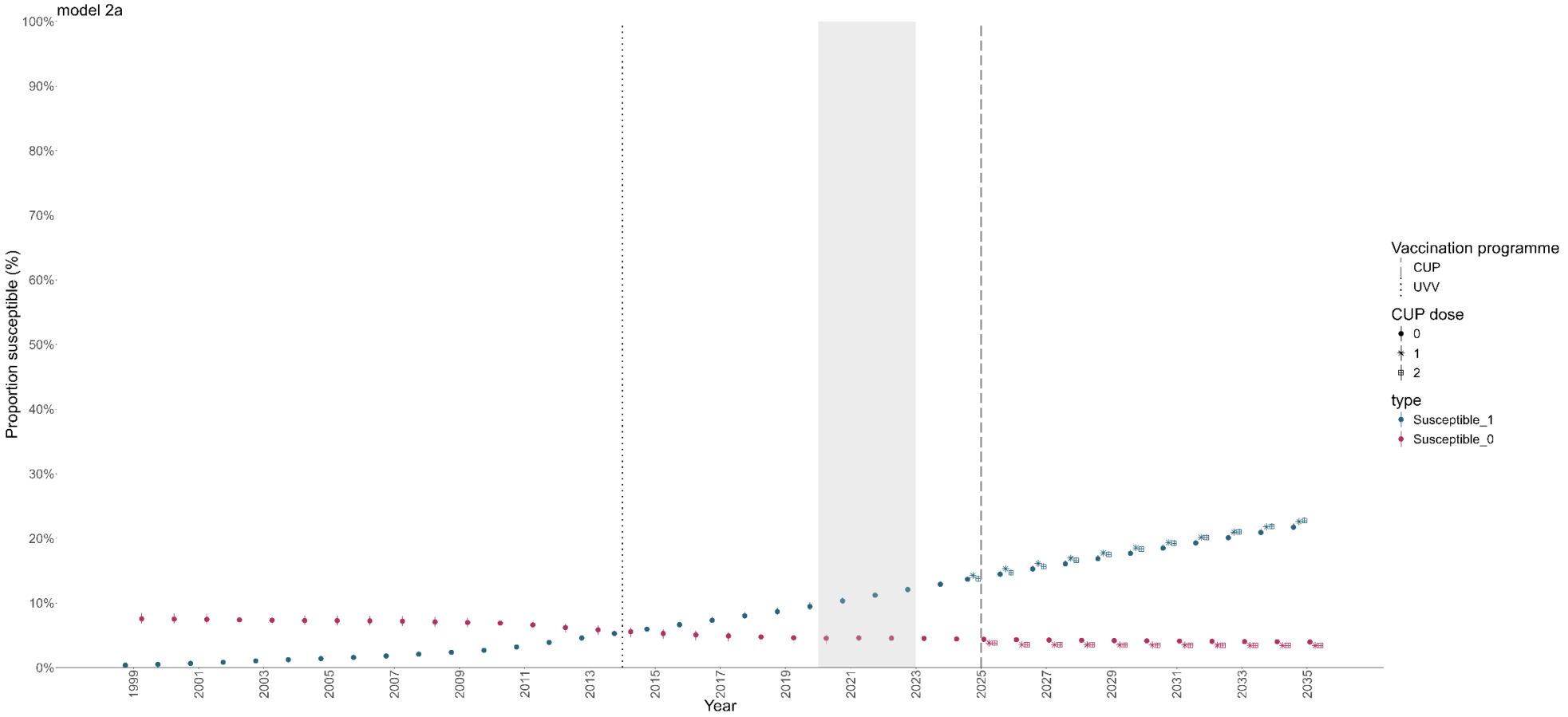
Alternative models with waning of partial immunity predicted more long-term natural infections

Compared to the main model (model 2a) [Figure 5.18a], the predicted trends and levels of age-specific natural and breakthrough infections was largely similar for model 1a, which has an additional compartment of temporary protection for vaccinees [Figure 5.18b]. Both models 1b and 2b allow vaccinees with partial immunity to wane and become completely non-immune, with model 1b retaining the temporary protection compartment. These two models simulated a higher proportion of individuals with no immunity than model 2a, with the highest levels of population susceptible to natural infection predicted by model 2b [Figures 5.15a, c and d]. The post-pandemic incidence of natural infections predicted by these two alternative models was also substantially higher than those for model 2a, with natural infections remaining the predominant infection type [Figures 5.18a, c and d]. Less breakthrough infections were predicted by models 1b and 2b than by model 2a.

The number of long-term total infections were projected to increase substantially only in model 2b, which would mainly be contributed by natural infections [Figures 5.16 and 5.17], as waning of both full but temporary immunity and partial immunity was allowed in this model. As natural infections are more likely than breakthrough infections to lead to severe varicella, the predicted increases in model 2b would lead to a substantial burden of medically attended varicella, including hospitalisations. It should be noted that the convergence of the parameter on duration of partial immunity for model 2b was poor during the parameterisation. This indicated the data available for model calibration did not support the waning of partial immunity, and this model

is less plausible compared to the main and other candidate models [*refer to earlier section 'Selection of main model'*].

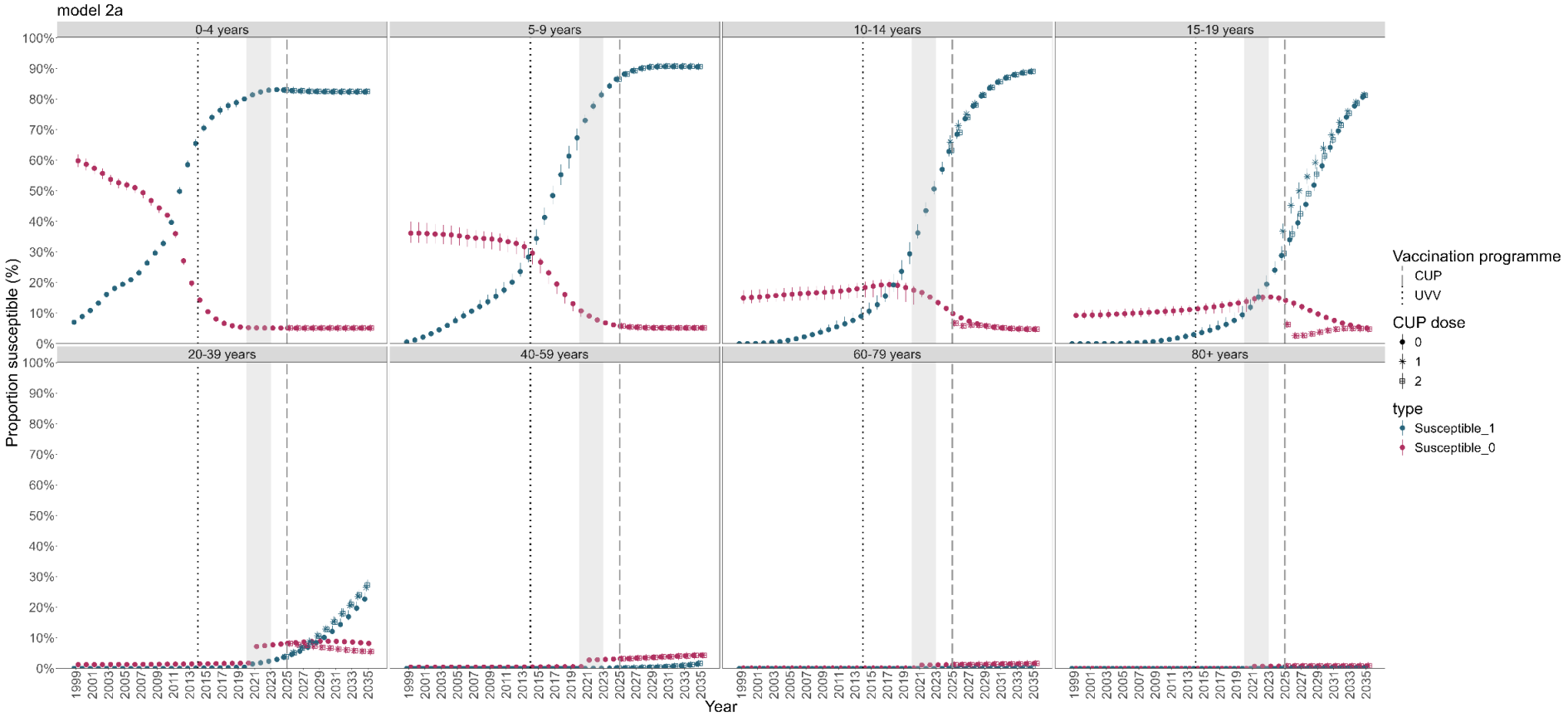
Figure 5.14. Model 2a simulations of the overall proportion of population susceptible to natural (Susceptible_0) and breakthrough varicella infections (Susceptible_1), 1999 to 2035, Hong Kong.



Note: Susceptible_0 (S) represents proportion with no immunity and are prone to natural infections, whilst Susceptible_1 (S1) represents proportions with partial immunity and are prone to breakthrough infections. Changes in population susceptibility under different catch-up programme (CUP) are presented by different shapes. The vertical dotted line represents UVV introduction in 2014. The grey rectangle represents NPI implemented against COVID-19 between 2020 and 2023. The vertical dashed line represents potential CUP in 2025. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.2.

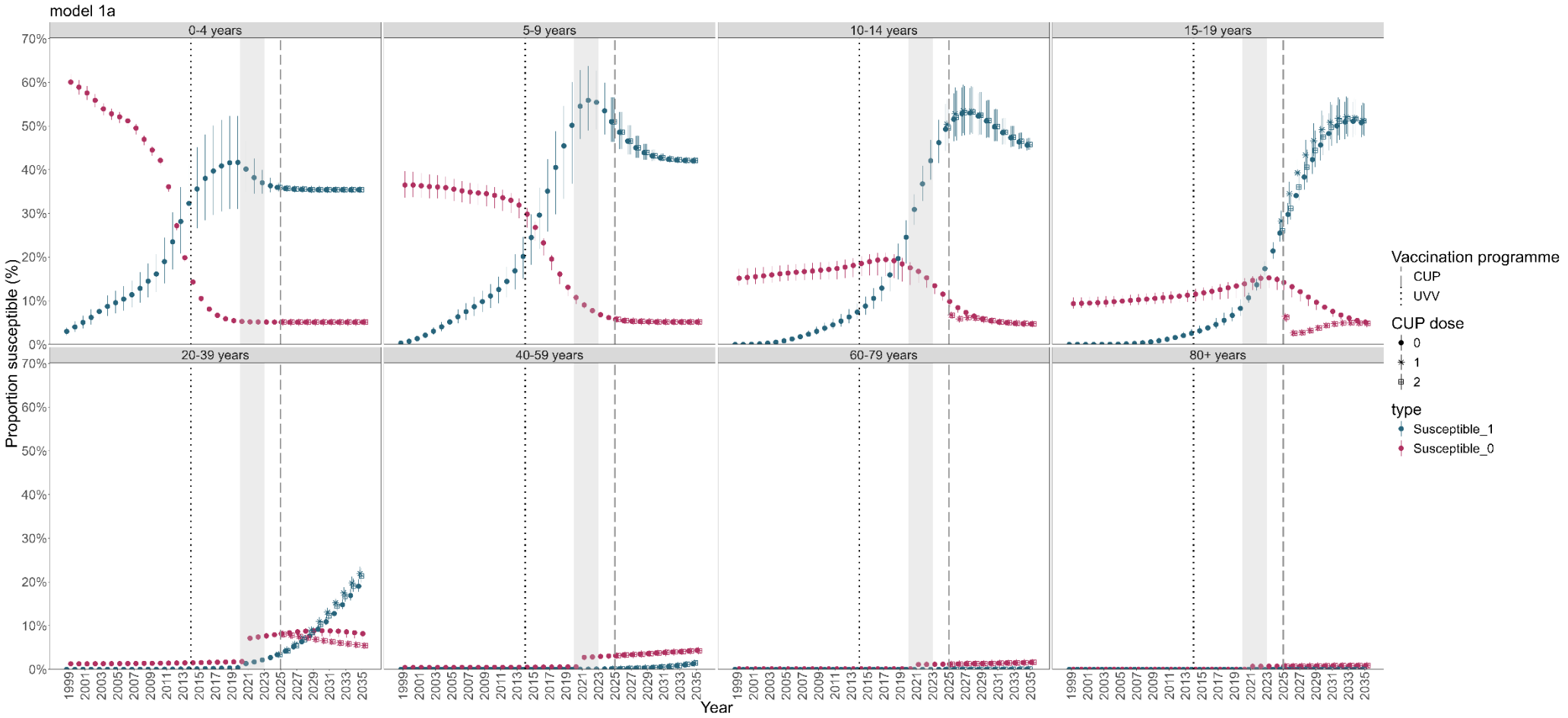
Figure 5.15. Model simulations of the age-specific proportion of population susceptible to natural (Susceptible_0) and breakthrough varicella infections (Susceptible_1) for (a) model 2a, (b) model 1a, (c) model 1b and (d) model 2b, 1999 to 2035, Hong Kong.

(a) Age-specific proportion of susceptibility, model 2a.



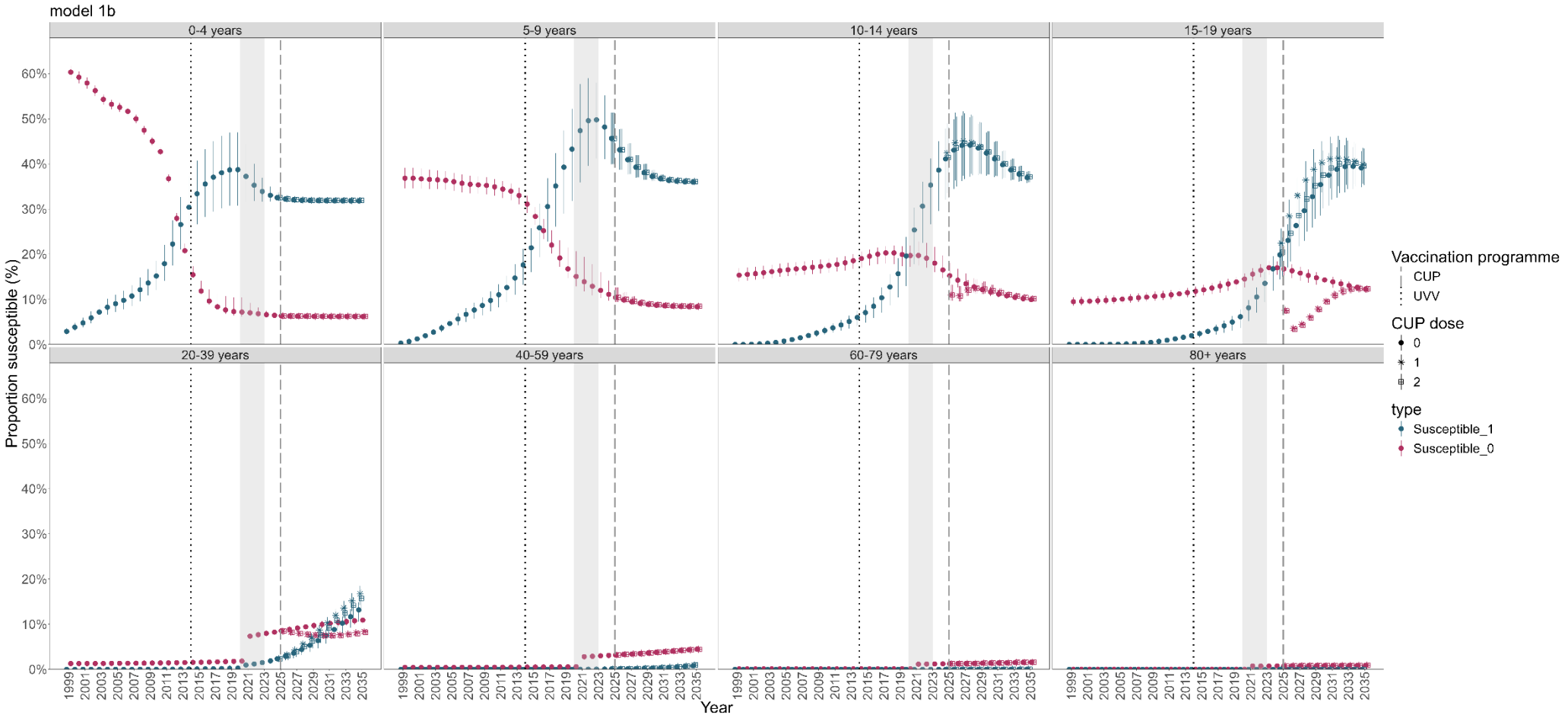
Note: Susceptible_0 (S) represents proportion with no immunity and are prone to natural infections, whilst Susceptible_1 (S1) represents proportions with partial immunity and are prone to breakthrough infections. Changes in population susceptibility under different catch-up programme (CUP) are presented by different shapes. The vertical dotted line represents UVV introduction in 2014. The grey rectangle represents NPI implemented against COVID-19 between 2020 and 2023. The vertical dashed line represents potential CUP in 2025. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.3a.

(b) Age-specific proportion of susceptibility, model 1a.



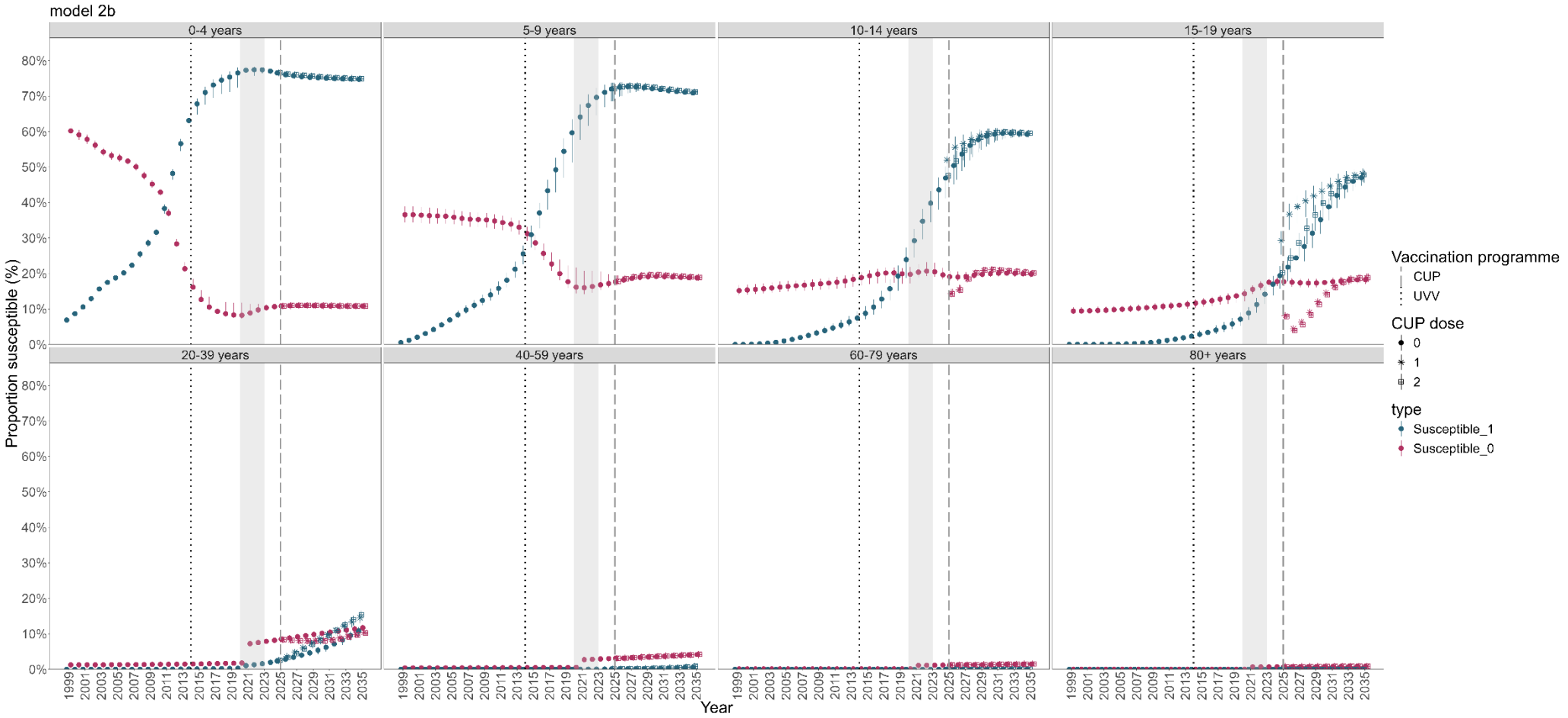
Note: Susceptible_0 (S) represents proportion with no immunity and are prone to natural infections, whilst Susceptible_1 (S1) represents proportions with partial immunity and are prone to breakthrough infections. Changes in population susceptibility under different catch-up programme (CUP) are presented by different shapes. The vertical dotted line represents UVV introduction in 2014. The grey rectangle represents NPI implemented against COVID-19 between 2020 and 2023. The vertical dashed line represents potential CUP in 2025. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.3b.

(c) Age-specific proportion of susceptibility, model 1b.



Note: Susceptible_0 (S) represents proportion with no immunity and are prone to natural infections, whilst Susceptible_1 (S1) represents proportions with partial immunity and are prone to breakthrough infections. Changes in population susceptibility under different catch-up programme (CUP) are presented by different shapes. The vertical dotted line represents UVV introduction in 2014. The grey rectangle represents NPI implemented against COVID-19 between 2020 and 2023. The vertical dashed line represents potential CUP in 2025. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.3c.

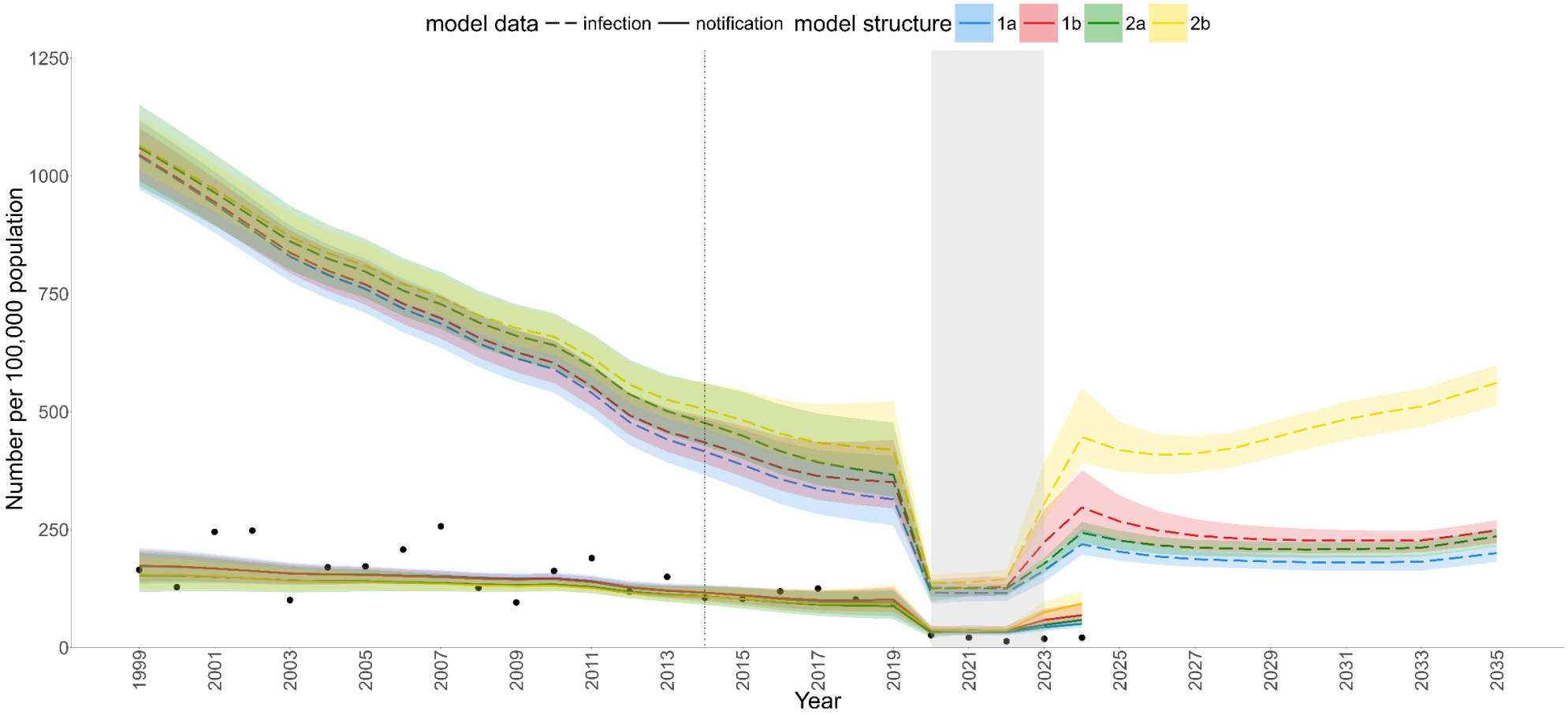
(d) Age-specific proportion of susceptibility, model 2b.



Note: Susceptible_0 represents proportion with no immunity and are prone to natural infections, whilst Susceptible_1 represents proportions with partial immunity and are prone to breakthrough infections. Changes in population susceptibility under different catch-up programme (CUP) are presented by different shapes. The vertical dotted line represents UVV introduction in 2014. The grey rectangle represents NPI implemented against COVID-19 between 2020 and 2023. The vertical dashed line represents potential CUP in 2025. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.3d.

Figure 5.16. Incidence of modelled varicella infections and notifications per 100,000 (a) all age (b) age-specific, 1999 to 2035, Hong Kong.

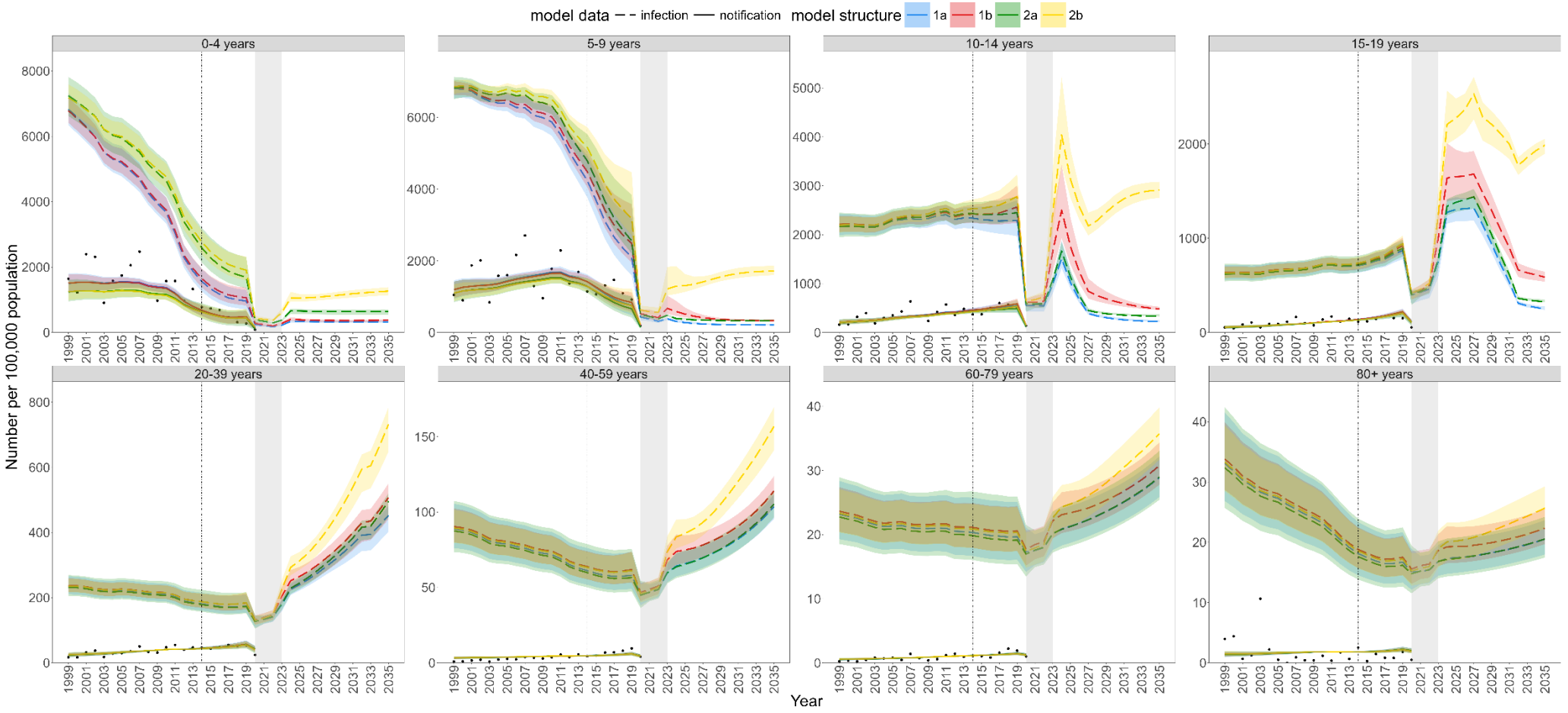
(a) All age incidence of varicella infections and notifications.



Note:

The dots and solid lines represent notification data observed and modelled between 1999 and 2024. Between 2021 and 2024, only data without age group were available. Data of 2024 were up to September only and was annualised; Dashed lines represent the simulations between 2021 and 2050; The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.4a.

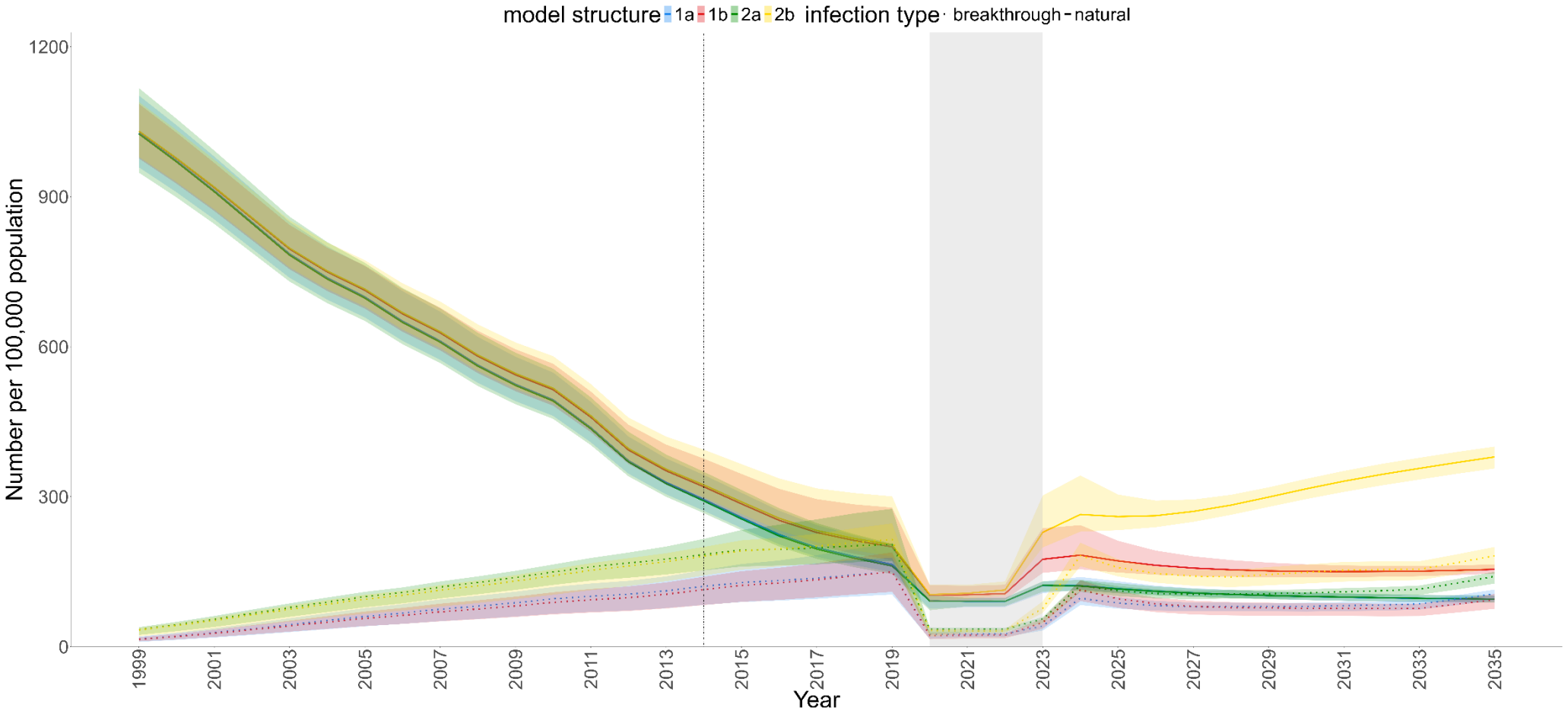
(b) **Age-specific incidence of varicella infections and notifications.**



Note:

The dots and solid lines represent notification data observed and modelled between 1999 and 2020; Dashed lines represent the simulations between 2021 and 2050; The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.4b.

Figure 5.17. Incidence of overall modelled varicella natural and breakthrough infections per 100,000, 1999 to 2035, Hong Kong.

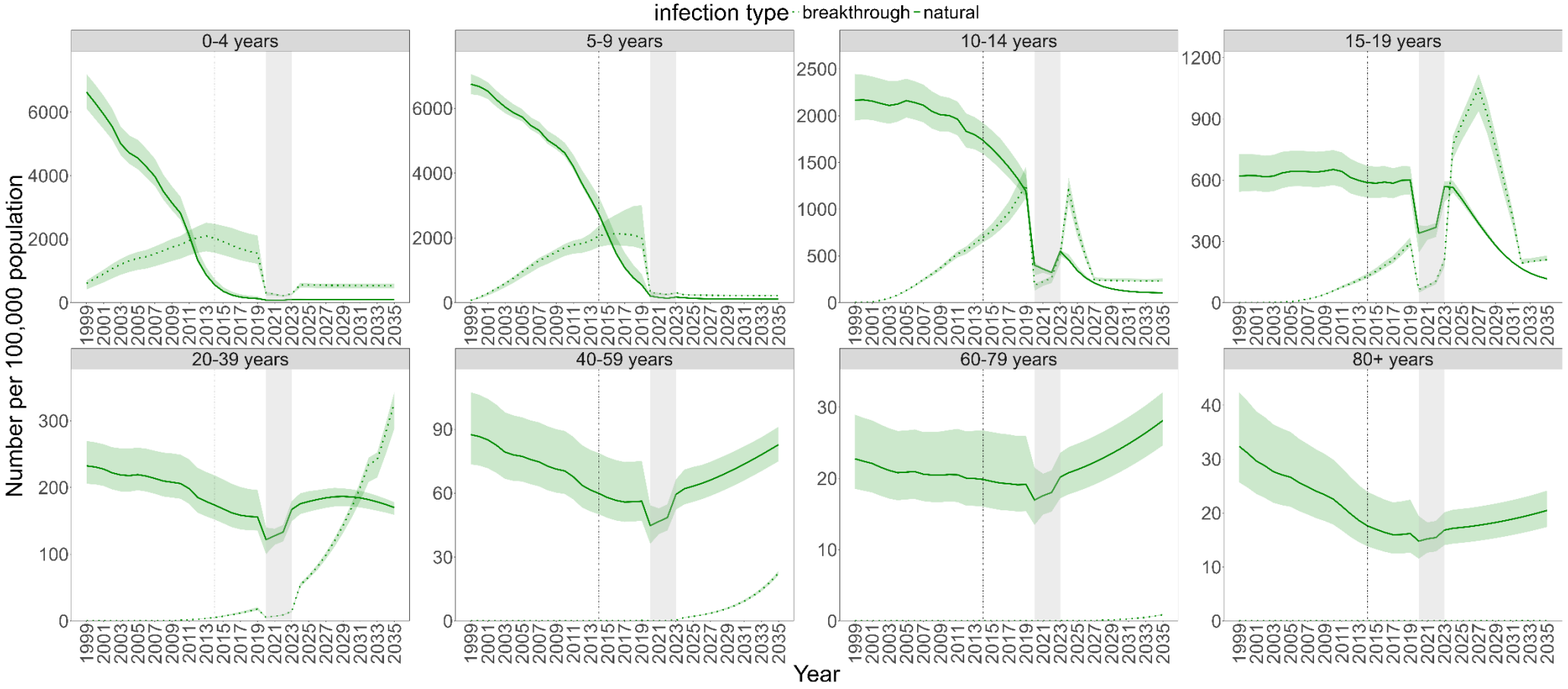


Note:

Solid lines represent period between 1999 and 2019 when the model was calibrated with varicella notification data; Dashed lines represent the simulations between 2020 and 2050; The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.5.

Figure 5.18. Age-specific modelled incidence of varicella natural and breakthrough infections per 100,000 for (a) model 2a, (b) model 1a, (c) model 1b and (d) model 2b, 1999 to 2035, Hong Kong.

(a) Model 2a



Note:

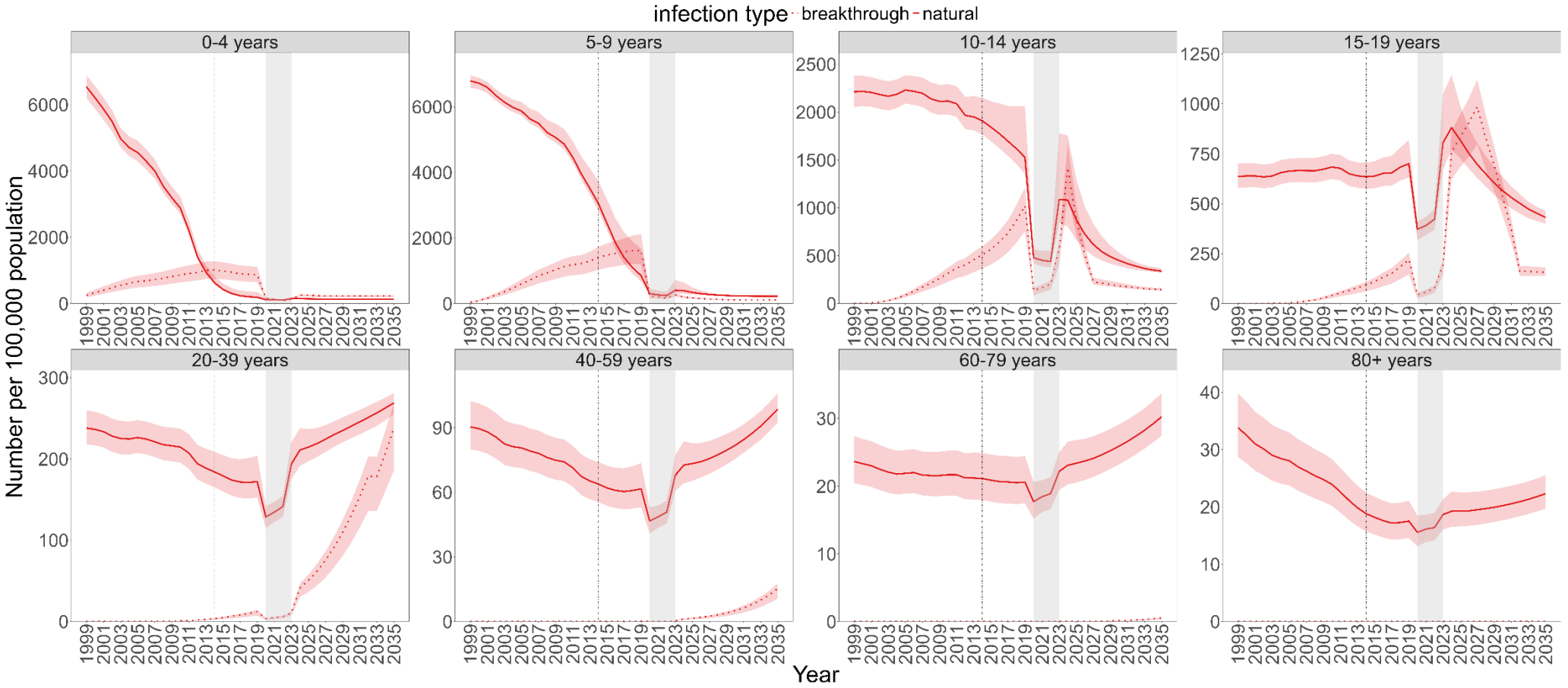
Solid lines represent natural infections whilst dotted lines represent breakthrough infections. The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.6a.

(b) Model 1a

Note:

Solid lines represent natural infections whilst dotted lines represent breakthrough infections. The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.6b.

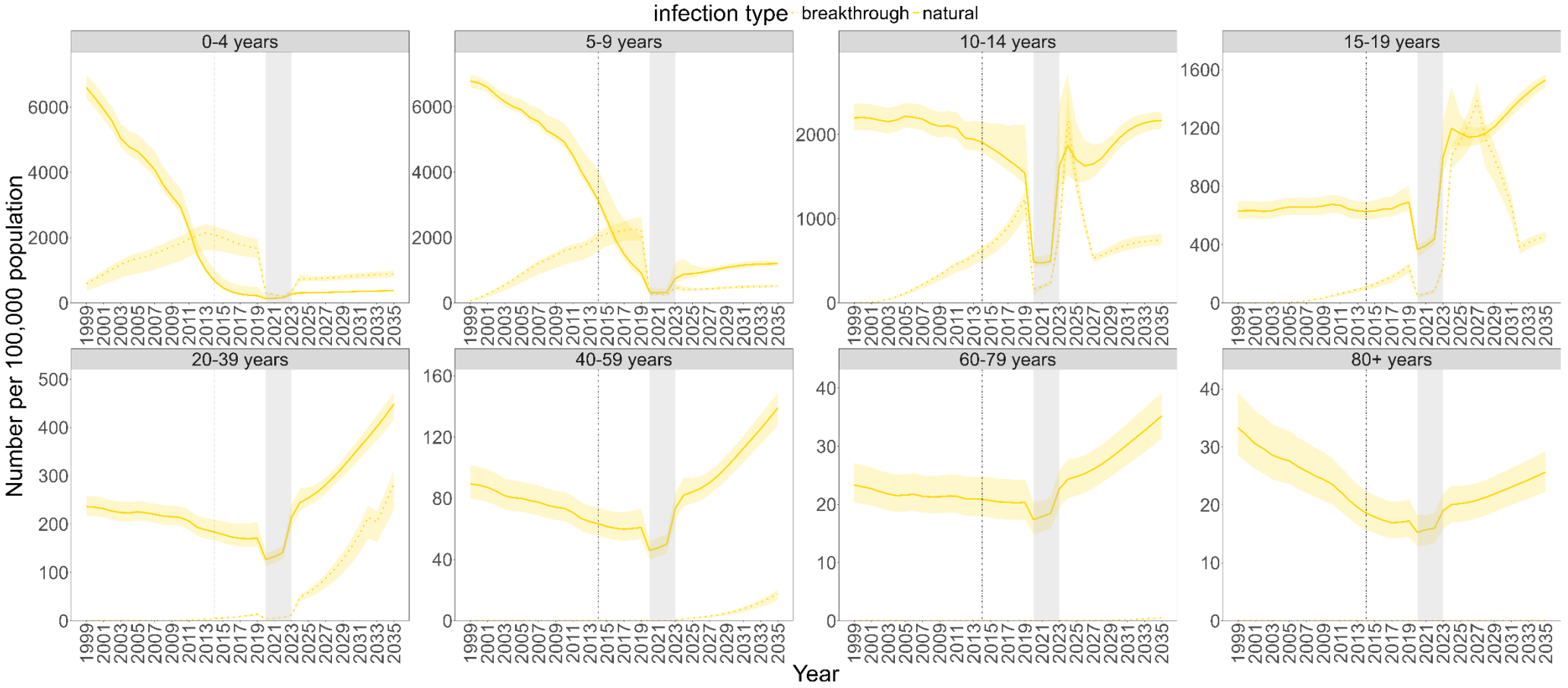
(c) Model 1b



Note:

Solid lines represent natural infections whilst dotted lines represent breakthrough infections. The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.6c.

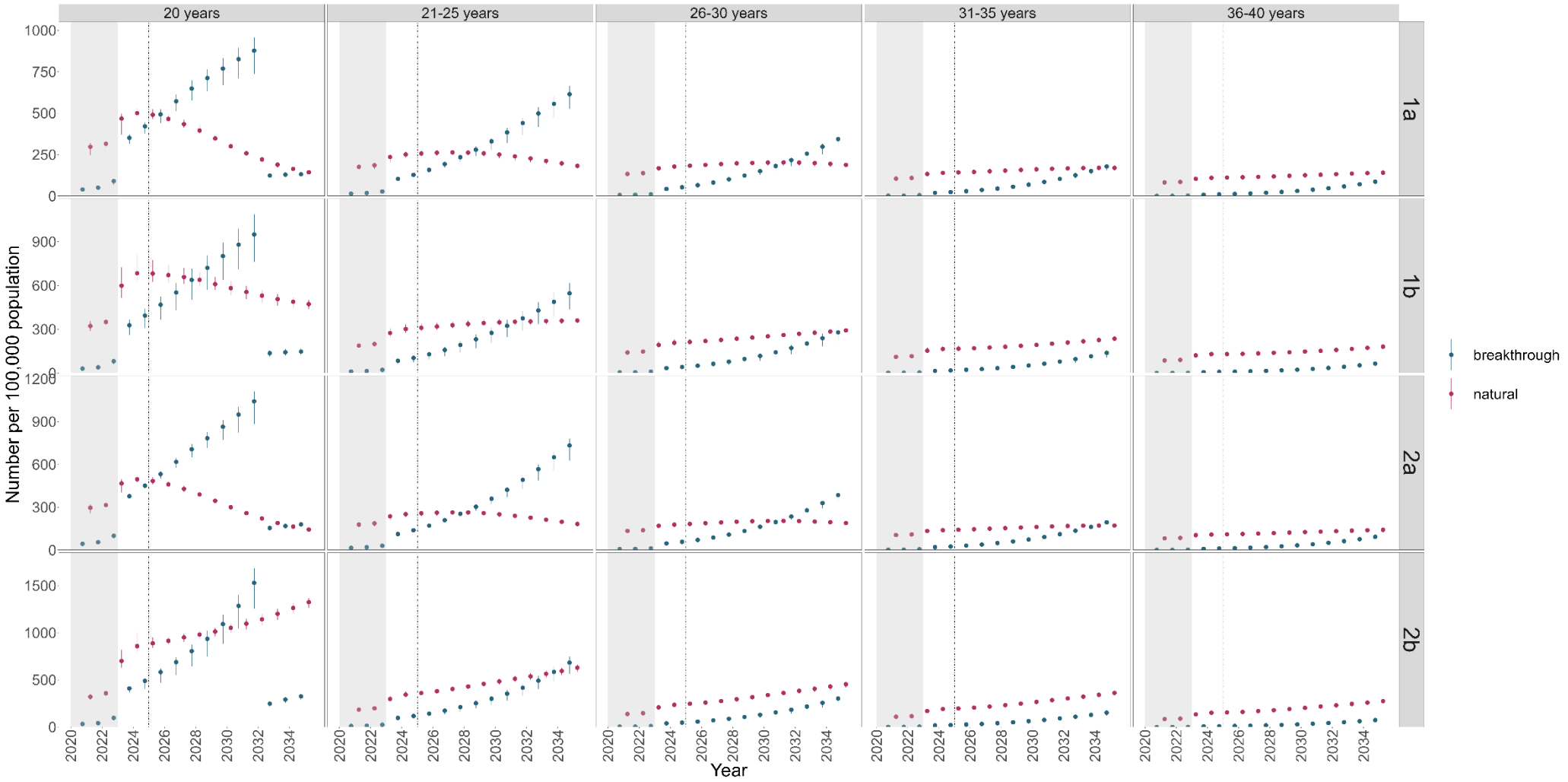
(d) Model 2b



Note:

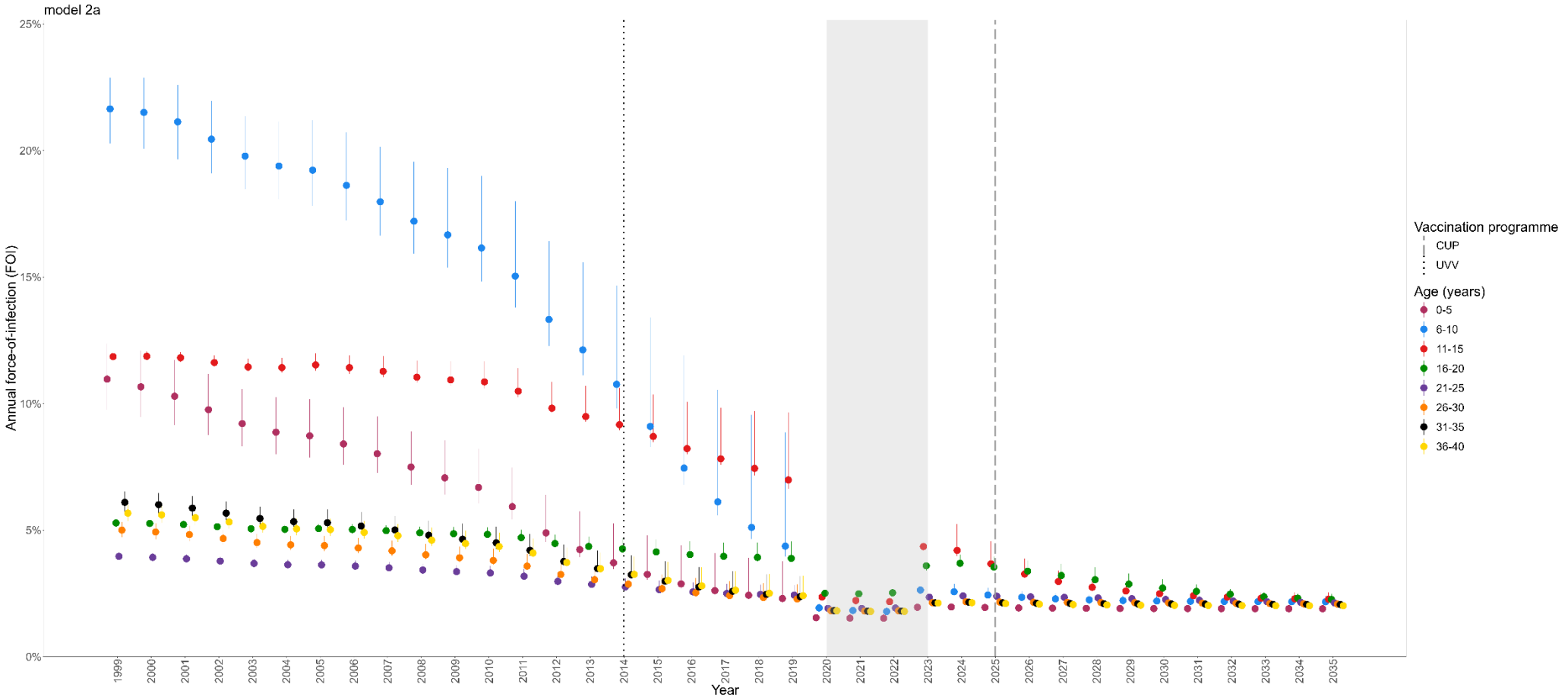
Solid lines represent natural infections whilst dotted lines represent breakthrough infections. The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.6d.

Figure 5.19. Age-specific modelled incidence of natural and breakthrough varicella infections per 100,000 for those aged 20 to 40 years with no catch-up programme for model 2a, 2020 to 2035, Hong Kong.



Note: The grey rectangle represents NPI implemented against COVID-19 between 2020 and 2023. The long-dash lines represent potential CUP in 2025. A longer projection to 2050 for illustrative purpose is available in [Supplementary Materials] as Figure S.5.7.

Figure 5.20. Age-specific annual force-of-infection (FOI) for model 2a, 1999 to 2035, Hong Kong.



Note: The vertical dotted line represents UVV introduction in 2014. The grey rectangle represents a period between 2020 and 2023 when NPI was implemented against COVID-19 between 2020 and 2023. The vertical dashed line represents potential CUP in 2025. FOI are presented according to the age groups of the contact matrix used in the model. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.8, which showed stable and low predicted FOIs for all age groups between 2036 and 2050.

Impact of a catch-up programme

All models predicted that achieving 80% uptake of a one- or two-dose varicella vaccine catch-up programme (CUP) in 2025 for cohorts born 2006 to 2012 would significantly reduce varicella incidence [Figures 5.21a]. After a CUP, the proportion of non-immune individuals (susceptible to natural infections) decreases immediately for those aged 10 to 14 years and 15 to 19 years, with reductions for those aged 20 to 39 years a few years after CUP [Figure 5.15a]. A greater reduction in overall varicella incidence is expected to be achieved by 2-dose CUP [Figure 5.22]. For instance, in my main model (model 2a) I predicted a 31% reduction of all varicella infections with a 2-dose CUP (IRR: 0.69 [95%CI: 0.69 to 0.70]) between 2025 and 2035, whereas 1-dose CUP averted only 12% of all varicella infections, compared to no CUP (IRR: 0.88 [95%CI: 0.87 to 0.89]) [Figure 5.23].

In the absence of a CUP, the cumulative incidence of varicella between 2025 and 2035 would be highest among those aged 15 to 19 years (model 2a cumulative incidence per 100,000: 359 [95%CI: 333 to 380]), followed by those aged 0 to 4 years (272 [95%CI: 234 to 297]), those aged 10 to 14 years (201 [95%CI: 193 to 221]), and similar levels for those aged 20 to 39 years (152 [95%CI: 139 to 160]) and those aged 5 to 9 (144 [95%CI: 141 to 156]) [Figure 5.22]. A two-dose CUP is expected to reduce 73% of infections for those aged 15 to 19 years (model 2a IRR: 0.28 [95%CI: 0.27 to 0.28]), 35% for those aged 20 to 39 years (IRR: 0.65 [95%CI: 0.64 to 0.65]) and 31% for those aged 10 to 14 years (IRR: 0.69 [95%CI: 0.68 to 0.71]) [Figure 5.23]. Similarly, the impact of a one-dose CUP is expected to be greatest in reducing varicella infections for those aged 15 to 19 years (model 2a IRR: 0.72 [95%CI: 0.70 to 0.73]), followed by those aged 10 to 14 years (IRR: 0.83 [95%CI: 0.81 to 0.85]) and those aged 20 to 39 years

(IRR: 0.90 [95%CI: 0.89 to 0.90]) [Figure 5.23]. A one-dose CUP is expected to reduce the peak incidence of the upsurge in these age groups, whereas the two-dose CUP is expected to prevent rebounds among those aged 10 to 19 years [Figure 5.24a]. Reductions in overall varicella infection incidence in remaining age groups are expected to be 10% or less for both one- and two-dose CUP [Figures 5.22 and 5.23].

The two-dose CUP is expected to substantially reduce the incidence of both natural and breakthrough infections for those aged 10 to 39 years [Figure 5.24b], whilst one-dose CUP is expected to achieve a similar impact on natural infections but would be less effective in reducing breakthrough infections [Figures 5.23 and 5.24b]. Increases in breakthrough infections were predicted for adults following one-dose (model 2a: 7% for those aged 20 to 39 years (IRR: 1.07 [95%CI: 1.06 to 1.09]) 10 years after CUP.

The predicted impact of one- and two-dose CUP by models 2a (main model) and 1a were similar [Figures 5.22 and 5.23]. The predicted reduction in infections (as reflected by IRR) of a CUP in model 2b was not as substantial as in model 2a, likely due to the possibility of waning of partial immunity acquired during the CUP vaccination.

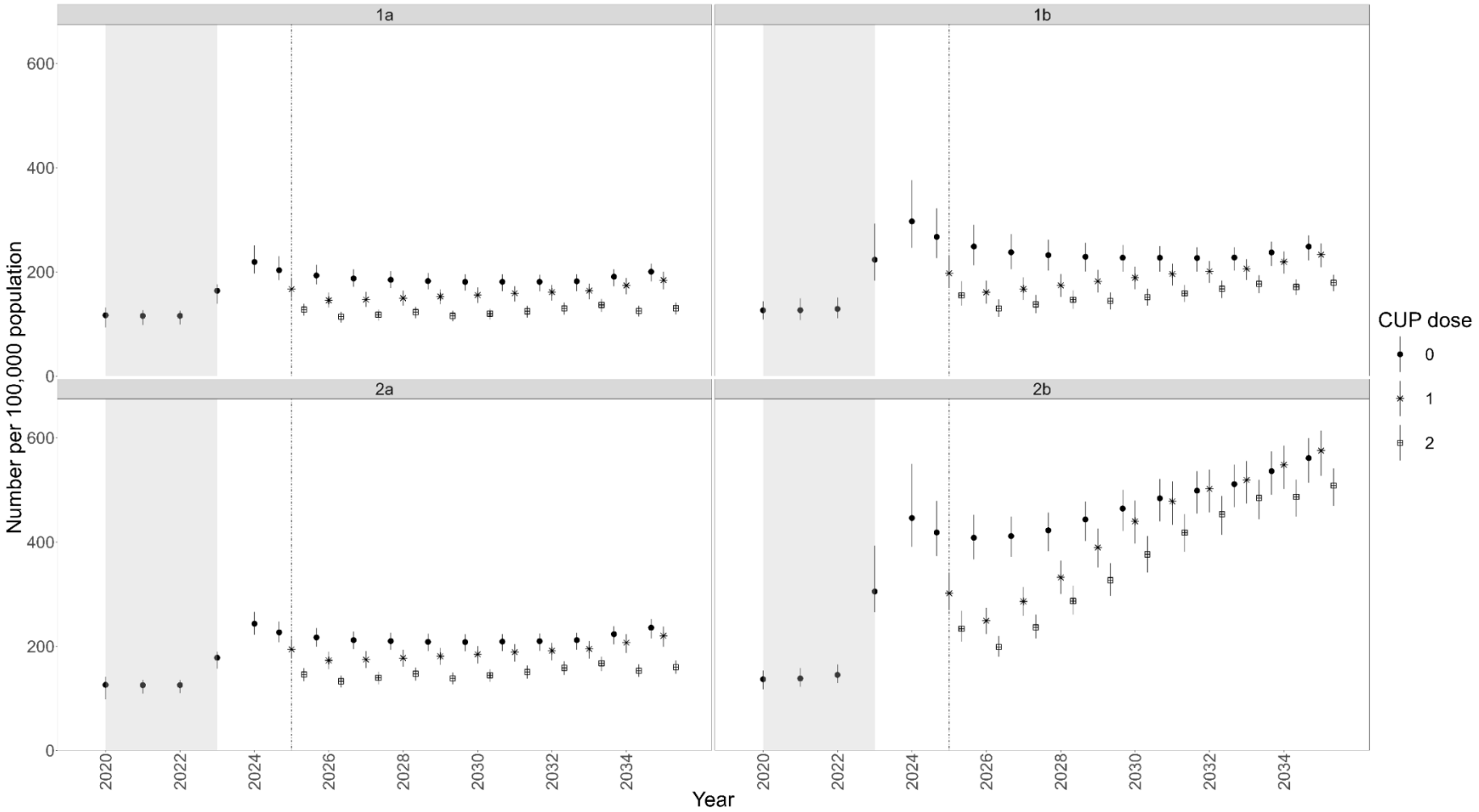
The model predicted a low level of varicella hospitalisations, with the highest rate for those aged 20 to 39 years (model 2a cumulative incidence between 2025 and 2035 per 100,000: 2.1 [95%CI: 1.7 to 2.4]) and those aged 0 to 4 years (1.7 [95%CI: 1.3 to 2.1]) and those aged 15 to 19 years (1.5 [95%CI: 1.3 to 1.7]) [Figure 5.28]. Both one- and two-dose CUP would significantly reduce the hospitalisation incidence for those aged 15 to 19 years (one- and two-dose CUP IRR: 0.35 [95%CI: 0.25 to 0.51] and 0.34 [95%CI: 0.24 to 0.50]) and for those aged 20 to 39 years (one- and two-dose CUP IRR: 0.69 [95%CI: 0.63 to 0.76] and 0.68 [95%CI:

0.62 to 0.75]) [Figure 5.29]. It should be noted that the predicted absolute reduction of varicella hospitalisations is low (1.0 and 0.7 per 100,000 for those aged 15 to 19 years and those aged 20 to 39 years) [Figure 5.28].

Sensitivity analyses on the impact of CUP were conducted to include varicella infections up to 2050 [Supplementary Figures S.5.10 to S.5.11]. The predicted longer-term impacts of CUP in reducing natural varicella are similar to those when only infections up to 2035 were included. In addition to the expected increase in breakthrough infections for adults aged 20 to 39 years following one-dose CUP, extending the analysis to 2050 resulted in 10% increases for those aged 40 to 59 years (IRR: 1.10 [95%CI: 1.08 to 1.11]) and 13% for those aged 60 to 79 years (IRR: 1.13 [95%CI: 1.06 to 1.20])), as well as an 18% increase for those aged 60 to 79 years (IRR: 1.18 [95%CI: 1.11 to 1.25]) following two-dose CUP.

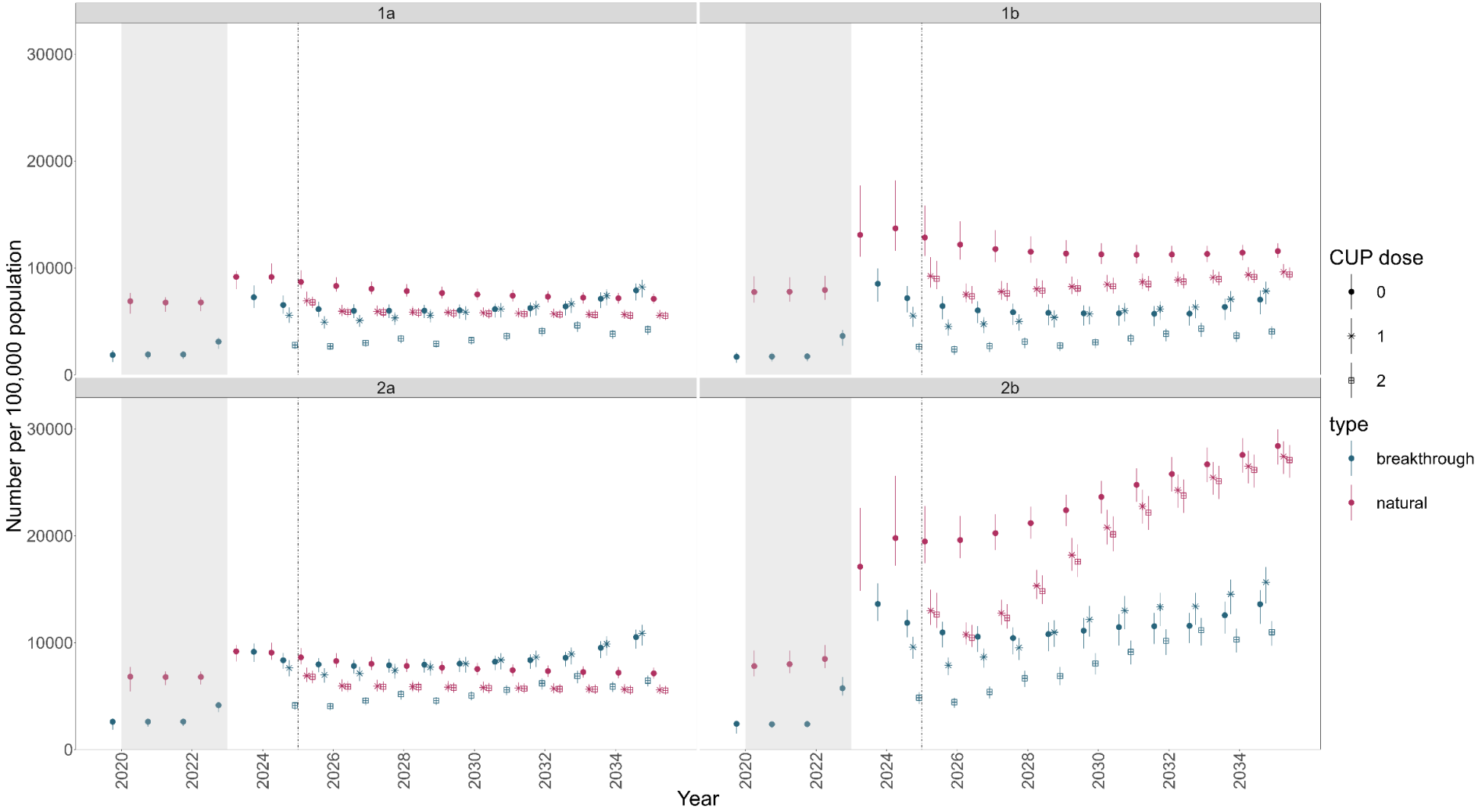
Figure 5.21. Model simulations of incidence of (a) all and (b) natural and breakthrough varicella infections per 100,000 with one- and two-dose catch-up programme, 2020 to 2035, Hong Kong.

(a) All varicella infections



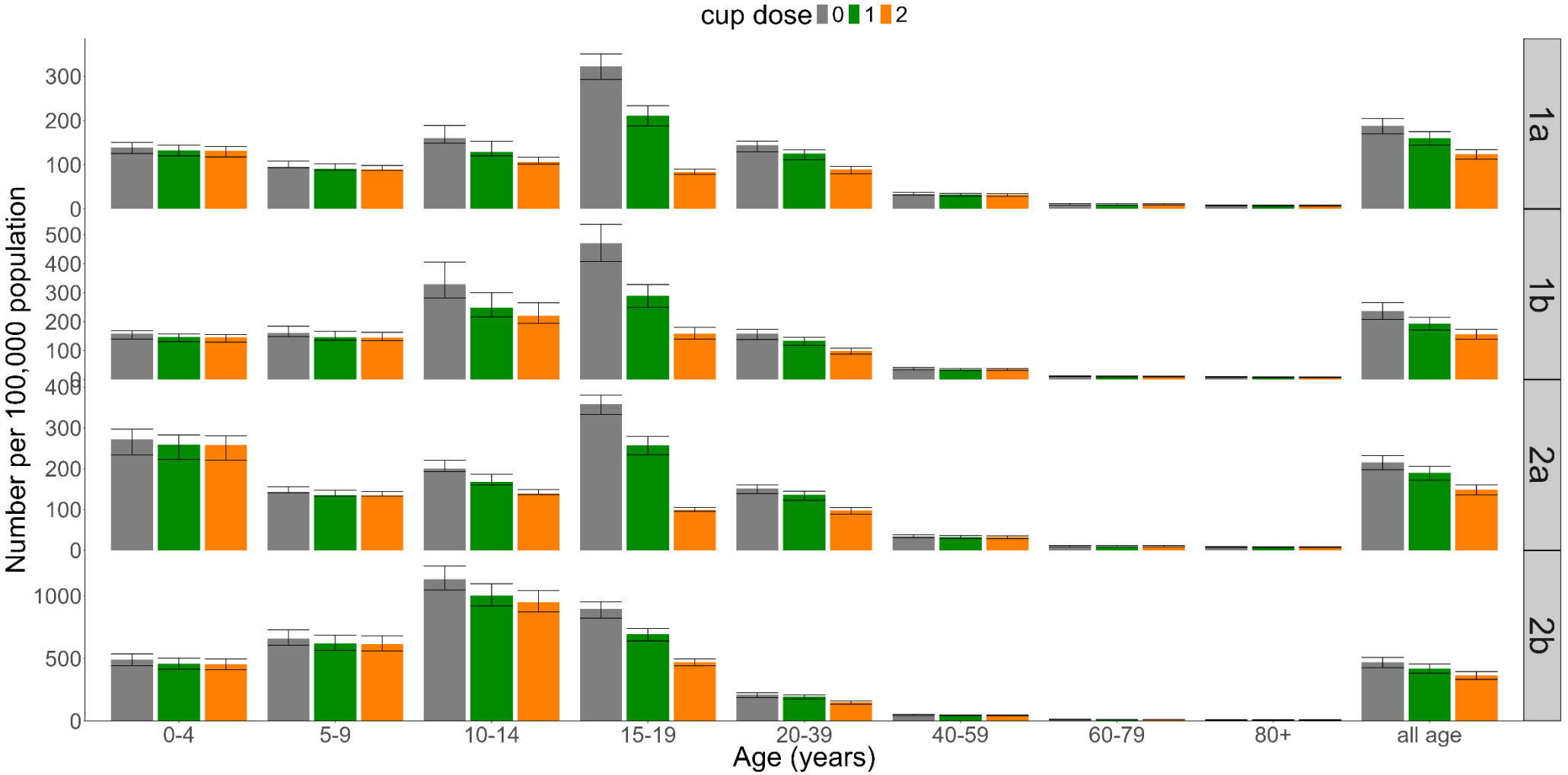
Note: The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. The vertical dashed line represents CUP in 2025. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.9a.

(b) Natural and breakthrough varicella infections



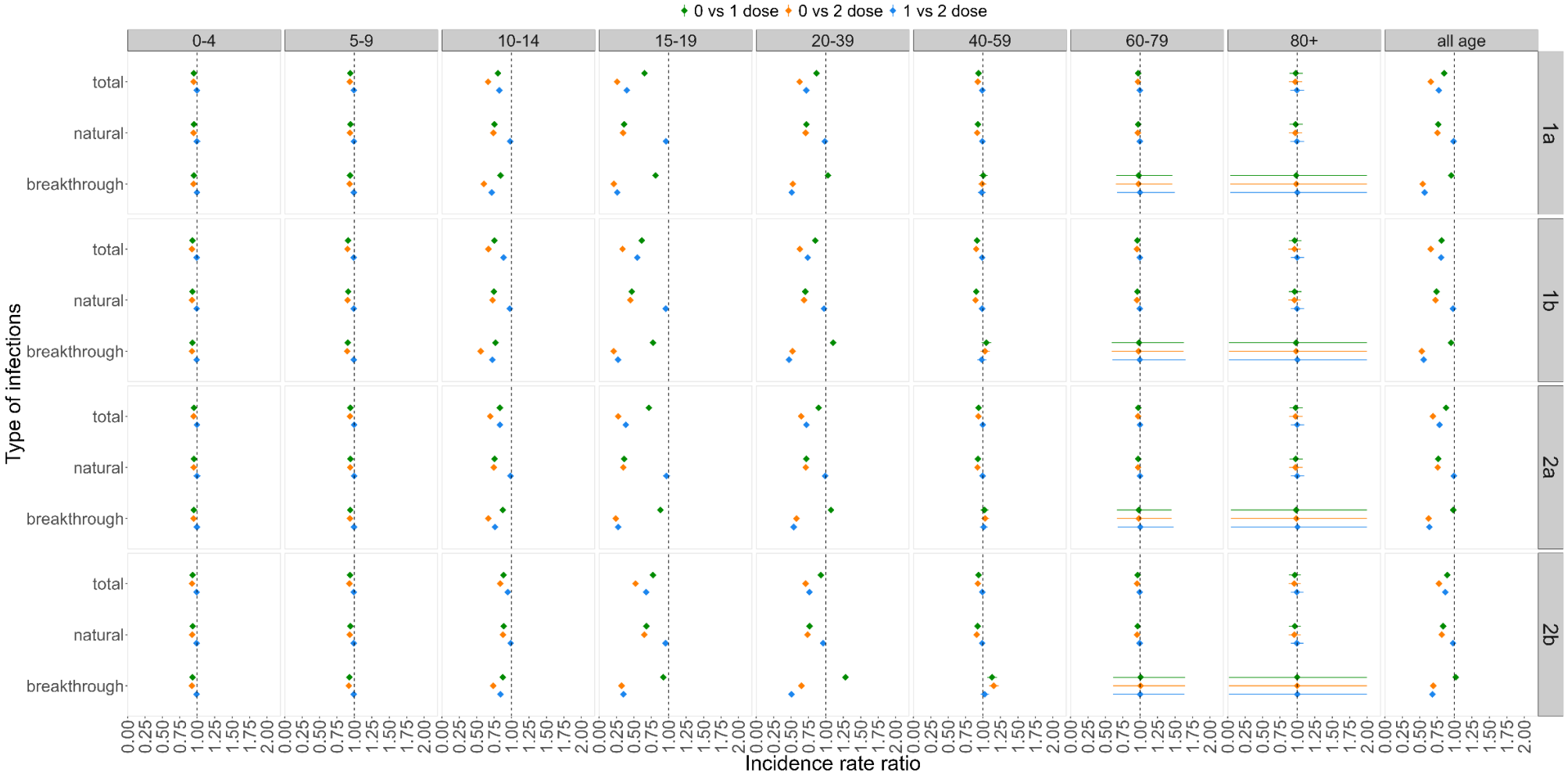
Note: The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. The vertical dashed line represents CUP in 2025. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.9b.

Figure 5.22. Cumulative incidence of simulated varicella infections per 100,000 with one- and two-dose catch-up programme for different models, 2025 to 2035, Hong Kong.



Note: Scales of y-axis differ by models. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.10.

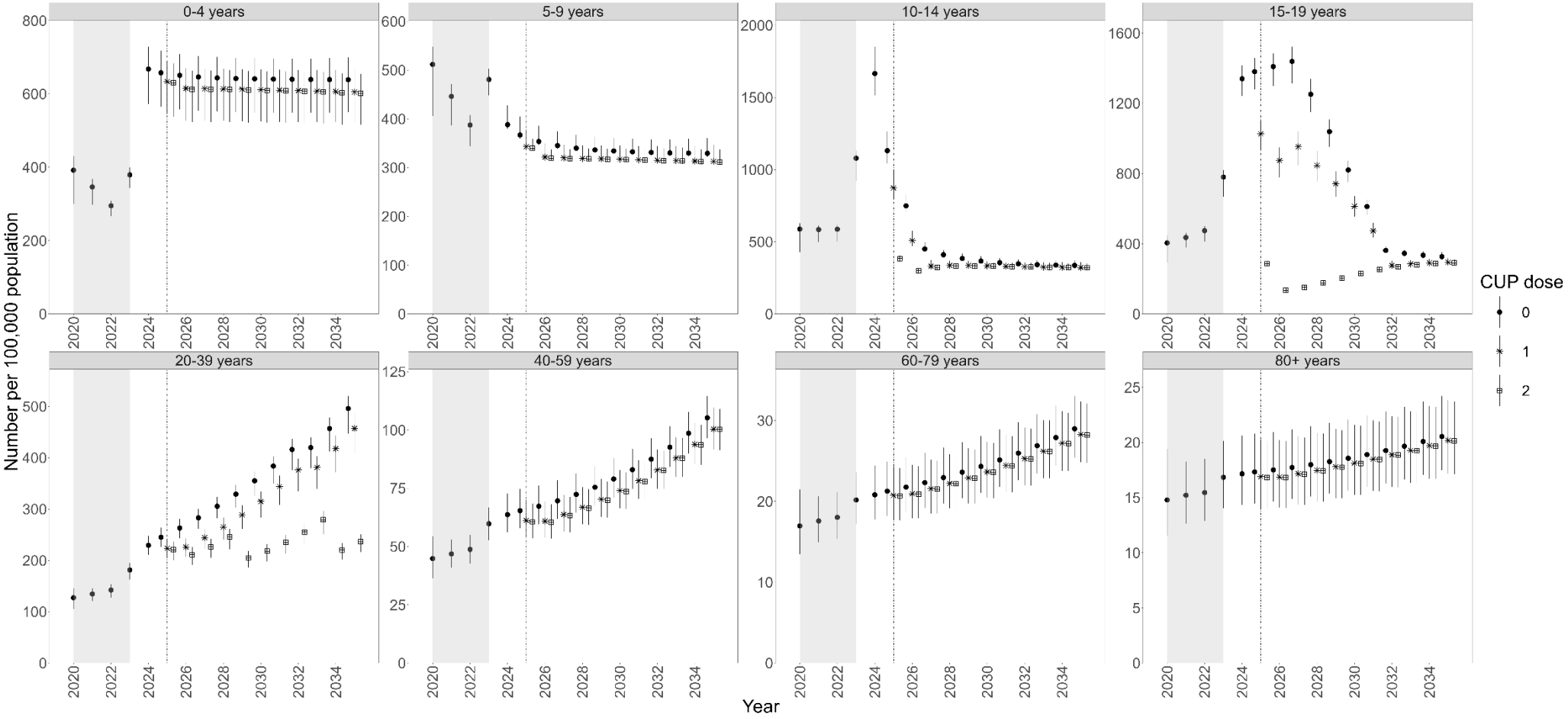
Figure 5.23. Incidence rate ratio of cumulative incidence of simulated varicella infections under different catch-up programme by age and models, 2025 to 2035, Hong Kong.



Note: An incidence rate ratio (IRR) under one indicates a lower incidence rate compared to the baseline and vice versa. The upper limit of IRR for adults aged over 80 years with breakthrough infections are over 2 for all models (between 22 to 60). For better visualistion they are limited to 2 in the above plot. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.11.

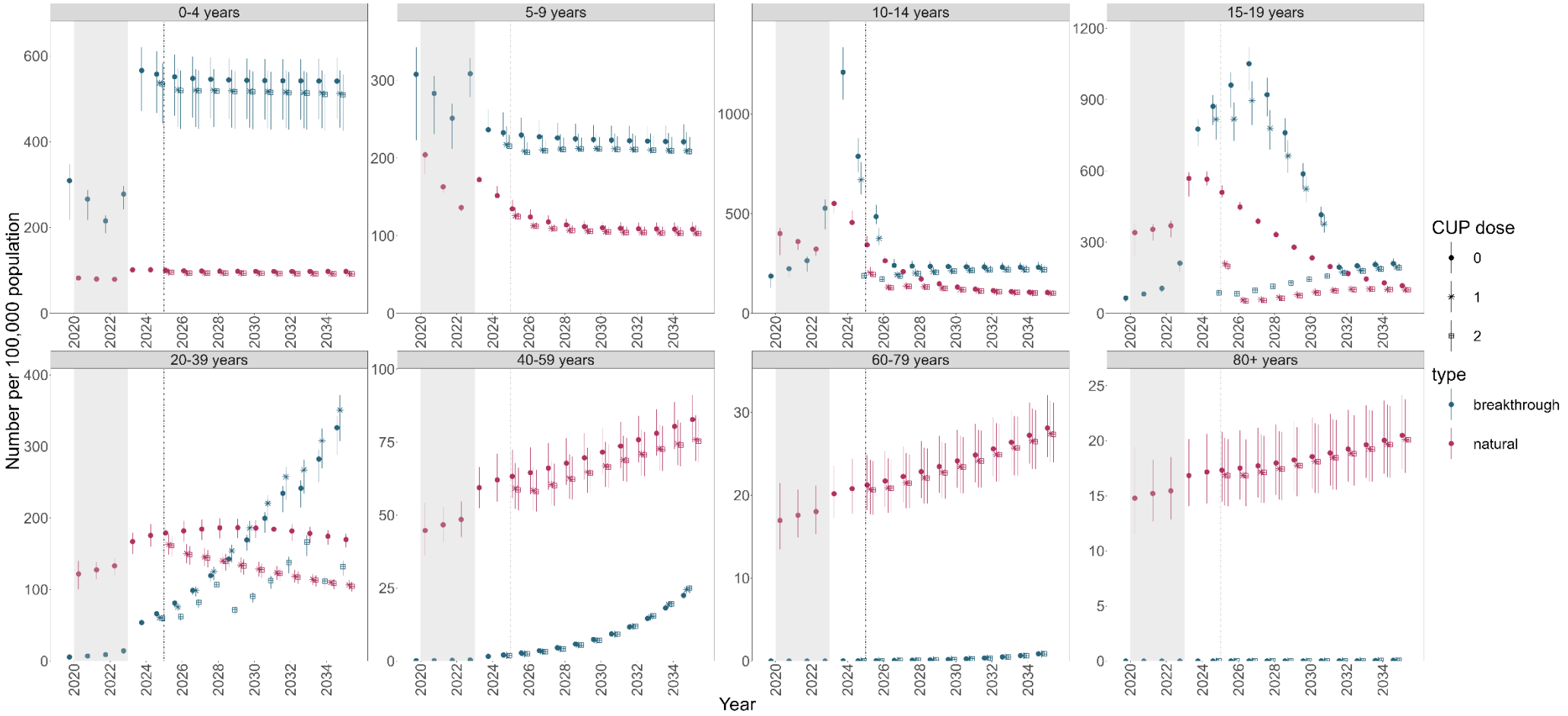
Figure 5.24. Model 2a simulations of age-specific incidence of (a) all and (b) natural and breakthrough varicella infections per 100,000 with one- and two-dose catch-up programme, 2020 to 2035, Hong Kong.

(a) All varicella infections



Note: The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. The vertical dashed line represents CUP in 2025. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.12a.

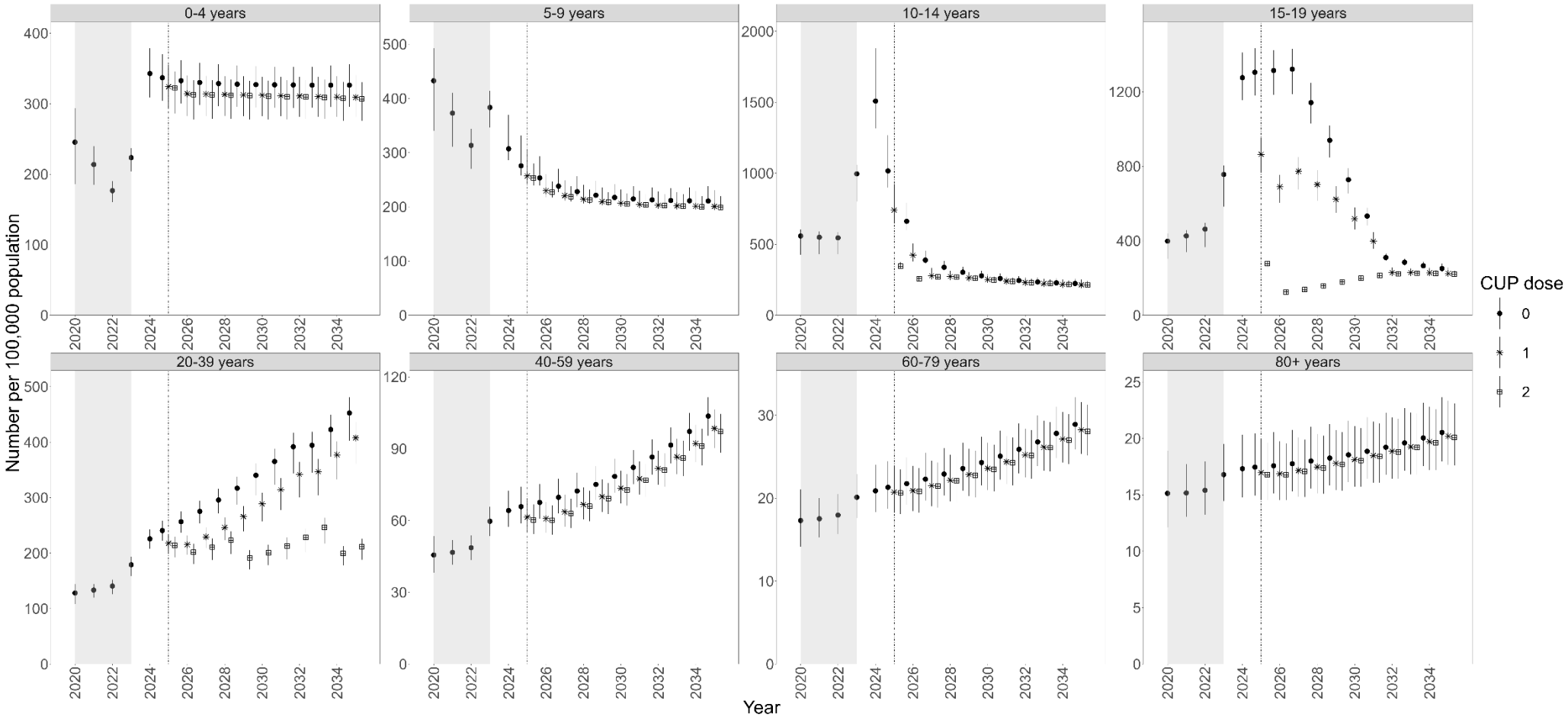
(b) Natural and breakthrough varicella infections



Note: The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. The vertical dashed line represents CUP in 2025. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.12b.

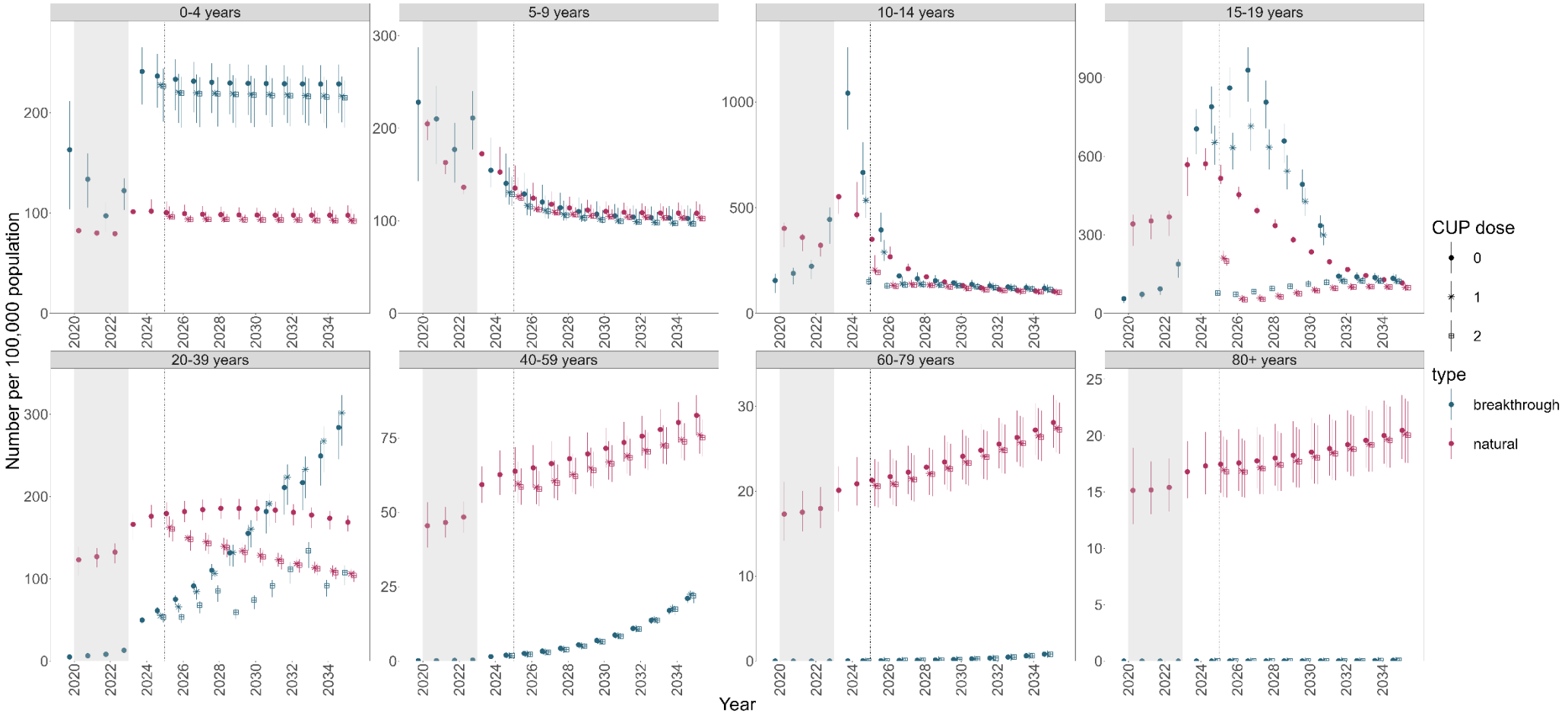
Figure 5.25. Model 1a simulations of age-specific incidence of (a) all and (b) natural and breakthrough varicella infections per 100,000 with one- and two-dose catch-up programme, 2020 to 2035, Hong Kong.

(a) All varicella infections



Note: The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. The vertical dashed line represents CUP in 2025. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.13a.

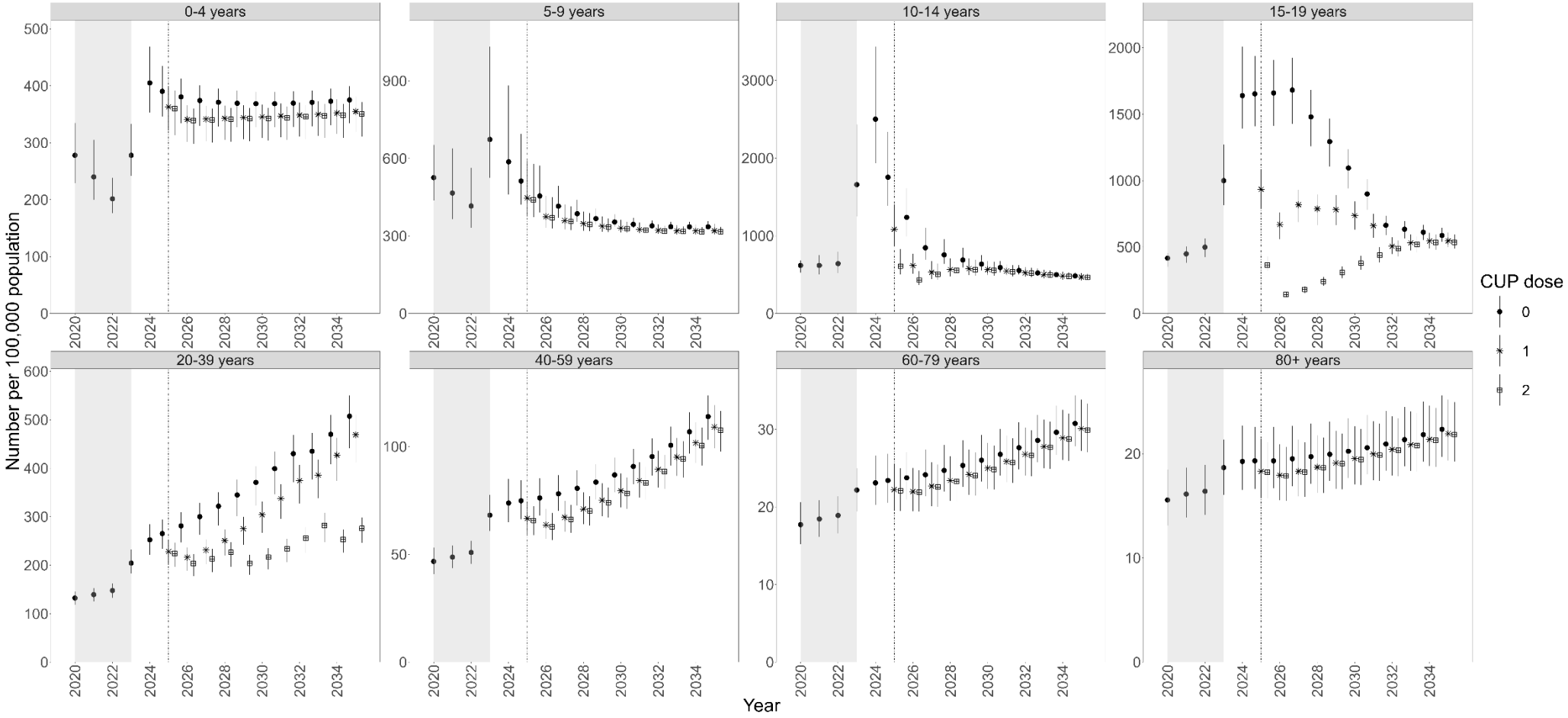
(b) Natural and breakthrough varicella infections



Note: The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. The vertical dashed line represents CUP in 2025. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.13b.

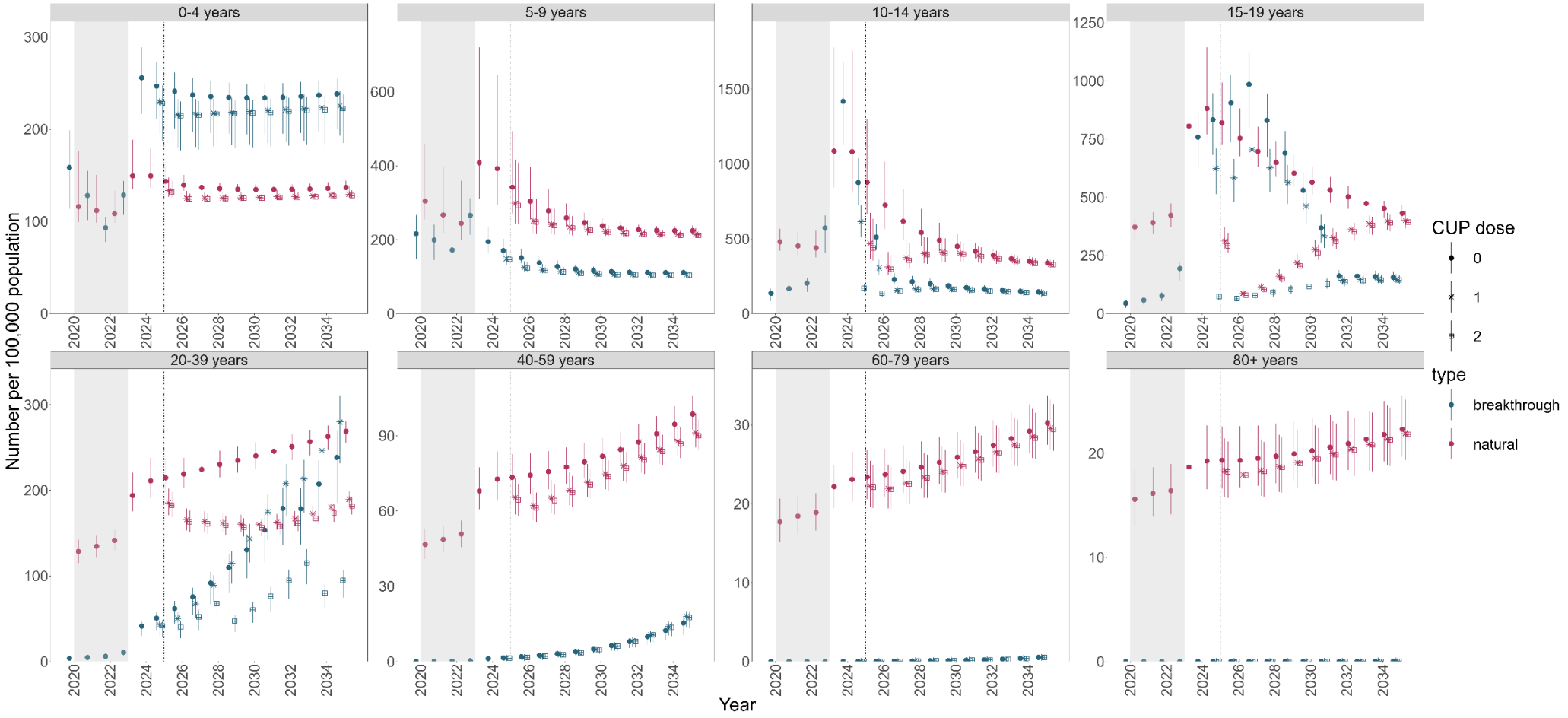
Figure 5.26. Model 1b simulations of age-specific incidence of (a) all and (b) natural and breakthrough varicella infections per 100,000 with one- and two-dose catch-up programme, 2020 to 2035, Hong Kong.

(a) All varicella infections



Note: The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.14a.

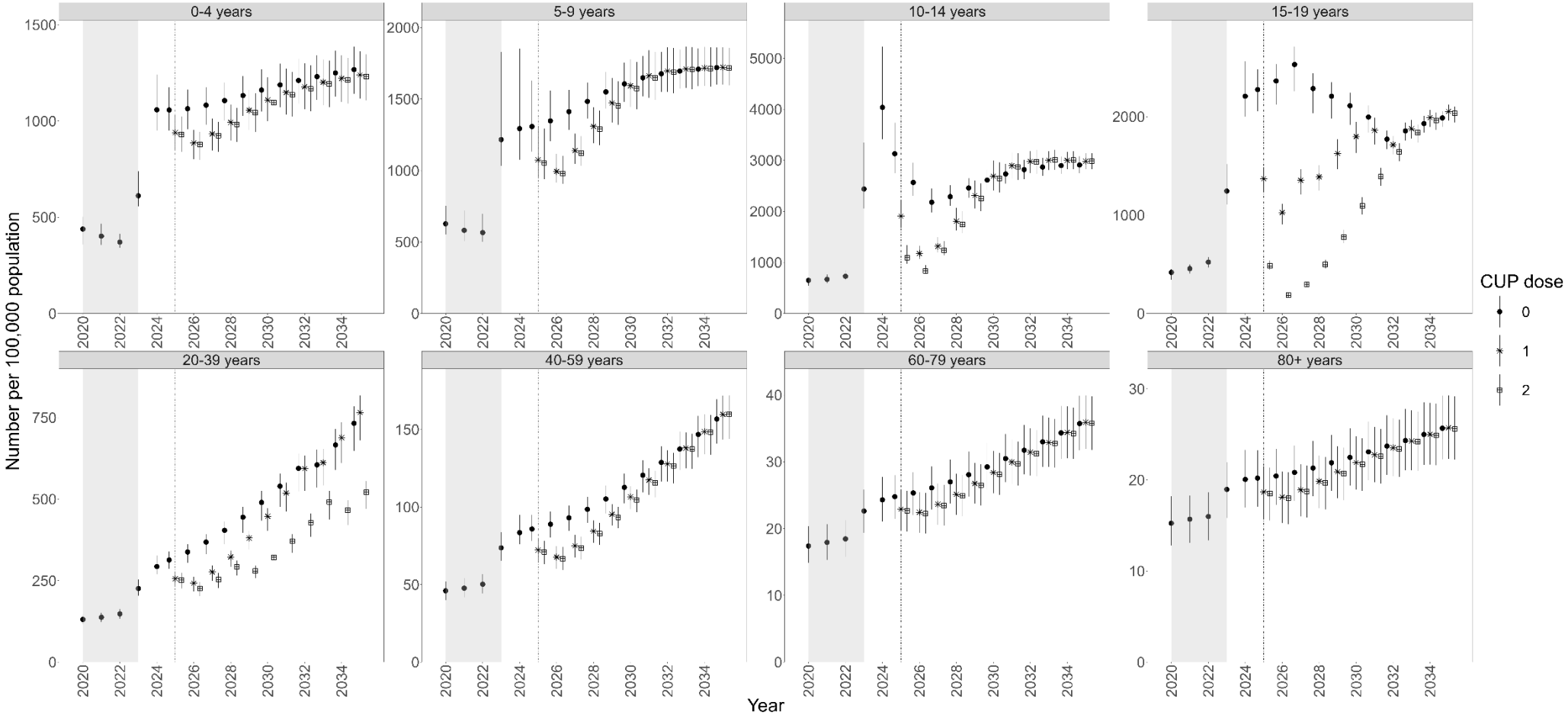
(b) Natural and breakthrough varicella infections



Note: The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.14b.

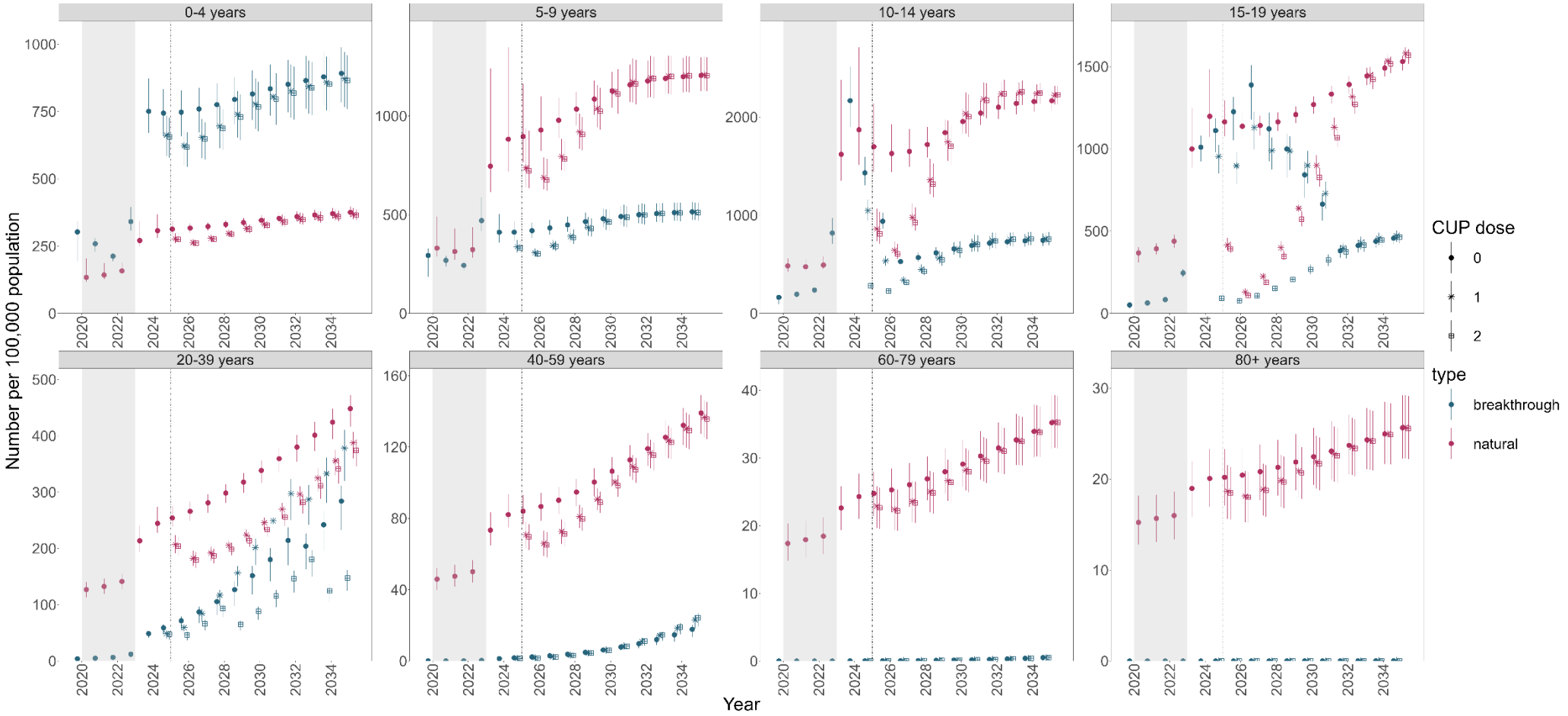
Figure 5.27. Model 2b simulations of age-specific incidence of (a) all and (b) natural and breakthrough varicella infections per 100,000 with one- and two-dose catch-up programme, 2020 to 2035, Hong Kong.

(a) All varicella infections



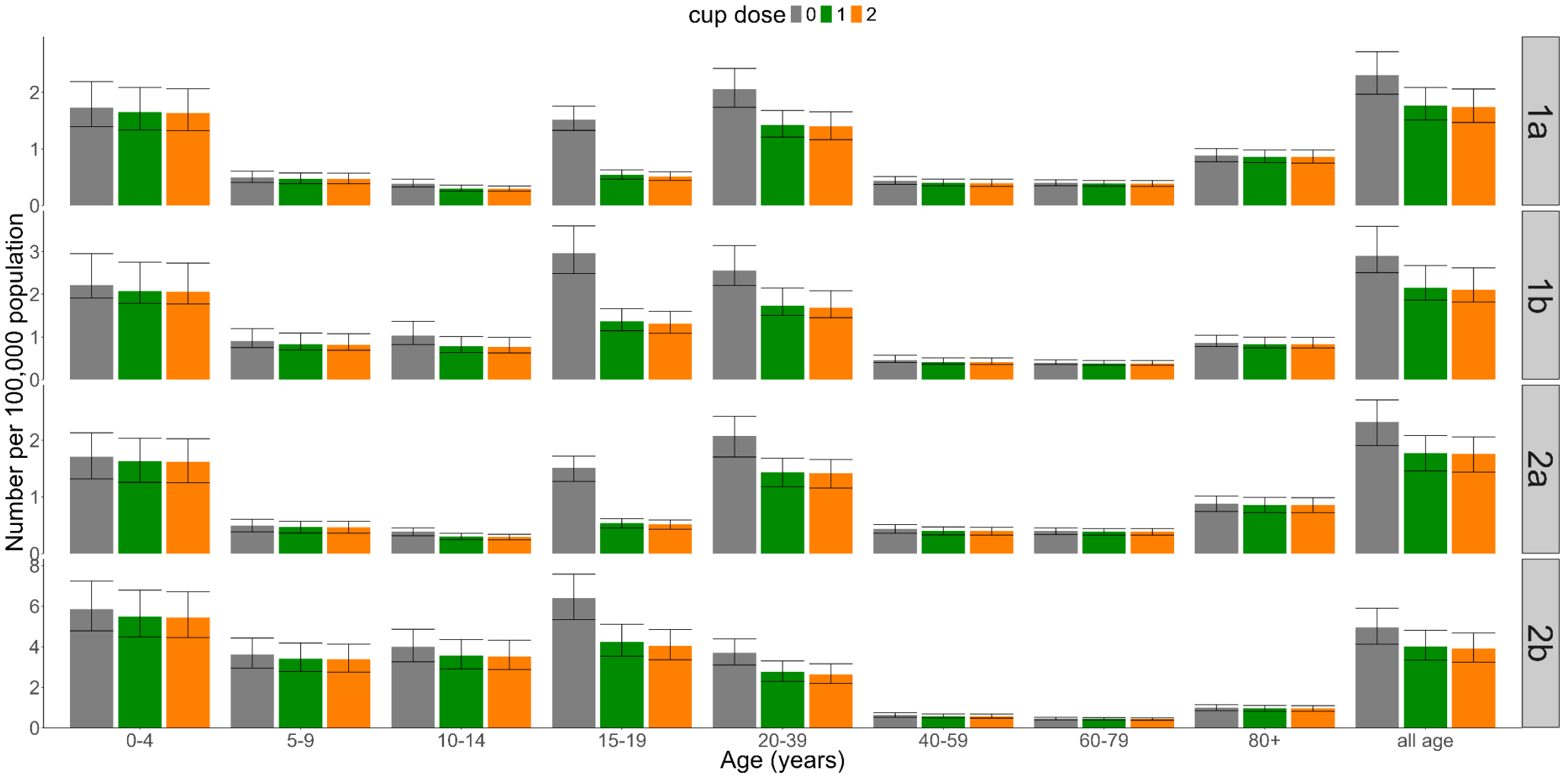
Note: The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.15a.

(b) Natural and breakthrough varicella infections



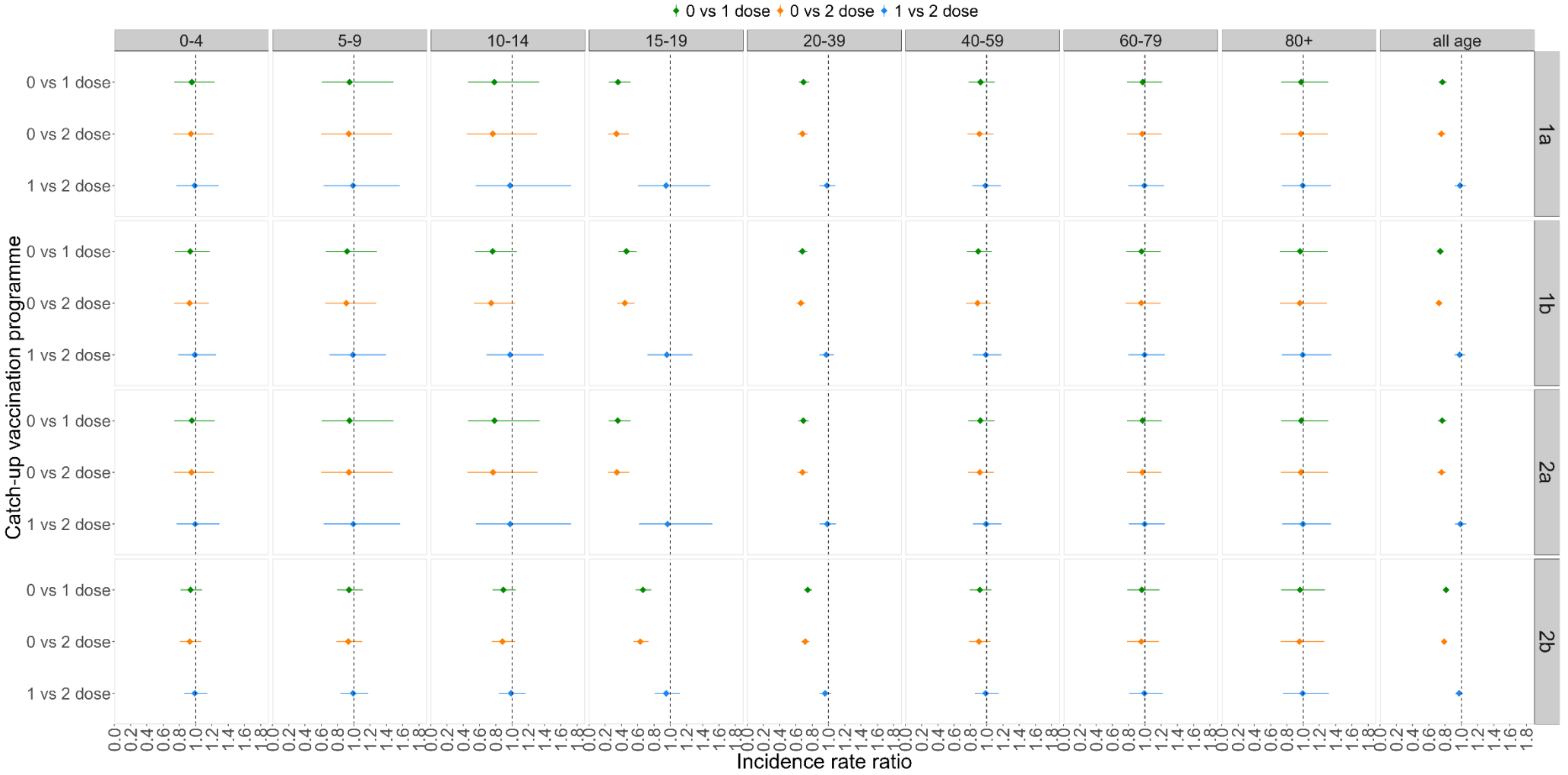
Note: The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.15b.

Figure 5.28. Cumulative incidence of simulated varicella hospitalisations per 100,000 with one- and two-dose catch-up programme for different models, 2025 to 2035, Hong Kong.



Note: Scales of y-axis differ by models. Only natural varicella was assumed to result in hospitalisations. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.16.

Figure 5.29. Incidence rate ratio of cumulative incidence of simulated varicella hospitalisations under different catch-up programme by age and models, 2025 to 2035, Hong Kong.



Note: An incidence rate ratio (IRR) under one indicates a lower incidence rate compared to the baseline and vice versa. Only natural varicella was assumed to result in hospitalisations. A longer projection to 2050 for illustrative purpose is available in Supplementary Materials as Figure S.5.17.

Discussion

Calibrated with over 20 years of seroprevalence and notification data, the model predicted resurgences of varicella infections for those aged 10 to 39 years after varicella transmission re-established as NPI effects against COVID-19 eased. The upsurges were predicted to mainly attribute to breakthrough infections for those aged 10 to 19 years and natural infections for those aged 20 to 39 years. These resurgences are expected to primarily affect cohorts born before 2013, who are not eligible for UVV and had low to medium vaccine uptake as preschoolers, as their susceptibility accumulated due to the reduction in varicella transmission following prolonged period of one-dose vaccination. The health burden of this predicted upsurge will mainly be on the primary care sectors, as the level of varicella hospitalisations was expected to be low (main model predictions among those aged 10 to 39 years between 2025 and 2035: 711 [95%CI: 664 to 761] varicella infections and 4.0 [95%CI: 3.3 to 4.6] hospitalisations per 100,000). The model also predicted that a 1- or 2-dose CUP targeting these cohorts will reduce the post-pandemic resurgence, with a nearly 3-fold greater reduction in infections expected from a 2-dose CUP. The burden of varicella will remain very low for young children aged under 10 years if high two-dose vaccine uptake can be maintained. Other findings of this modelling study will be discussed in detail in the following sections.

Successful inception of UVV alone was insufficient in reducing health inequality arising from private vaccination

Unlike Hong Kong, most countries started UVV without having an extended period of intermediate vaccine uptake in the private market. Despite the increasing number of countries who adopted a 2-

dose varicella vaccination programme, some countries still retain a 1-dose programme with the aim of reducing severe varicella diseases (46). Both Australia and South Korea have kept a funded 1-dose programme since their implementation in 2005, with the former having an adolescent catch-up programme and a revised recommendation of a second dose vaccine (118). Second dose varicella vaccine is now recommended in Australia to reduce the risk of breakthrough varicella, though it is not funded under its National Immunisation Program schedule (257). South Korea did not use a CUP but a vaccine uptake in private market as high as 73% before UVV (66), which was comparable to the situation in Hong Kong. Varicella notifications remained substantial in older children and adolescents for both countries 10 years after programme implementation (66, 67). Similar to Hong Kong, the implementation of a 2-dose UVV in Japan in 2014 quickly increased the vaccine uptake from 20% in the 1990s and about 50% before 2014, to 90% after the UVV (96). Varicella incidence among children under ten years of age decreased between 2014 and 2019, with an increase in incidence among teenagers in the same period (96). The experience in these countries in observing the age shift of varicella disease burden seem similar to the results of this modelling study, as a prolonged period of one-dose varicella vaccination is expected to lower the transmission and disease burden of those vaccinated, leaving the unvaccinated with a reduced chance of acquiring immunity via natural infections at younger ages, with lower complication risks. Hence, the disparities of private varicella vaccination among cohorts not eligible for UVV in Hong Kong might lead to health inequalities, as parents of those unvaccinated were likely to be less affluent and/ or less confident in varicella vaccination. These unvaccinated children would have acquired natural immunity via infections if there had been little or no private vaccination. Even if private vaccination persisted, offering CUP to these children along with the UVV roll-out would have protected them with partial immunity via vaccination and the risk of developing complications and severe disease is lower from breakthrough varicella (1).

Despite a successful inception of UVV, the model showed a continuous increase in both notifications and infections among older children and adolescents in the absence of CUP. There was some recent empirical evidence supporting this prediction. In December 2024, the Department of Health Hong Kong published an update on varicella epidemiology, which showed that the rate of varicella notifications per 100,000 for those aged 12 to 17 years increased from 58 in 2022 to 142 per 100,000 in 2024 while the notification rate in younger children remained very low (258). In 2024, these adolescents aged 12 to 17 years accounted for the highest proportion of varicella notifications (31%), followed by children aged 6 to 11 years (11%) and those aged 1 to 5 years (10%) (258). This observation suggested a continuous shift of notified varicella to adolescents. Further analysis on the risk of complications and hospitalisations associated with this increase in adolescents is warranted.

Potential impact and practical considerations of catch-up vaccination programme

The model simulation provided a prediction of the expected impact of a CUP for non-UVV eligible cohorts. Offering vaccination to those born 2006 to 2012, aged 13 to 19 years in 2025 may not only suppress an upsurge of varicella in a few years' time, but also reduce the incidence of natural infections when these cohorts reach young adulthood in later years. This is especially important as infection during pregnancy may result in complications for the fetus or newborn, which can lead to permanent congenital defects. A clinical trial has indicated that adolescents aged 13 to 17 years have a lower seroconversion rate and geometric mean titres than younger children after one dose of the monovalent Varivax (259). In addition, a study on healthcare workers receiving varicella vaccines showed that 31% of those initially responded would lose detectable antibodies levels after

a mean follow-up of 4.6 years (182). Therefore, a 2-dose CUP may be more appropriate for Hong Kong as the target cohorts would be aged 13 to 19 years by 2025. Delaying CUP further may result in a lower and less durable immune response for the target cohorts, which could lead to a diminished impact in reducing infections and diseases. Nevertheless, implementation of CUP will depend on the feasibility and acceptance of varicella vaccination for adolescents and young adults. Although a 2-dose CUP was predicted to have a greater impact in reducing varicella infections, delivering two doses of varicella vaccines to the CUP-eligible cohorts with high uptakes would be more costly and more difficult to achieve than a 1-dose programme. In addition, the 1-dose CUP is expected to reduce the incidence of natural varicella to a similar extent to the 2-dose CUP. The main incremental benefit of the 2-dose programme is its effect in reducing the incidence of breakthrough cases. Both one- and two-dose CUP are expected to reduce about 65% and 32% of varicella hospitalisation among those aged 15 to 19 years and those aged 20 to 39 years, but the predicted hospitalisation rate without CUP is very low at 1.5 and 2.1 per 100,000 between 2025 and 2035. Therefore, the main benefits of CUP would be the reduction of varicella in primary care settings. Several countries adopting varicella vaccine in their childhood immunisation programme have offered catch-up vaccination for older children and/ or adolescents. In the US, the CUP was initially 1-dose for children up to 12 years of age, which was extended to include a second dose in 2007 (55). On the other hand, the CUP for Australia consists of only one dose whilst the ones for Canada and Germany consists of two (252, 254, 260).

Similar to the adolescent varicella CUP in the US (55), Canada (252) and Australia (253), the CUP in Hong Kong was simulated targeting individuals without immunity from prior infection and/ or vaccination). This targeted CUP approach will limit vaccine wastage by avoiding vaccinating those already infected and/ or vaccinated. However, there will be hurdles in rolling out this targeted CUP.

First, it would be difficult to ascertain the infection and/ or vaccination status as parental or self-recall of varicella may be inaccurate and childhood vaccination records may not be complete. Antibody testing prior to varicella CUP is logistically challenging and unlikely to be cost-effective. Several varicella seroprevalence studies with subjects including children, medical and nursing students, healthcare workers and military recruits reported over 90% positive predictive values of self-/ parental reported varicella history, with negative predictive values ranging from 3% to 67% (261-265). Therefore, a self-reported negative history of varicella may not be a reliable indicator of a lack of immunity and a certain degree of vaccine wastage would be expected. A cost-effectiveness analysis based on the model simulations while taking into account various costs such as vaccines and its storage, programme delivery, vaccine wastage, medical costs of adverse events, etc. would better inform policy-makers on the merits of different CUP options.

The model predicted increases in breakthrough infections among those aged 20 to 39 years with one-dose but not two-dose CUP between 2025 and 2035. This is due to an increase in the proportion vaccinated following the CUP and a lower 1-dose VE against acquiring breakthrough infections (14% estimated for 1-dose vs 66% assumed for 2-dose). Furthermore, the model also predicted increases of 13% and 18% in breakthrough infections among adults aged 60 to 79 years following 1- and 2-dose CUP, when the projections were extended to 2050. It should be noted that the incidence of breakthrough infections in these adults was estimated to be very low (4.8 [95%CI: 4.5 to 5.0] per 100,000) and the absolute increase in incidence expected was only 0.6 and 0.8 per 100,000 for 1- and 2-dose CUP, respectively. The model was set up using differential equations to control the flow of populations between different age and disease compartments. As ageing occurs continuously at an average rate, a small number of individuals might age earlier or later than the assumed rate, which might contribute to this apparent accelerated increase in incidence of

breakthrough infections.

Characteristics of varicella vaccine effects

In this study, models were calibrated with real-world pre- and post-vaccine seroprevalence and notification data. Several vaccine efficacy related parameters were included in the model calibration such that the better fitted model(s) could be identified, and our understanding of the mechanistic action of the vaccine could be improved. A number of published varicella model studies include the temporary protection compartment, in which transient yet full immunity can be boosted to become permanent upon effective contact with an infectious person (61, 65, 76, 101, 118, 120, 123, 125-129, 133, 134). While high $VE\_temp\_protection_1$ was estimated for this state of protection in this study (model 1a: 71.3% [95%CI: 56.9 to 89.4%]; model 1b: 72.1% [95%CI: 57.1 to 88.1%]), the median estimate of the duration of this temporary protection ($d\_temp\_protection_1$) was about 6 years. Hence most of the 1-dose vaccinees may develop temporary but full immunity against varicella infections, but the level of immunity will drop rather quickly to a partial immune level such that most vaccinees would become susceptible to breakthrough infections. The shorter duration estimated showed that the assumption of 25 years or above of this temporary protection might have been too long (61, 118, 237). Similar fitting by model 2a without such a compartment indicated this may not be a significant pathway of protection for 1-dose varicella vaccination, in view of the substantial incidence of breakthrough infections. Both model fitting and forward simulation between models 1a and 2a (main model) were similar.

For those who are only partially immune and are susceptible to the milder breakthrough varicella (*Susceptible_1*), the 1-dose VE against acquiring breakthrough infections ($VE\_infection_1$) was

estimated to be low between 12.3% (95%CI: 4.6 to 24.4%) for model 1b and 14.1% (95%CI: 5.1 to 27.9%) for model 2a. These estimates are much lower than the 88% of $VE\_infection_1$ ($b_1 = 0.12$) assumed in the early Halloran model based on panel of expert opinions (133), and is much closer to the 27% vaccine efficacy ($b_1 = 0.73$) estimated by Brisson *et al.* using clinical trial data of MSD mVV (130) and the 10% vaccine effectiveness estimated by Gao *et al.* using the post-UVV surveillance data from the US (123). Once acquired, breakthrough infections are less likely to progress to symptomatic disease that might be notified (*VE_progression* for model 2a: 59.0% [95%CI: 20.3 to 82.2%]) and unlikely to further transmit the virus, as the median VE against onward transmission ($VE\_transmission_1$) was estimated to be at least 97% for all models. These estimations should be inferred with the immunological responses against varicella. Both humoral and cellular immunity are important in the protection against varicella with different roles. Humoral immunity is believed to be crucial in neutralising extra-cellular viruses and hence prevention of infection (2, 23). On the other hand, cellular immunity suppresses intracellular spread of the viruses, development of symptoms and severe disease, as well as reactivation of latent VZV (1, 2). Defects in cellular immunity but not humoral immunity were found to be associated with disseminated and fatal varicella diseases (2). Although both humoral and cellular immunity is stimulated following varicella vaccination, the lower level of IgG in one-dose vaccinees suggests that humoral immunity induced after vaccination may not be sufficient to protect against infections (23). These conform with the observation of high incidence of breakthrough infections despite achieving a high one-dose vaccine uptake in the US when UVV was first rolled out (50). CMI is often not directly measured in immunogenicity studies of varicella vaccination, but a sufficient level may have been elicited to prevent development of disease following one dose of vaccine. Meta-analysis of observational studies showed that the pooled VE of one dose varicella against all and moderate/ severe varicella was 81% (95%CI: 78% to 84%)

and 98% (95%CI: 97% to 99%), respectively (57). In my varicella VE estimation using varicella notification data, the 1-dose VE was 69% (95%CI: 67% to 71%) against any varicella and higher at 75% (95%CI: 53% to 87%) against hospitalisation and 85% (95%CI: 49% to 96%) against complicated varicella [Chapter 3]. The high 1-dose VE against moderate/ severe but not mild varicella indicates that the vaccine-induced immune response is effective in moderating disease severity. It should be noted that *VE_progression* estimated in the model cannot be directly compared to those estimated in clinical studies, as *VE_progression* is not only affected by the severity of disease leading to medical consultation, but also the vigilance to notify. The 1-dose VE against notified varicella estimated using the screening method in Chapter 3 (69%) is comparable to the combined median model estimates of the reduced risk against infection and disease progression once infected i.e. $1 - (1 - VE\_infection_1)*(1 - VE\_progression)$ or 64%.

The high VE against onward transmission ($VE\_transmission_1$) may be related to the effect of the vaccine in attenuating disease severity. In unvaccinated individuals, airborne transmission is believed to be the main route of VZV spread (2, 23). It is unclear if the viral load in the upper respiratory tract of vaccinees is reduced compared to the unvaccinated, but if vaccine-induced cellular immunity effectively alleviates disease severity by limiting the intracellular spread of the virus, the replication of viruses may also be suppressed. Physical contact also contributes to VZV transmission (2, 23). The risk of onward transmission of vaccine-type VZV (vt-VZV) in vaccinees with leukemia is proportional to number of skin lesions developed (2). In general, fewer lesions are developed for breakthrough varicella (usually fewer than 50, compared to 250 to 500 in unvaccinated cases). Hence, it is reasonable to assume vaccinees with breakthrough varicella will pose lower risk of onward transmission of wild-type VZV (wt-VZV) through physical contacts. Secondary attack rate in household outbreaks of wt-VZV from vaccinees with breakthrough

varicella was estimated to be 37% in one study, which is substantially lower than the high attack rate (over 80%) reported from unvaccinated cases (2).

The partial immunity acquired through one-dose vaccination also appears to be rather durable, as the fit to data for models 1b and 2b with pathways of waning of partial immunity (from partial (*S1*) to no immunity (*S*)) was inferior to the ones without, and the data did not support a good convergence of the posterior samples of *d_S1*. The absence of natural varicella resurgence among highly vaccinated cohorts in the US also does not support the waning of partial immunity to be substantial, at least since inception of their UVV in 1996 (50). As shown in the model simulations, a sizeable number of non-UVV eligible cohorts receiving mainly 1-dose varicella vaccine would remain partially immune and is predicted to develop breakthrough infections when they reach adolescence or adulthood. Further, model calibration using post-vaccine era data with a prolonged period of universal 2-dose vaccination would help determine the incremental benefits of second dose vaccination on these aspects of vaccine protection.

Model fit to notification data showed temporal changes in reporting sensitivity

The decreases in varicella notifications for children under 10 years of age and increases in notifications for those aged 10 years or above were captured by the models, after taking into account various vaccine efficacy parameters and changes in notification sensitivity (estimated to be a 6% increase per year). The inclusion of the later parameter is especially important in achieving a good fit to the adult data. Although mandatory notification allows for territory-wide surveillance of varicella, my previous analysis showed they are likely under-reported [Chapter 2] and temporal variation of reporting sensitivity would bias the analysis of the long-term trend, especially with

implementation of universal vaccination that is expected to impact disease epidemiology. An increase in notification sensitivity among children was also estimated between 2000 and 2010 based on analysis of the early serological data [Chapter 2]. The sensitivity of varicella notification may be affected by changes in health seeking behaviour over the years. Also, awareness to varicella by the public and reporting parties, including healthcare workers and schools, may improve following the introduction of UVV and publicity of varicella and shingles vaccination in the private market. Increase in notifications might also be attributed to misclassification of shingles in adults, as AED attendance and hospitalisations related to shingles were shown to have increased during the study period [Chapter 4.3]. Although the increase in notification sensitivity was unlikely to be uniform across different ages, a single parameter was estimated to avoid over-fitting of the model.

In addition to variation in reporting sensitivity, varicella notifications in Hong Kong depend mainly on clinical diagnosis. This may affect the specificity of the notification system, especially for breakthrough varicella. In Minnesota US, enhanced laboratory surveillance between 2016 and 2023 found that 56% of suspected varicella with 1-dose vaccination tested negative by varicella PCR (266). Alternative laboratory detection included enteroviruses (11%) and HSV-1 (5%). Only 22% vaccinees with clinical diagnoses at a medical facility were detected with varicella, compared to 66% who did not. Therefore, clinical diagnosis of varicella may be unreliable in the post-vaccine era. Laboratory confirmation of non-invasive specimens (such as oral fluid) from notified cases, even only on a representative subset of notified cases, should be explored to understand the specificity of varicella notifications. This will allow adjustment of the varicella notifications to obtain a more accurate estimate of the disease burden in the post-UVV era.

Modelled seroprevalence differed from the observed for young children with high vaccine uptake after UVV

A better fit to seroprevalence data, especially for 2015 and 2020 when varicella vaccine uptake in young children was rapidly increasing, was achieved by most models when the IgG test sensitivity was fitted rather than assumed to be fixed at 88%. As EIA assays of various sensitivity were used over the years, the estimated IgG test sensitivity to vaccine-induced immunity would be a more realistic representation of the collective sensitivity of these assays (169). Despite a good overall fit, there were differences in the observed and modelled seroprevalences for those aged 1 to 4 years in 2015 and 2020 when IgG test sensitivity was estimated. As shown in my previous analysis in Chapter 4.2, the observed seroprevalence for those aged 1 to 4 years in 2015 was likely under-estimated, as the lower than expected observed seroprevalence would leave no or little room for seroprevalence contributed by infections. This was highly unlikely given the abundance of varicella notifications and modelled infections in these children [Figure 5.16b]. After incorporating both the observed seroprevalence and notification data in the model calibration, as well as allowing a lower IgG test sensitivity to vaccine-induced immunity to be estimated after model calibration (median estimated sensitivity: 31% for models 1a and 1b; 53% to 55% for models 2a and 2b), the seroprevalence modelled were higher than the observed. This demonstrated the benefits of incorporating multiple data sources to better understand disease epidemiology, especially when both data had their limitations i.e. IgG test sensitivity and sampling issue for serology [Chapter 4.2] and reporting sensitivity for notifications [Chapter 4.3]. On the other hand, the estimated IgG test sensitivities (31% to 55%) were too low to achieve a good fit for those aged 1 to 4 years in 2020 (which should be as high as 88% based on over 98% of uptake in these children and the assumption of a 5% primary vaccine failure rate [detailed in Method '*Candidate models with*

alternative model structures']). This may indicate a higher antibody level elicited shortly after receiving the first dose of varicella vaccine and/ or the EIA assay used in 2020 having a significantly higher test sensitivity to vaccine-induced antibody than other assays used in earlier years. As discussed in Chapter 4.2, a more reliable serological assay to detect vaccine-induced antibody and availability of quantitative IgG levels, such as a glycoprotein (gp)-ELISA, would allow a more appropriate cut-off to define seropositivity in the post-vaccine era. It should also be noted that sampling issues might have contributed to the lower-than-expected sensitivity of the IgG assay.

Limitations of the modelling study

There are several limitations that may affect the interpretation and reliability of long-term projections of this modelling study. First, as described in Chapter 4.3, the Hong Kong population has been ageing considerably during the study period and there are fewer newborns in recent years. Likewise, with reduced class size and fewer pupils per schools, contacts among children might become less frequent [Chapter 2]. When calculating the likelihood of the varicella notifications during the model fitting, I took into account the temporal changes in age-specific population by scaling modelled number of infections with the actual population in the respective age and year. Nevertheless, variations in age-specific contacts might have contributed to the decrease in VZV transmission over the years and the vaccine effect might have been over-estimated.

Second, the compartments and age structure of the model may lead to imprecision of the long-term projections. To balance precision with computational efficiency, the model population was grouped into one-year cohorts for those aged 20 years or below and five-year cohorts for those aged

between 21 and 100 years. To reduce complexity, a one-dose model was used as the majority of the children opted for private vaccination received only one dose and UVV eligible children would have received their second dose only starting in 2020. These combinations would sufficiently reflect varicella vaccination before 2033, as the UVV eligible cohort born in 2013 are still 20 years of age or below and they would only fall into one-year age groups in the model. When these individuals reach 21 years of age, they will be grouped into five-year age groups (21 to 25 years) that consist of older non-UVV eligible persons who would mostly have only received one dose of vaccine. During forward simulation, two dose VE was adopted for a five-year age group when the majority of the cohorts are UVV eligible i.e. have received two doses of vaccine. The impact of vaccine for adults would be under-estimated when one-dose VE was used despite some of the UVV eligible cohorts included having received two doses. Likewise, the impact would have been over-estimated when two-dose VE was used despite not all cohorts included in those five-year age groups having received two doses. Although these inaccuracies might largely balance out, the year-by-year projections beyond 2033 would be less precise.

Third, model projections become less accurate when the time period of simulation is extended. The main analysis of the model projections in this study was only 10 years after the start of CUP, with longer-term projections serving for illustrative purposes only. As the model is an approximation of a complex system that includes not only disease immunity and epidemiology, but also other societal characteristics. The accuracy of model projections is affected by various factors, including population demographics, social contact pattern, attitudes, uptakes to varicella vaccination, as well as changes in health care provision and utilisation, etc. Some of these factors would likely change over a long period of time. Therefore, it is sensible to focus on short-term model projections as long-term projections are highly unlikely to be accurate.

In addition, uncertainty of model simulations during and after the COVID-19 pandemic exists due to several factors. For instance, any potential protective effect of masking may be reduced in close contacts and the effect of masking may be overstated. Although NPIs were lifted in March 2023, there might be ripple effects on the risk reduction behaviour affecting disease transmission after the pandemic. Individuals may more often wear face masks in public areas, even if not mandatory (186) and many adults continue to work from home part of the time. The effect of NPIs might also vary within each year, as reflected by within-year differences in risk reduction behaviour by cross-sectional surveys conducted in 2020 and 2022 (267, 268). Although the model with the POLYMOD contact matrix achieved a good fit to the pre-pandemic data, contacts may be reduced if in-person working and classes shift to more remote mode after the pandemic. As such, the predicted resurgence of varicella may be delayed as the FOI would be lower, decreasing the value of any CUP.

Furthermore, health-seeking behaviour and notification sensitivity likely have changed during and after the pandemic. Age-specific notification data were also not available after 2020 for model calibration. Although not included in model calibration, the notification rates per 100,000 predicted by the models between 2021 and 2024 were higher than the observed data [Figure 5.16]. A lack of age-specific notification data and other potential changes in behaviour would affect the prediction of the size and timing of any future upsurge in cases. Third, an increasing number of residents after 2020 would have received 2-doses of varicella vaccine. On top of the 1-dose VE estimated during model calibration, forward simulations also depend on 2-dose VE which is referenced from other modelling studies. Further model calibration with 2-dose data can improve the reliability of these parameters.

Lastly, a static force of varicella infection contributed by HZ was estimated referencing the age-specific risk of HZ in a Taiwan study. This may differ from the risk of HZ in the Hong Kong population and the incidence may also have changed over the years. In future, varicella model incorporating compartments corresponding to HZ diseases and vaccination would provide a more accurate evaluation of the dynamics between varicella and shingles. With the rapidly ageing population in Hong Kong, understanding the cost-effectiveness of shingles vaccination to support decisions on funded vaccination should also be a priority.

Conclusion

In Hong Kong, one-dose varicella vaccination in the private sector for over 15 years and a publicly funded programme significantly reduced VZV transmission in the community, as the modelled varicella infections decreased from 1,060 per 100,00 in 1999 when private vaccination just started, to 366 per 100,00 in 2019, five years after the start of universal vaccination. With less varicella infections in the community before the pandemic and the reduction in VZV transmission during the pandemic due to the NPIs, non-immune and partially immune individuals further accumulated. The models project a post-pandemic resurgence of varicella which will consist of both natural and breakthrough infections, as the number of individuals with partial immunity has been increasing with more children receiving only one dose of vaccine during the years before UVV. A 1- or 2-dose CUP for older children and adolescents left out of UVV could significantly suppress this varicella upsurge.

Supplementary materials

Table S.5.1. Ratio of modelled notification due to natural varicella to hospitalisation data, Hong Kong, 2004 to 2019.

Figure S.5.1. Model fit to varicella notification data by model structure and fitting or fixing IgG test sensitivity towards vaccine-induced antibody, Hong Kong, 1999 to 2020 for (a) 0 to 19 years or below and (b) 20 years or above.

Figure S.5.2. Model 2a simulations of the overall proportion of population susceptible to natural (Susceptible_0) and breakthrough varicella infections (Susceptible_1), 1999 to 2050, Hong Kong.

Figure S.5.3. Model simulations of the age-specific proportion of population susceptible to natural (Susceptible_0) and breakthrough varicella infections (Susceptible_1) for (a) model 2a, (b) model 1a, (c) model 1b and (d) model 2b, 1999 to 2050, Hong Kong.

Figure S.5.4. Incidence of modelled varicella infections and notifications per 100,000 (a) all age (b) age-specific, 1999 to 2050, Hong Kong.

Figure S.5.5. Incidence of overall modelled varicella natural and breakthrough infections per 100,000, 1999 to 2050, Hong Kong.

Figure S.5.6. Age-specific modelled incidence of varicella natural and breakthrough infections per 100,000 for (a) model 2a, (b) model 1a, (c) model 1b and (d) model 2b, 1999 to 2050, Hong Kong.

Figure S.5.7. Age-specific modelled incidence of natural and breakthrough varicella infections per 100,000 for those aged 20 to 40 years with no catch-up programme for model 2a, 2020 to 2050, Hong Kong.

Figure S.5.8. Age-specific annual force-of-infection (FOI) for model 2a, 1999 to 2050, Hong Kong.

Figure S.5.9. Model simulations of incidence of (a) all and (b) natural and breakthrough varicella infections per 100,000 with one- and two-dose catch-up programme, 2020 to 2050, Hong Kong.

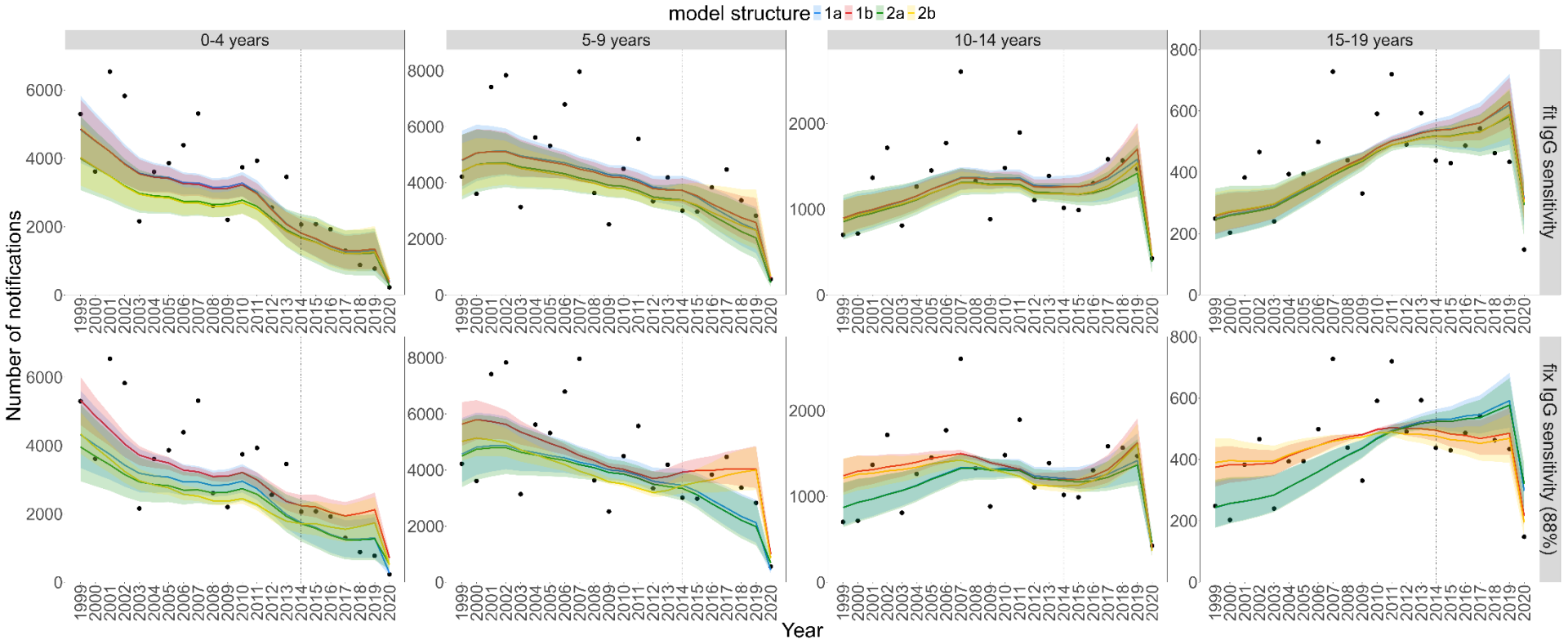
Figure S.5.10. Cumulative incidence of simulated varicella infections per 100,000 with one- and two-dose catch-up programme for different models, 2025 to 2050, Hong Kong.

Table S.5.1. Ratio of modelled notification due to natural varicella to hospitalisation data, Hong Kong, 2004 to 2019.

Age group (years)	Number of hospitalisation	Model							
		1a		1b		2a		2b	
		Number of notification	Ratio	Number of notification	Ratio	Number of notification	Ratio	Number of notification	Ratio
0 to 4	1669	29259	0.06	30040	0.06	23797	0.07	24806	0.07
5 to 9	874	49146	0.02	51022	0.02	44939	0.02	47022	0.02
10 to 14	353	18213	0.02	18942	0.02	17468	0.02	18216	0.02
15 to 19	309	7072	0.04	7276	0.04	6931	0.04	7134	0.04
20 to 39	1129	13978	0.08	14050	0.08	13901	0.08	13950	0.08
40 to 59	240	1739	0.14	1735	0.14	1737	0.14	1729	0.14
60 to 79	101	194	0.52	193	0.52	194	0.52	193	0.52
80+	68	83	0.82	83	0.82	83	0.82	83	0.83

Figure S.5.1. Model fit to varicella notification data by model structure and fitting or fixing IgG test sensitivity towards vaccine-induced antibody, Hong Kong, 1999 to 2020 for (a) 0 to 19 years or below and (b) 20 years or above.

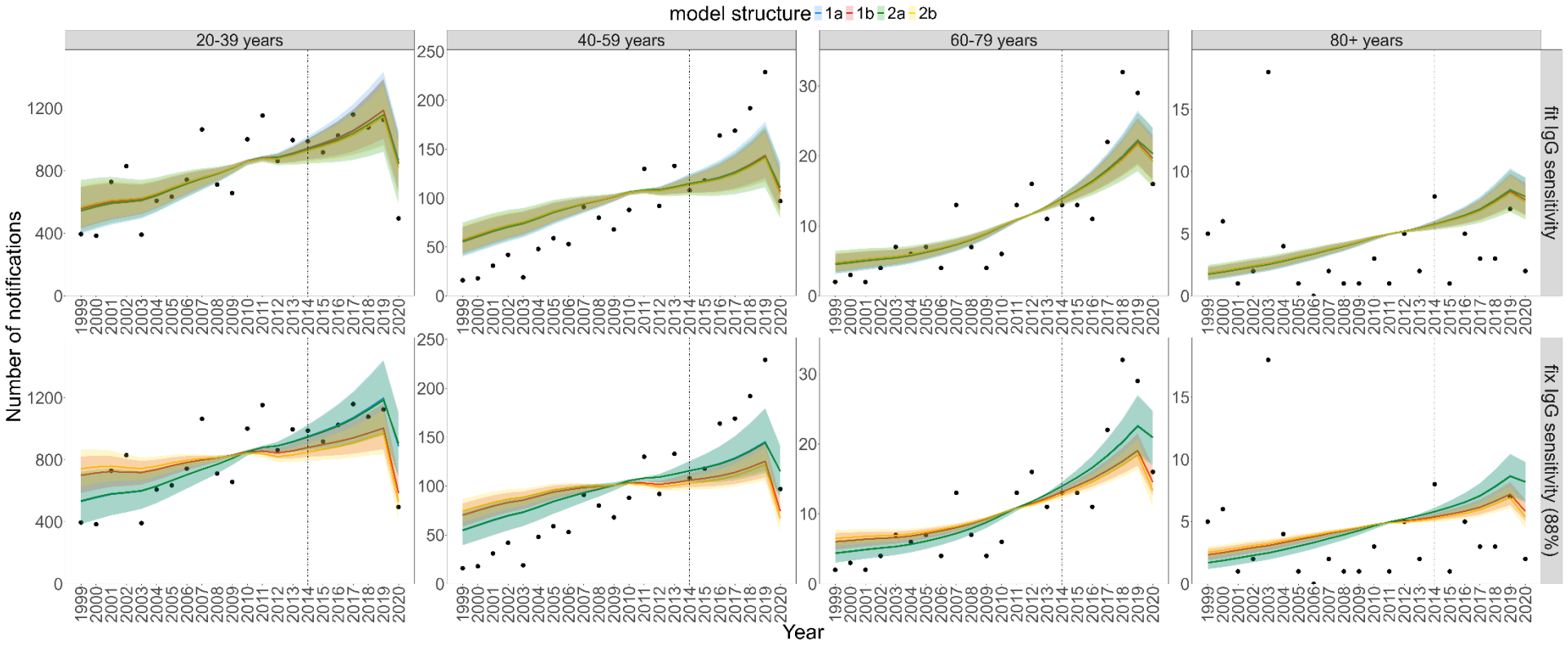
(a) 0 to 19 years or below



Dots: observed notification; Line (ribbon): modelled notification.

The upper row shows the observed and modelled notifications of different models with IgG test sensitivity to vaccine-induced immunity estimated. The lower row shows the observed and modelled notifications of different models with IgG test sensitivity to vaccine-induced immunity fixed at 88%. The vertical dashed line indicates the launch of UVV in 2014. Data fit included notifications of all ages between 1999 (first year of notification started) and 2019 (last year of age-specific notification data available before COVID-19 pandemic). Data of 2020 were not included in model calibration due to the effects of NPIs on varicella transmission.

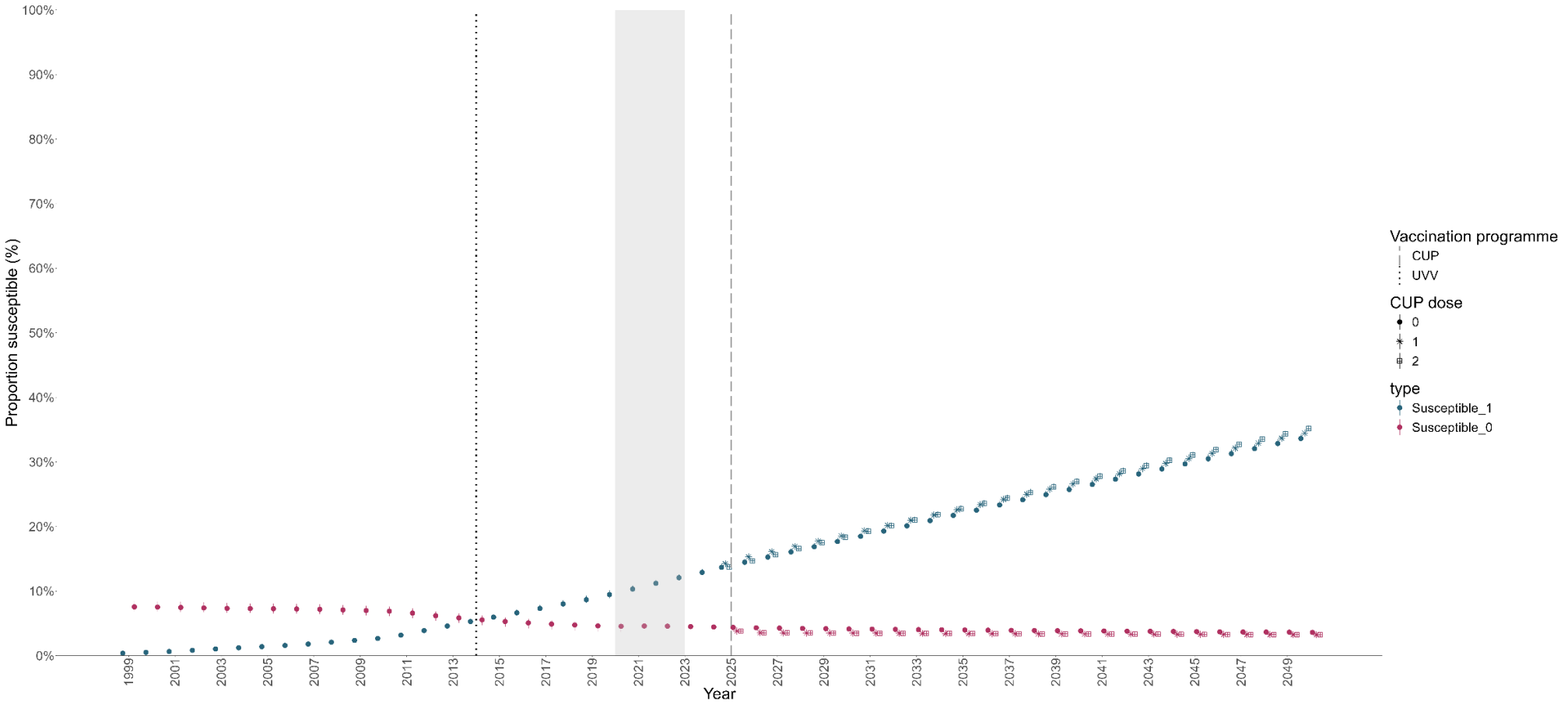
(b) 20 years or above.



Dots: observed notification; Line (ribbon): modelled notification.

The upper row shows the observed and modelled notifications of different models with IgG test sensitivity to vaccine-induced immunity estimated. The lower row shows the observed and modelled notifications of different models with IgG test sensitivity to vaccine-induced immunity fixed at 88%. The vertical dashed line indicates the launch of UVV in 2014. Data fit included notifications of all ages between 1999 (first year of notification started) and 2019 (last year of age-specific notification data available before COVID-19 pandemic). Data of 2020 were not included in model calibration due to the effects of NPIs on varicella transmission.

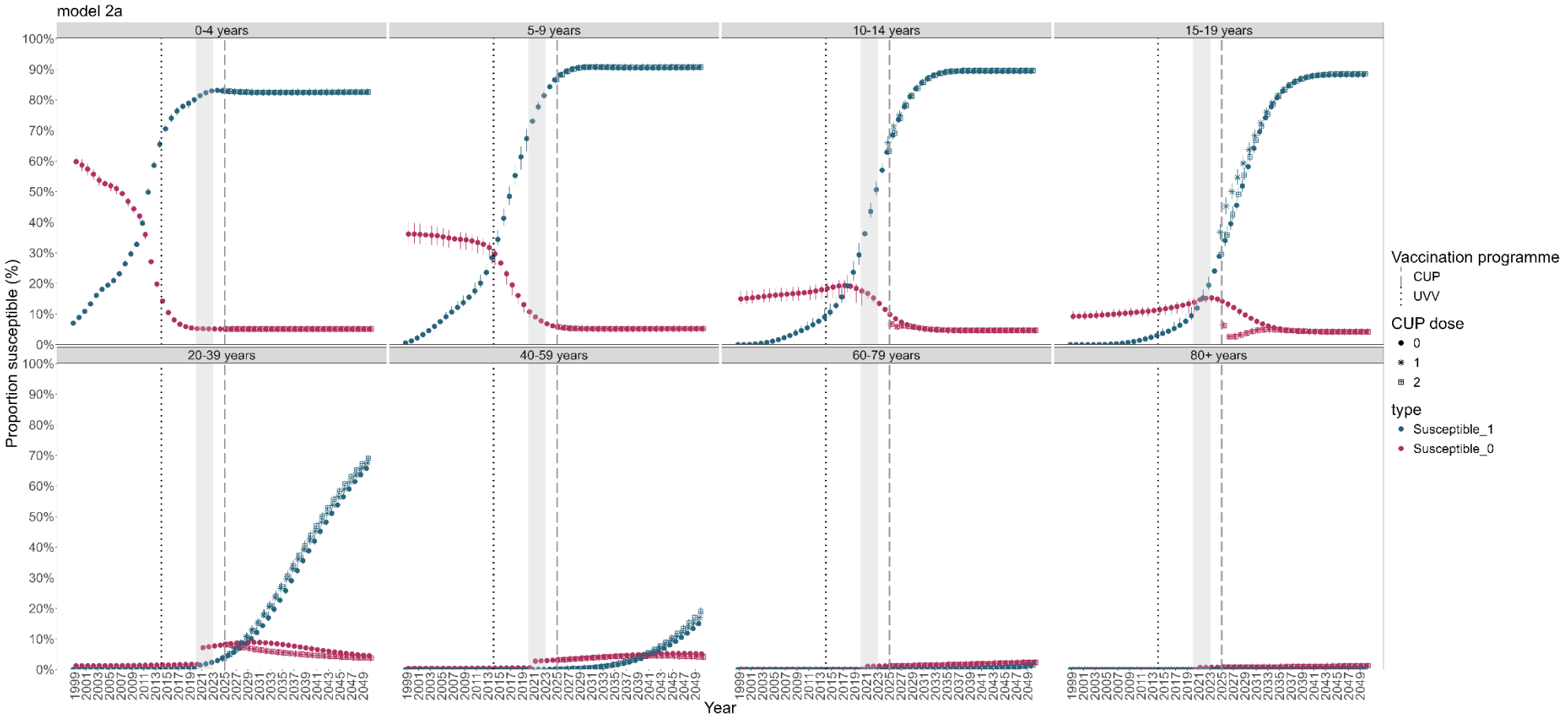
Figure S.5.2. Model 2a simulations of the overall proportion of population susceptible to natural (Susceptible_0) and breakthrough varicella infections (Susceptible_1), 1999 to 2050, Hong Kong.



Note: Susceptible_0 (S) represents proportion with no immunity and are prone to natural infections, whilst Susceptible_1 (S1) represents proportions with partial immunity and are prone to breakthrough infections. Changes in population susceptibility under different catch-up programme (CUP) are presented by different shapes. The vertical dotted line represents UVV introduction in 2014. The grey rectangle represents NPI implemented against COVID-19 between 2020 and 2023. The vertical dashed line represents potential CUP in 2025.

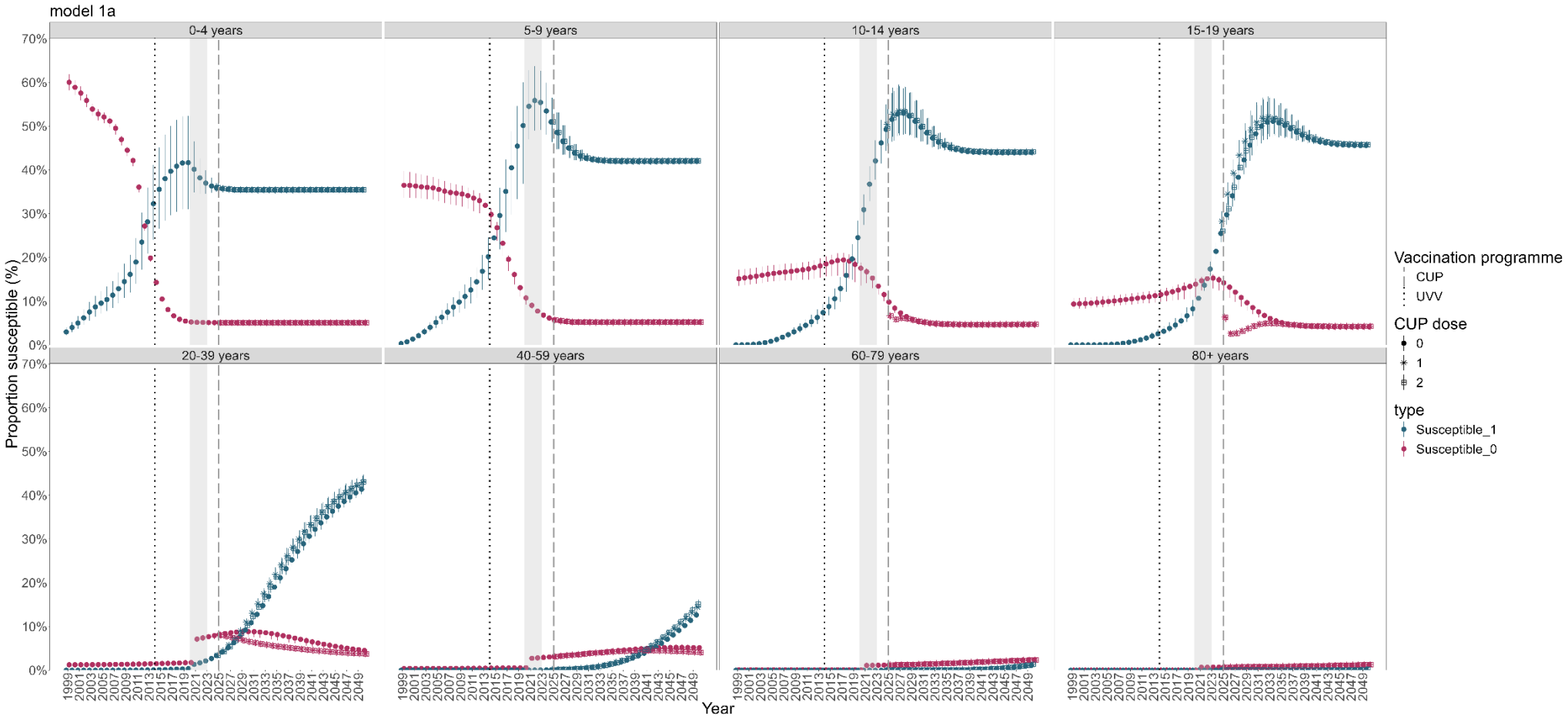
Figure S.5.3. Model simulations of the age-specific proportion of population susceptible to natural (Susceptible_0) and breakthrough varicella infections (Susceptible_1) for (a) model 2a, (b) model 1a, (c) model 1b and (d) model 2b, 1999 to 2050, Hong Kong.

(a) Age-specific proportion of susceptibility, model 2a.



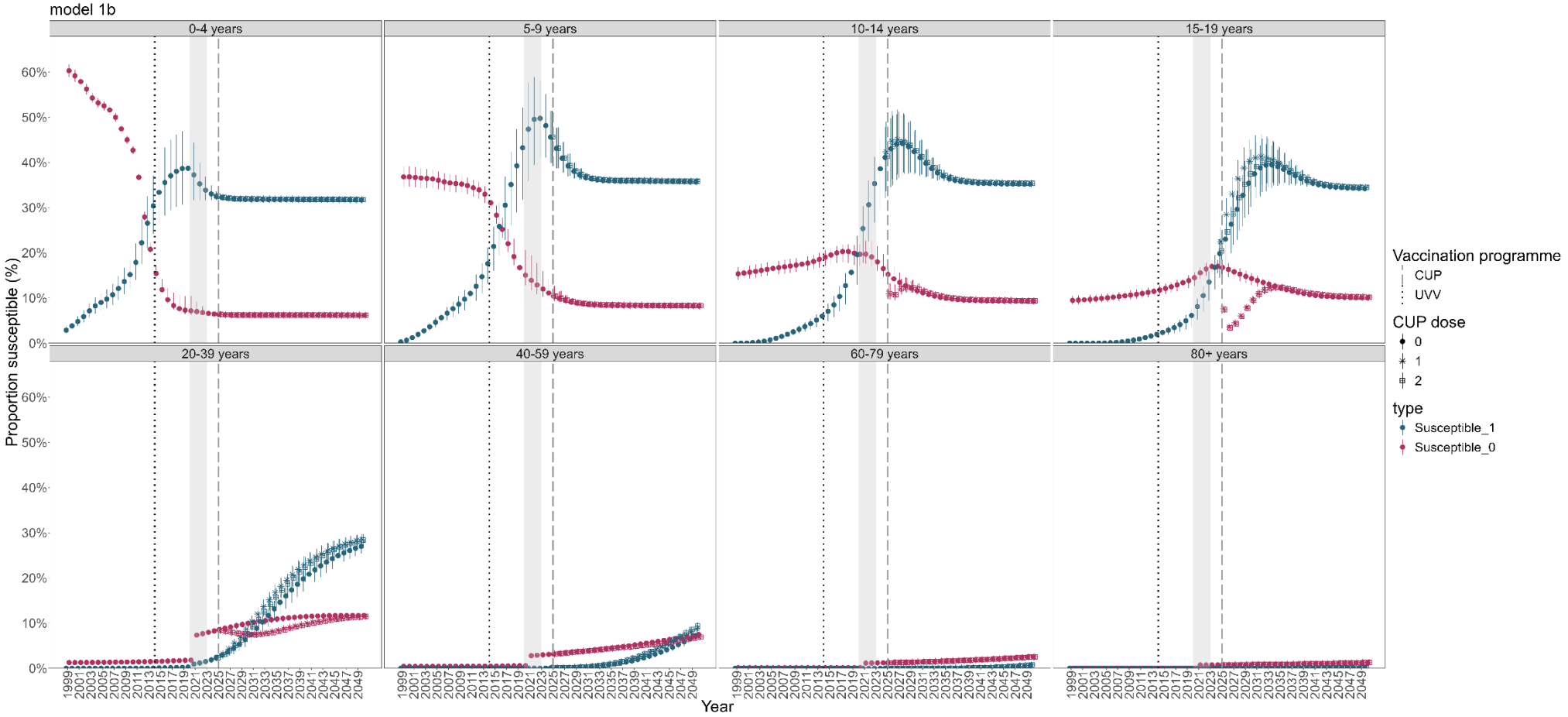
Note: Susceptible_0 (S) represents proportion with no immunity and are prone to natural infections, whilst Susceptible_1 (S1) represents proportions with partial immunity and are prone to breakthrough infections. Changes in population susceptibility under different catch-up programme (CUP) are presented by different shapes. The vertical dotted line represents UVV introduction in 2014. The grey rectangle represents NPI implemented against COVID-19 between 2020 and 2023. The vertical dashed line represents potential CUP in 2025.

(b) Age-specific proportion of susceptibility, model 1a.



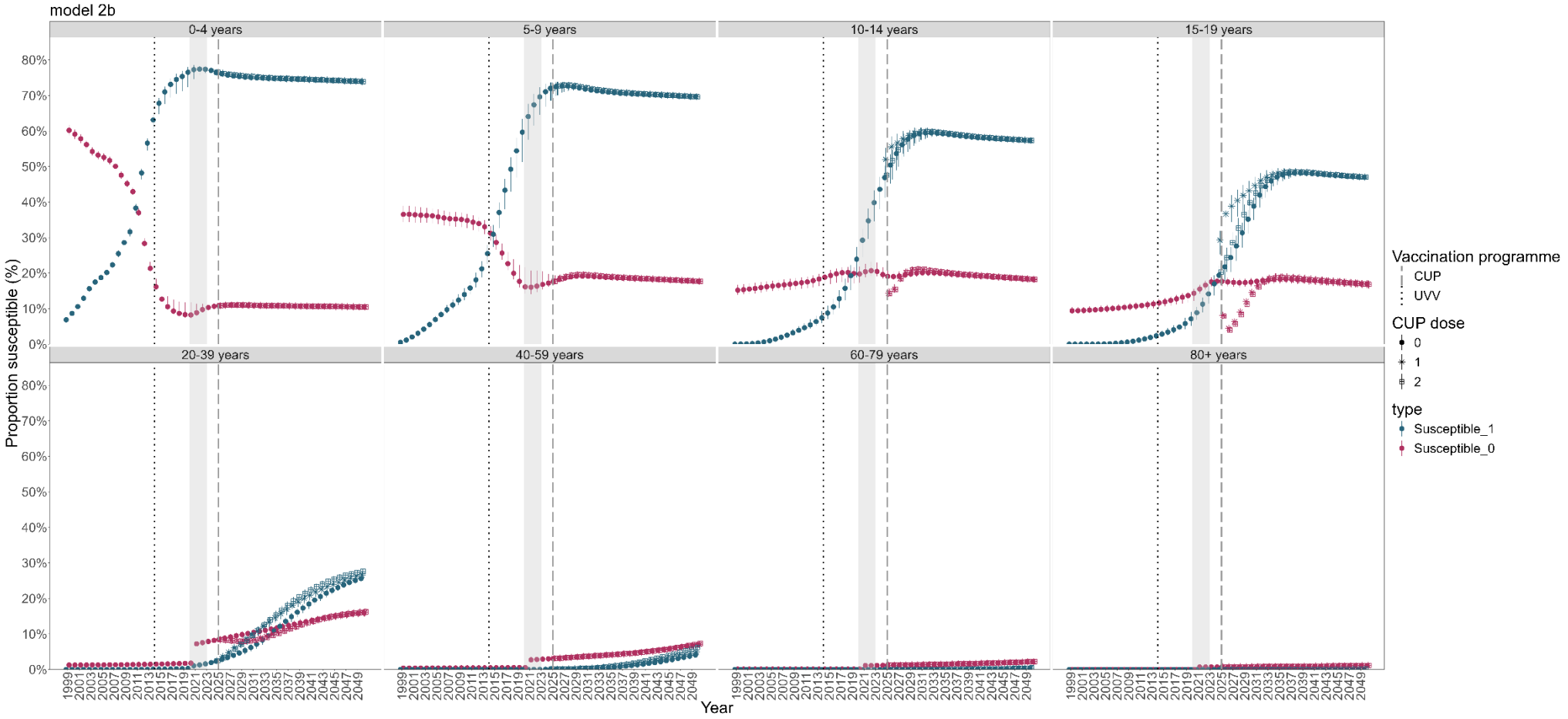
Note: Susceptible_0 (S) represents proportion with no immunity and are prone to natural infections, whilst Susceptible_1 (S1) represents proportions with partial immunity and are prone to breakthrough infections. Changes in population susceptibility under different catch-up programme (CUP) are presented by different shapes. The vertical dotted line represents UVV introduction in 2014. The grey rectangle represents NPI implemented against COVID-19 between 2020 and 2023. The vertical dashed line represents potential CUP in 2025.

(c) Age-specific proportion of susceptibility, model 1b.



Note: Susceptible_0 (S) represents proportion with no immunity and are prone to natural infections, whilst Susceptible_1 (S1) represents proportions with partial immunity and are prone to breakthrough infections. Changes in population susceptibility under different catch-up programme (CUP) are presented by different shapes. The vertical dotted line represents UVV introduction in 2014. The grey rectangle represents NPI implemented against COVID-19 between 2020 and 2023. The vertical dashed line represents potential CUP in 2025.

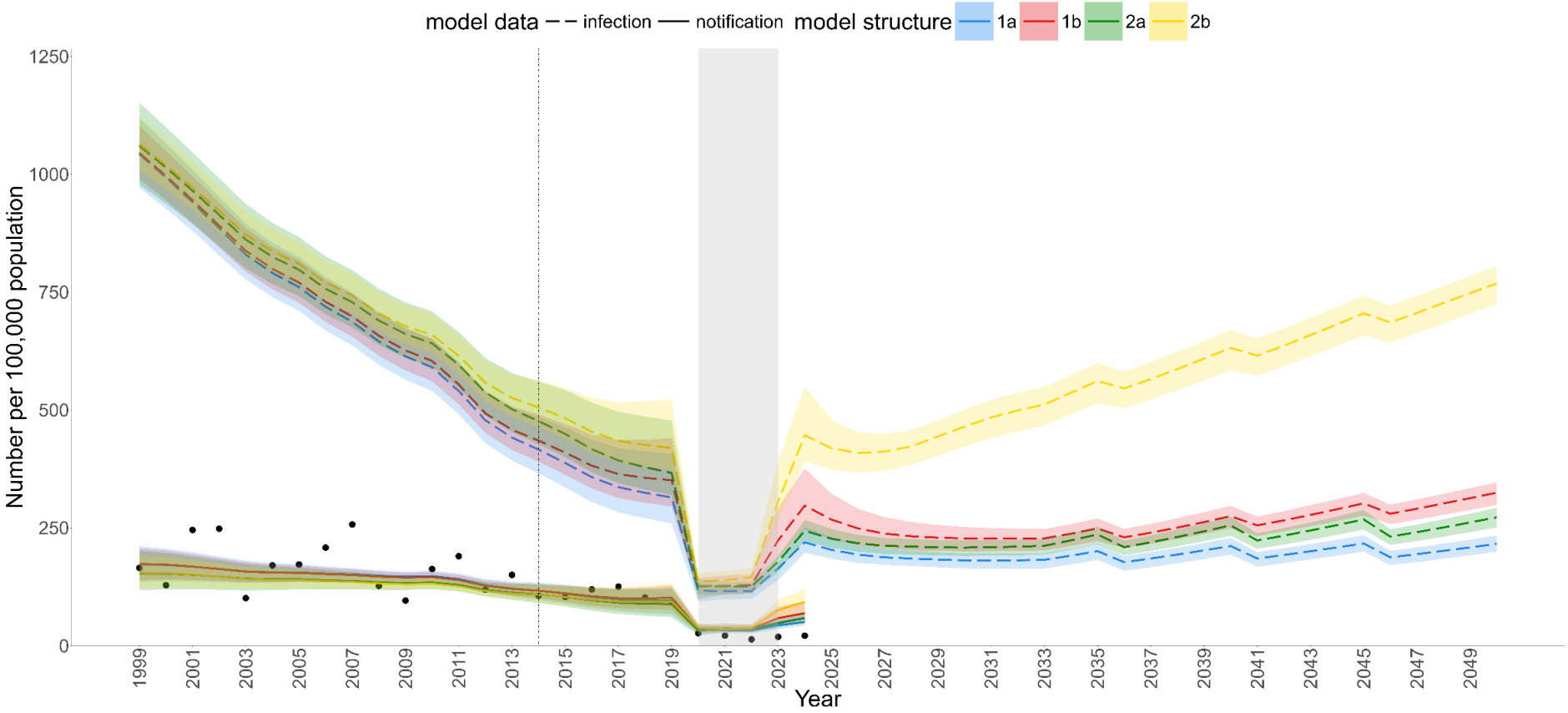
(d) Age-specific proportion of susceptibility, model 2b.



Note: Susceptible_0 represents proportion with no immunity and are prone to natural infections, whilst Susceptible_1 represents proportions with partial immunity and are prone to breakthrough infections. Changes in population susceptibility under different catch-up programme (CUP) are presented by different shapes. The vertical dotted line represents UVV introduction in 2014. The grey rectangle represents NPI implemented against COVID-19 between 2020 and 2023. The vertical dashed line represents potential CUP in 2025.

Figure S.5.4. Incidence of modelled varicella infections and notifications per 100,000 (a) all age (b) age-specific, 1999 to 2050, Hong Kong.

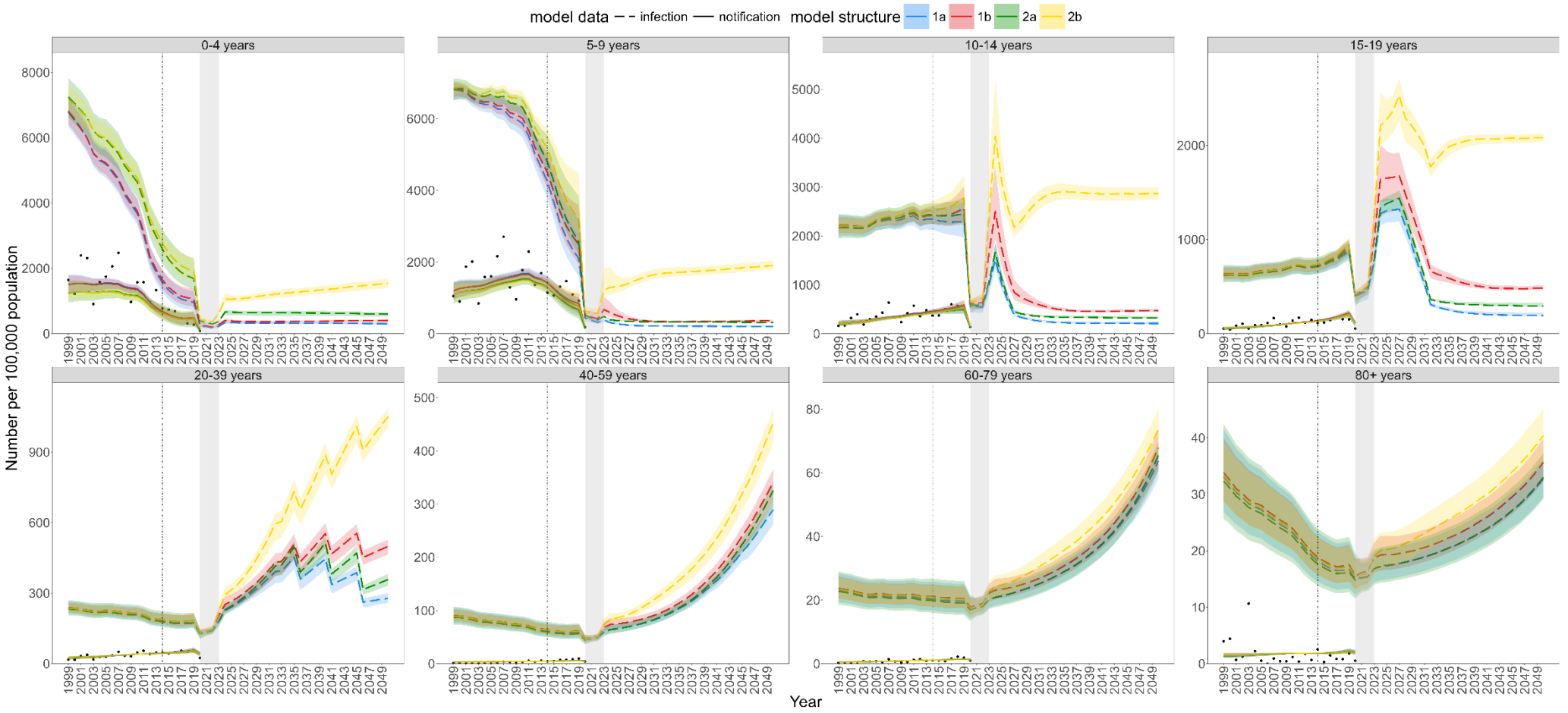
(a) All age incidence of varicella infections and notifications.



Note:

The dots and solid lines represent notification data observed and modelled between 1999 and 2024. Between 2021 and 2024, only data without age group were available. Data of 2024 were up to September only and was annualised; Dashed lines represent the simulations between 2021 and 2050; The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic.

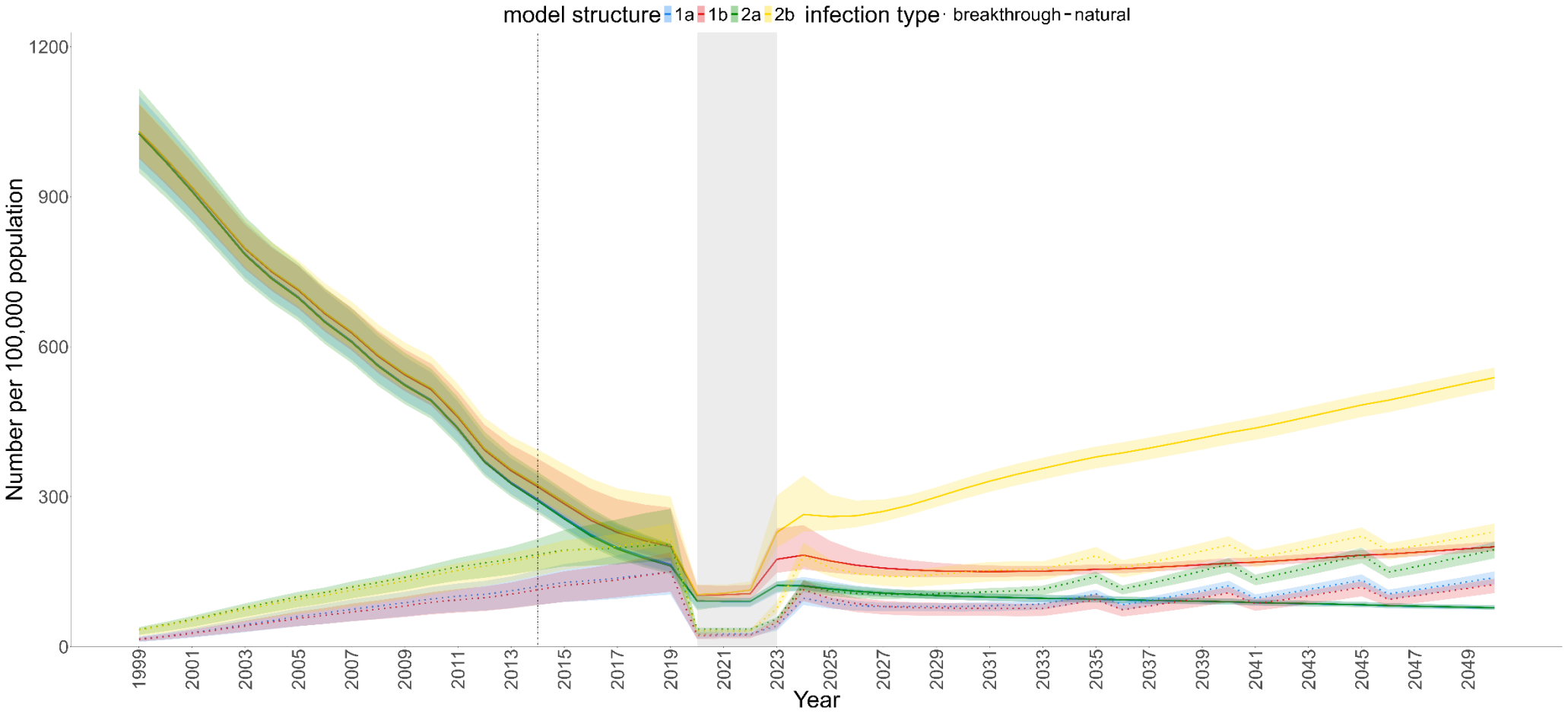
(b) **Age-specific incidence of varicella infections and notifications.**



Note:

The dots and solid lines represent notification data observed and modelled between 1999 and 2020; Dashed lines represent the simulations between 2021 and 2050; The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic.

Figure S.5.5. Incidence of overall modelled varicella natural and breakthrough infections per 100,000, 1999 to 2050, Hong Kong.

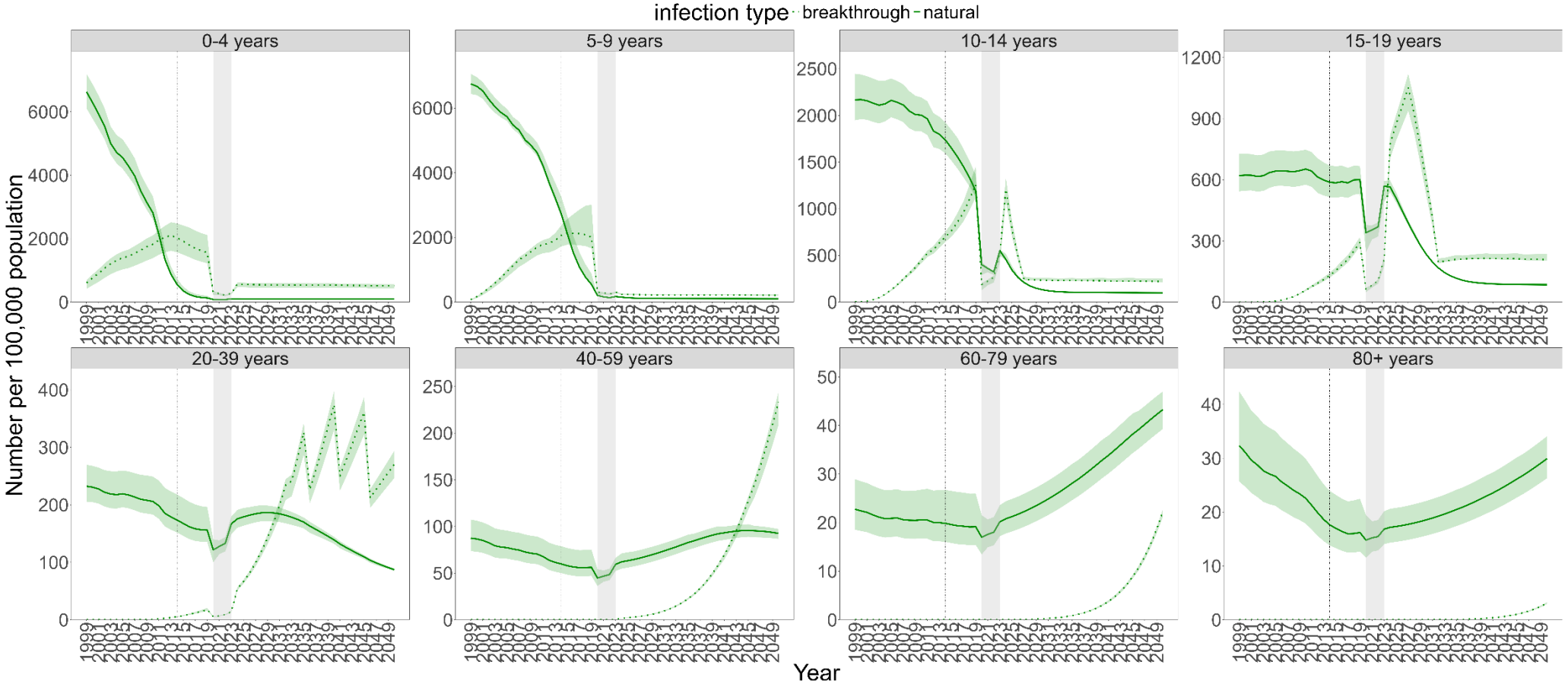


Note:

Solid lines represent period between 1999 and 2019 when the model was calibrated with varicella notification data; Dashed lines represent the simulations between 2020 and 2050; The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic.

Figure S.5.6. Age-specific modelled incidence of varicella natural and breakthrough infections per 100,000 for (a) model 2a, (b) model 1a, (c) model 1b and (d) model 2b, 1999 to 2050, Hong Kong.

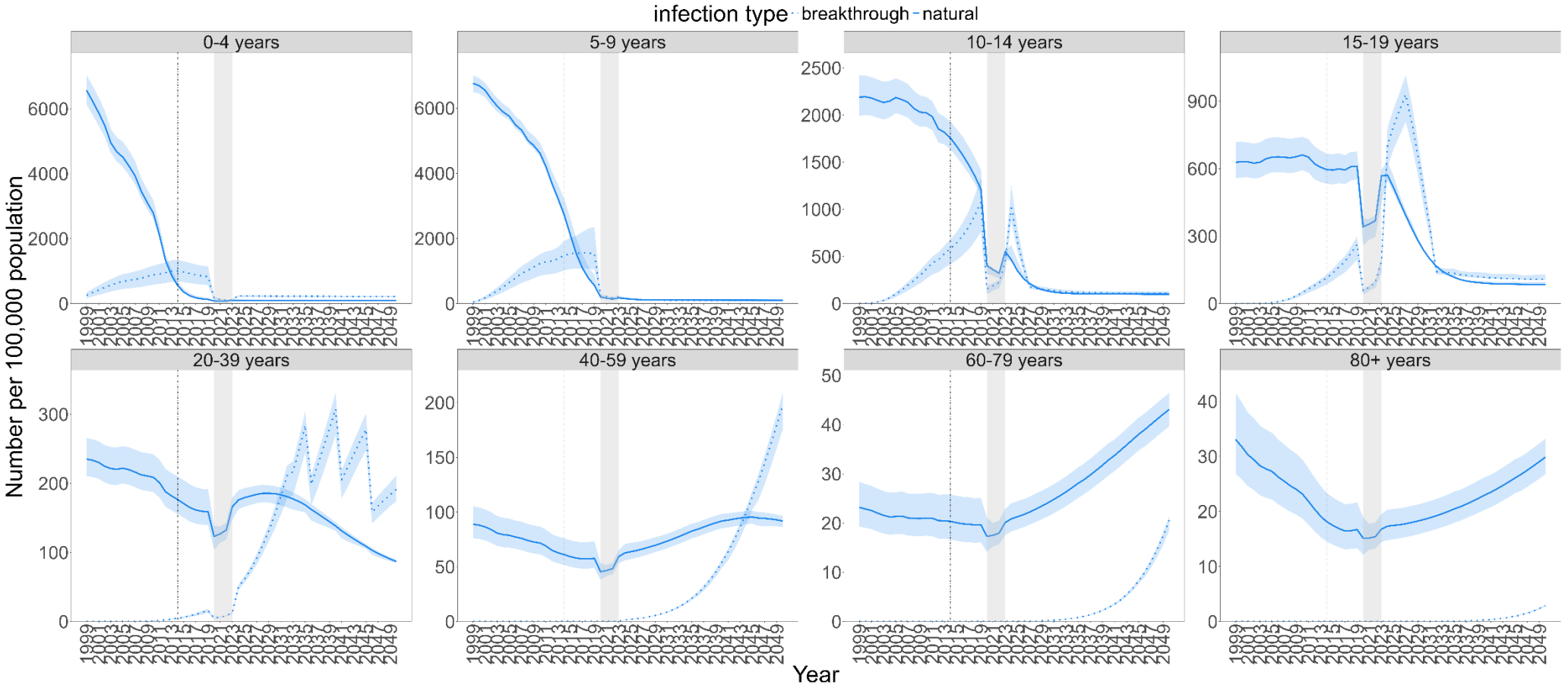
(a) Model 2a



Note:

Solid lines represent natural infections whilst dotted lines represent breakthrough infections. The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic.

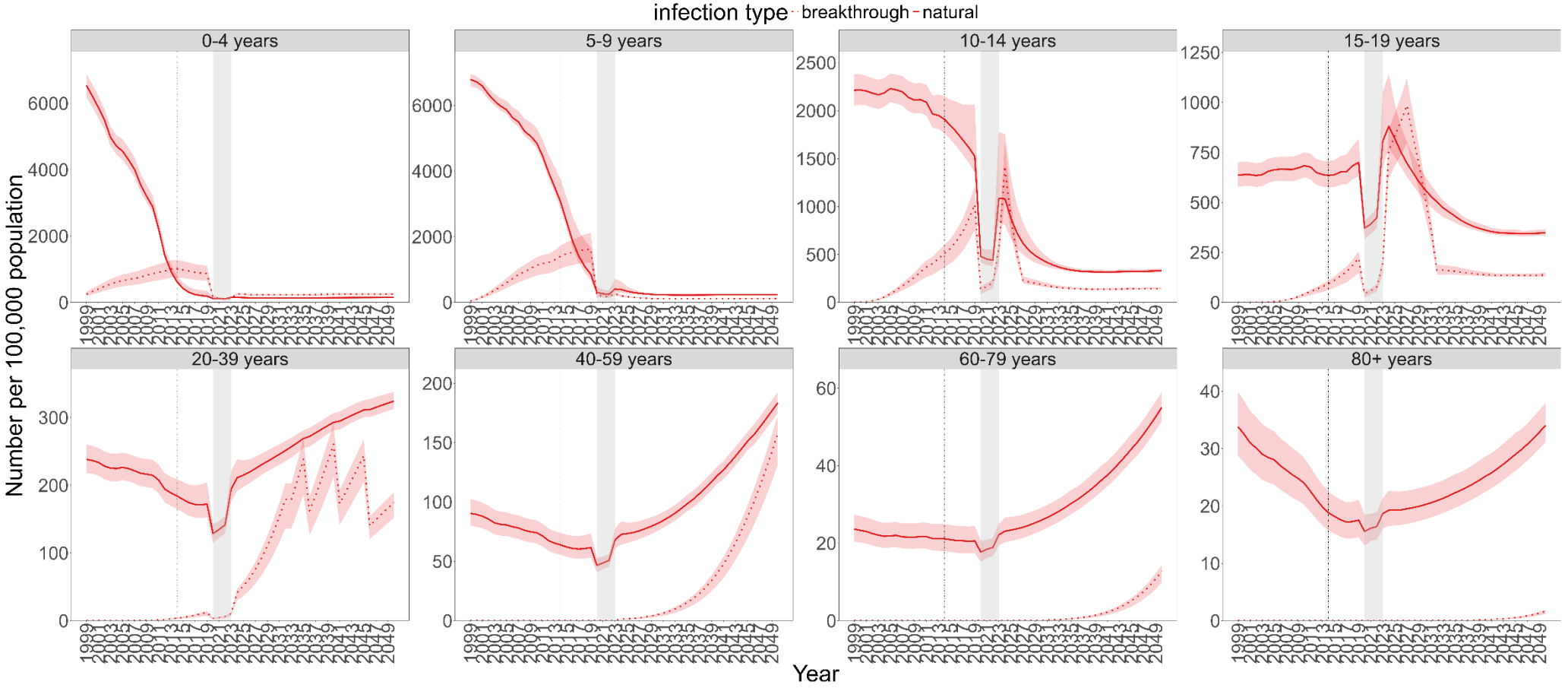
(b) Model 1a



Note:

Solid lines represent natural infections whilst dotted lines represent breakthrough infections. The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic.

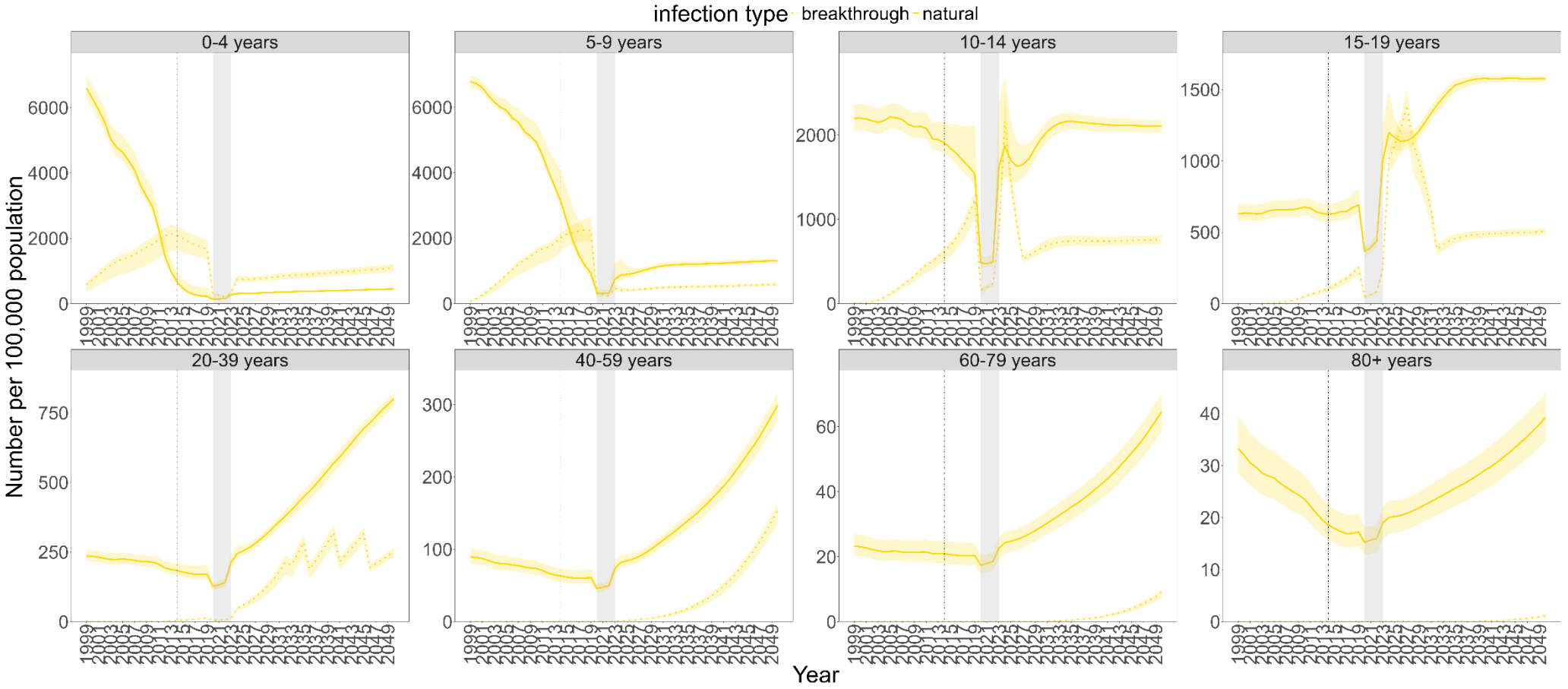
(c) Model 1b



Note:

Solid lines represent natural infections whilst dotted lines represent breakthrough infections. The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic.

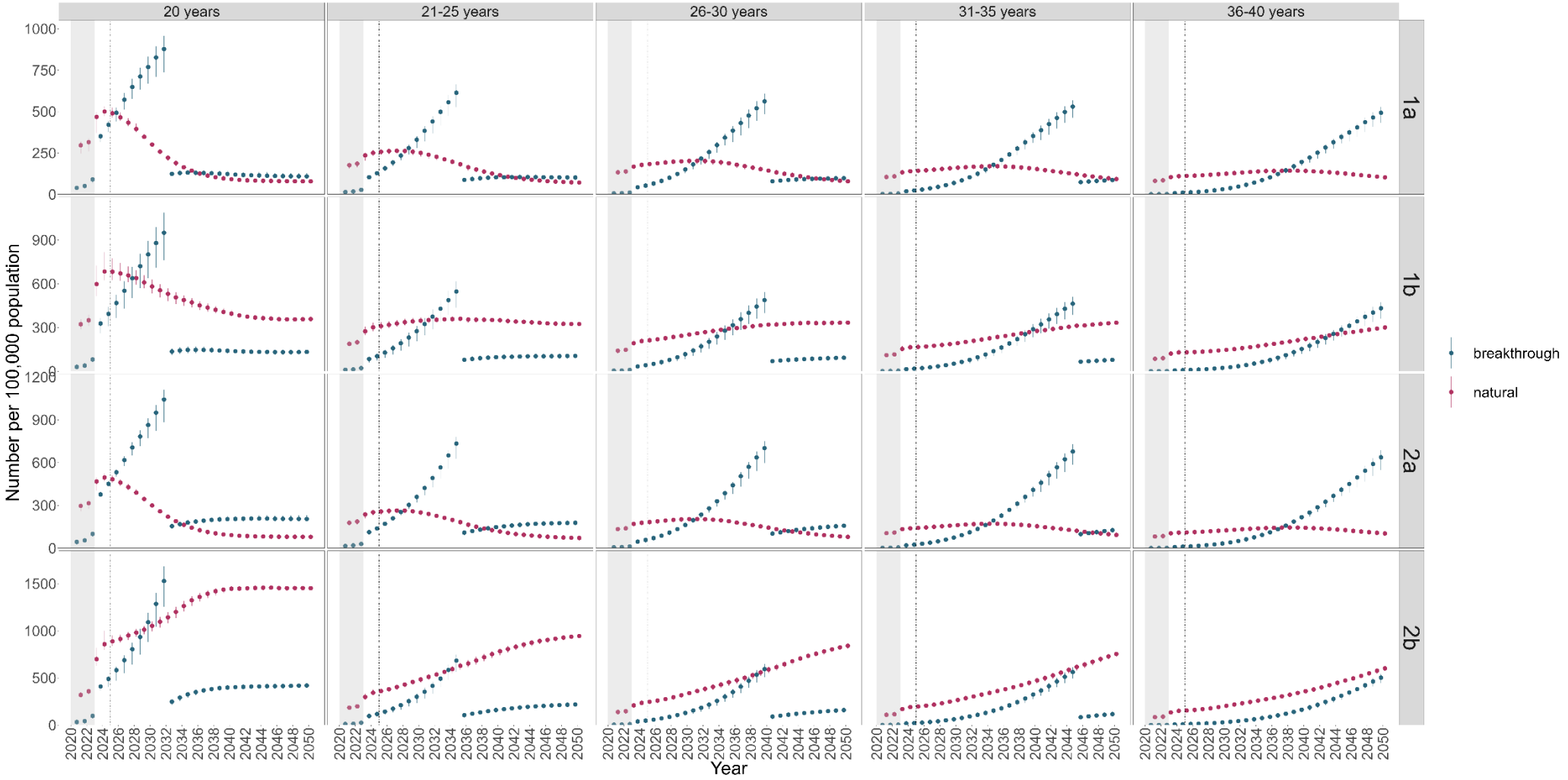
(d) Model 2b



Note:

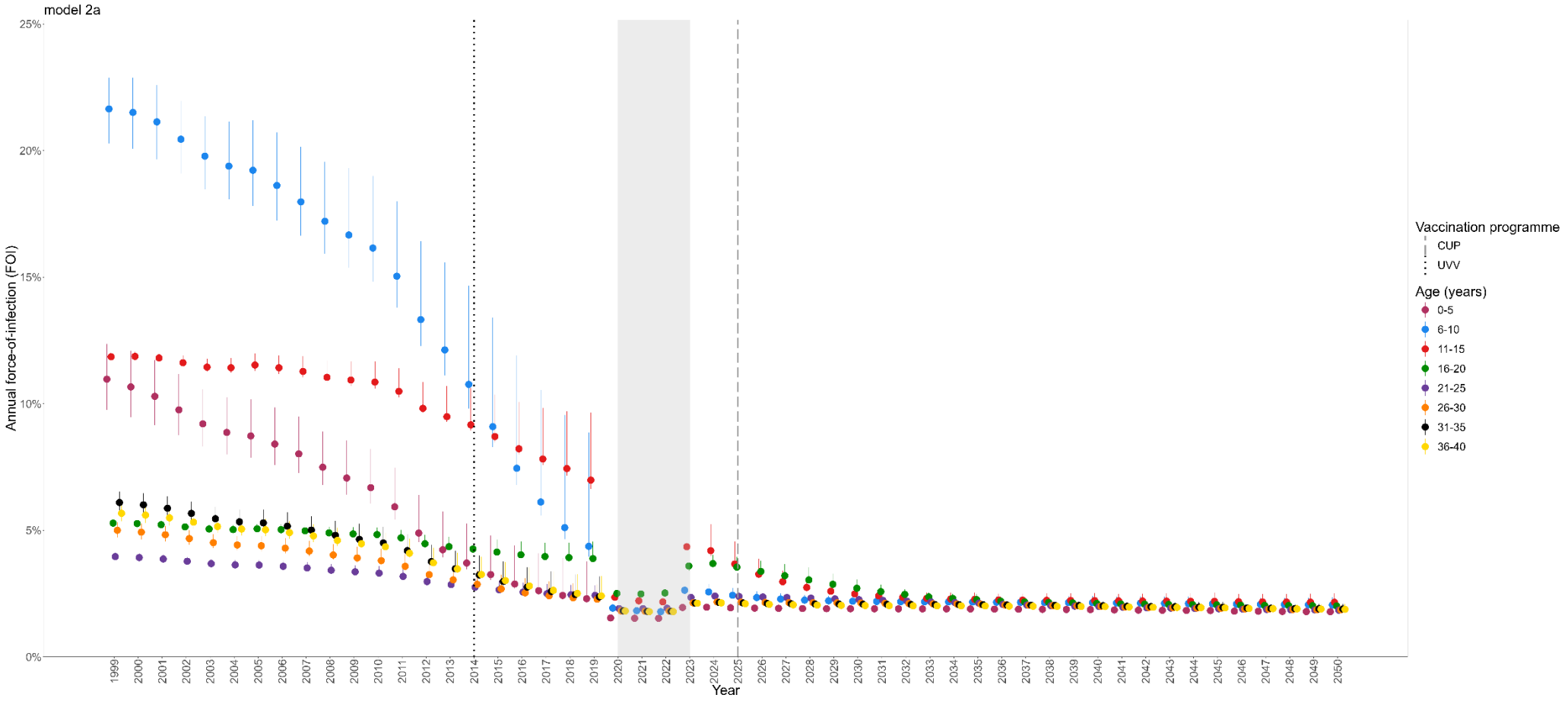
Solid lines represent natural infections whilst dotted lines represent breakthrough infections. The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic.

Figure S.5.7. Age-specific modelled incidence of natural and breakthrough varicella infections per 100,000 for those aged 20 to 40 years with no catch-up programme for model 2a, 2020 to 2050, Hong Kong.



Note: The grey rectangle represents NPI implemented against COVID-19 between 2020 and 2023. The long-dash lines represent potential CUP in 2025.

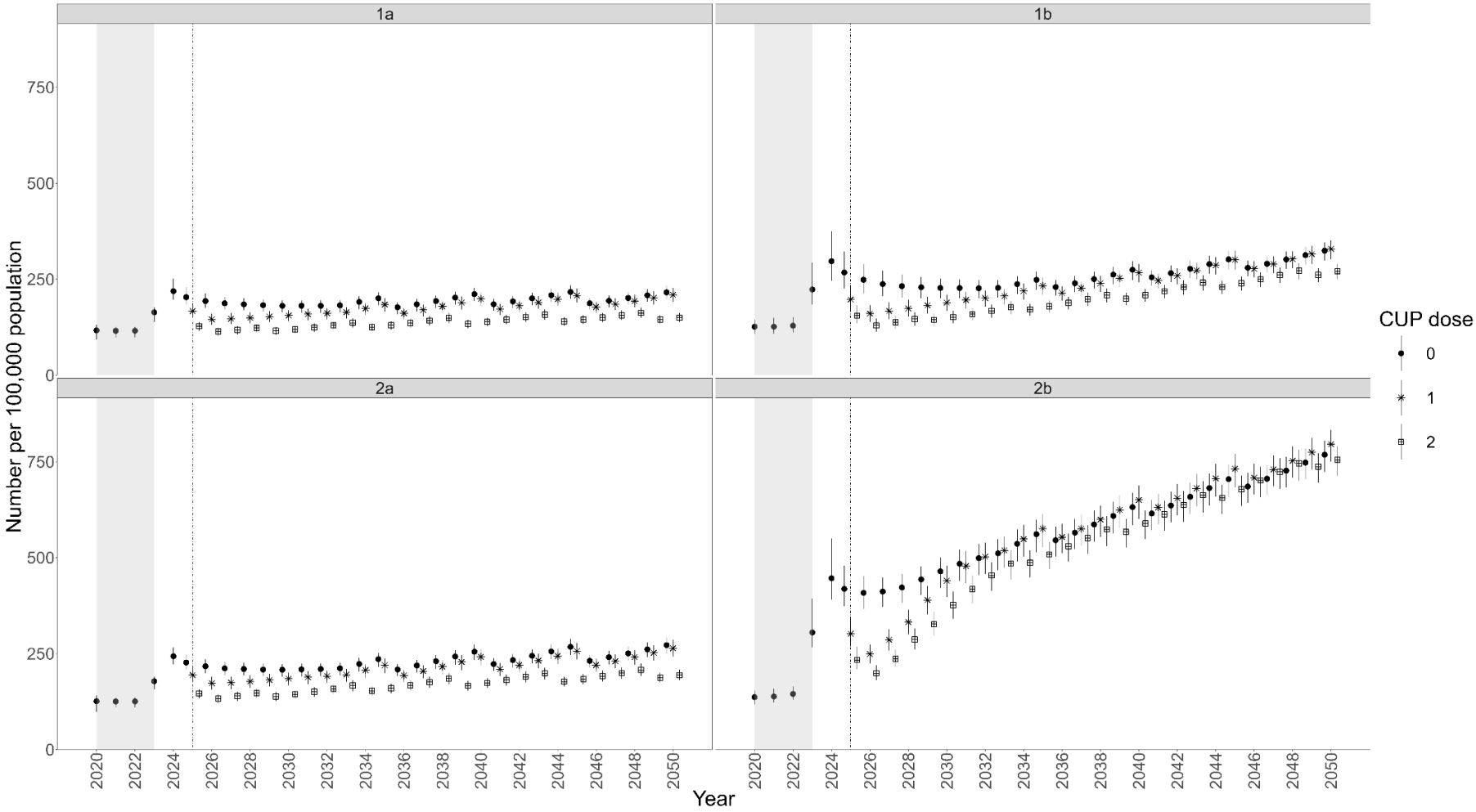
Figure S.5.8. Age-specific annual force-of-infection (FOI) for model 2a, 1999 to 2050, Hong Kong.



Note: The vertical dotted line represents UVV introduction in 2014. The grey rectangle represents a period between 2020 and 2023 when NPI was implemented against COVID-19 between 2020 and 2023. The vertical dashed line represents potential CUP in 2025. FOI are presented according to the age groups of the contact matrix used in the model.

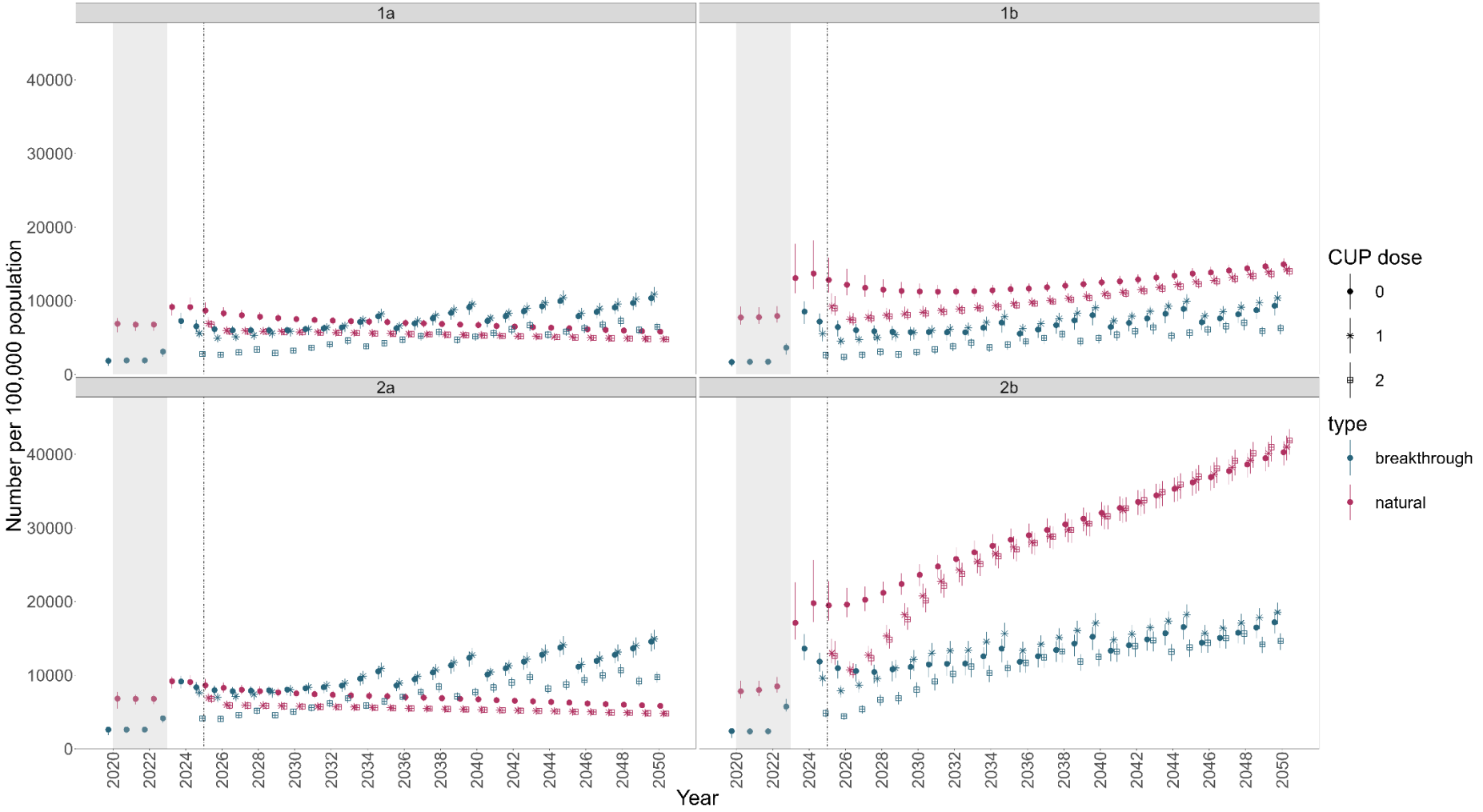
Figure S.5.9. Model simulations of incidence of (a) all and (b) natural and breakthrough varicella infections per 100,000 with one- and two-dose catch-up programme, 2020 to 2050, Hong Kong.

(a) All varicella infections



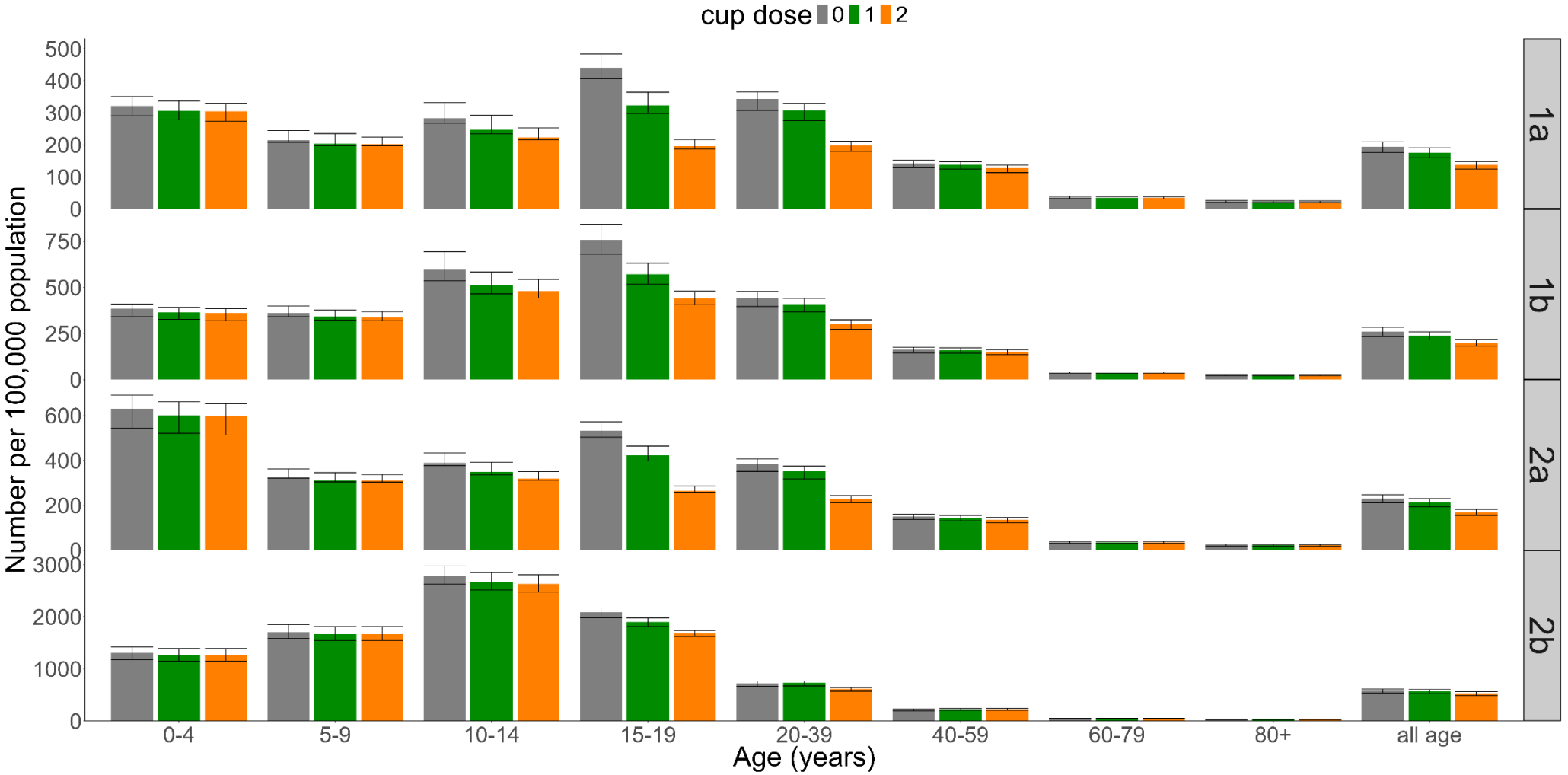
Note: The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. The vertical dashed line represents CUP in 2025.

(b) Natural and breakthrough varicella infections



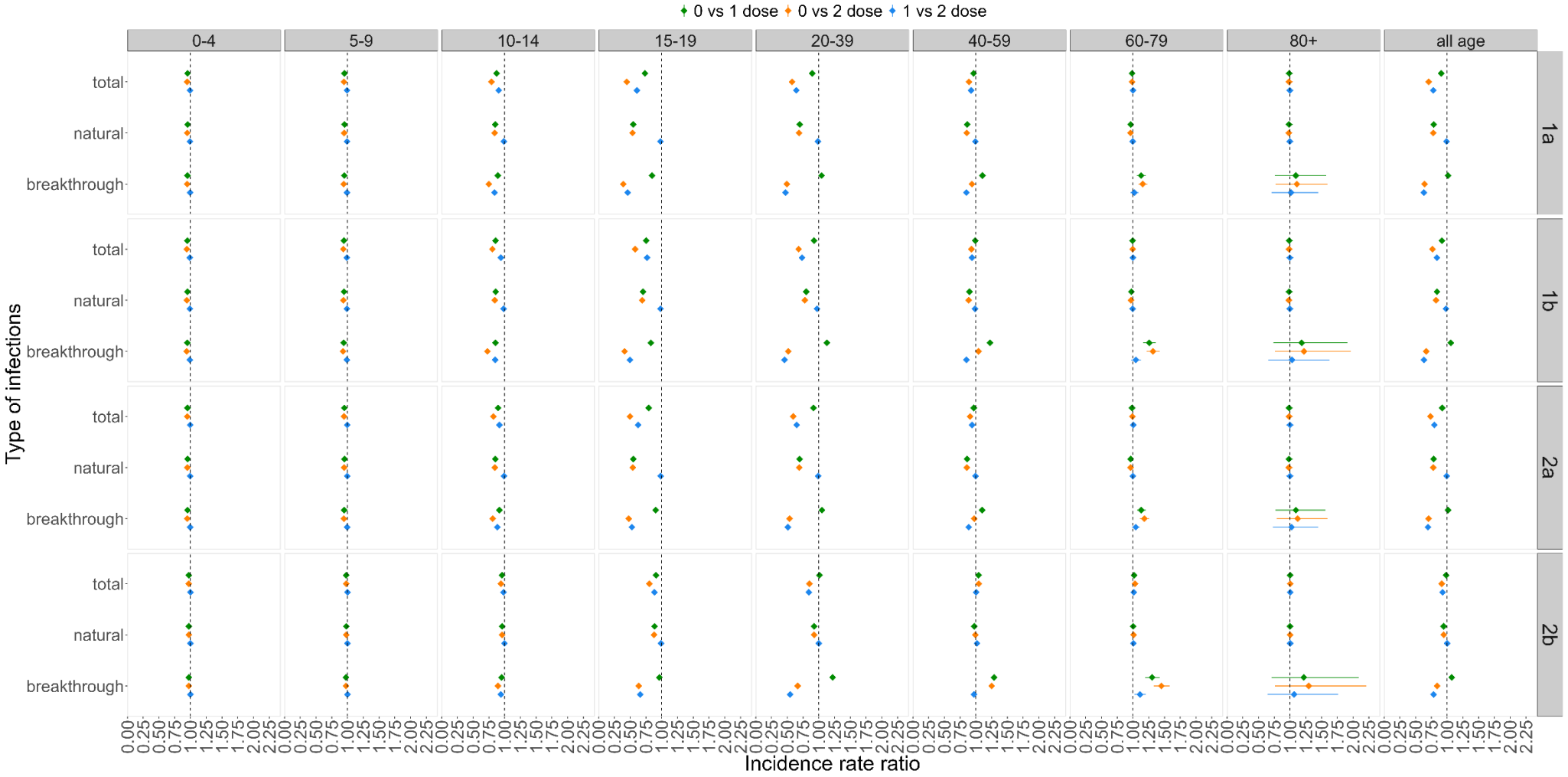
Note: The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. The vertical dashed line represents CUP in 2025.

Figure S.5.10. Cumulative incidence of simulated varicella infections per 100,000 with one- and two-dose catch-up programme for different models, 2025 to 2050, Hong Kong.



Note: Scales of y-axis differ by models.

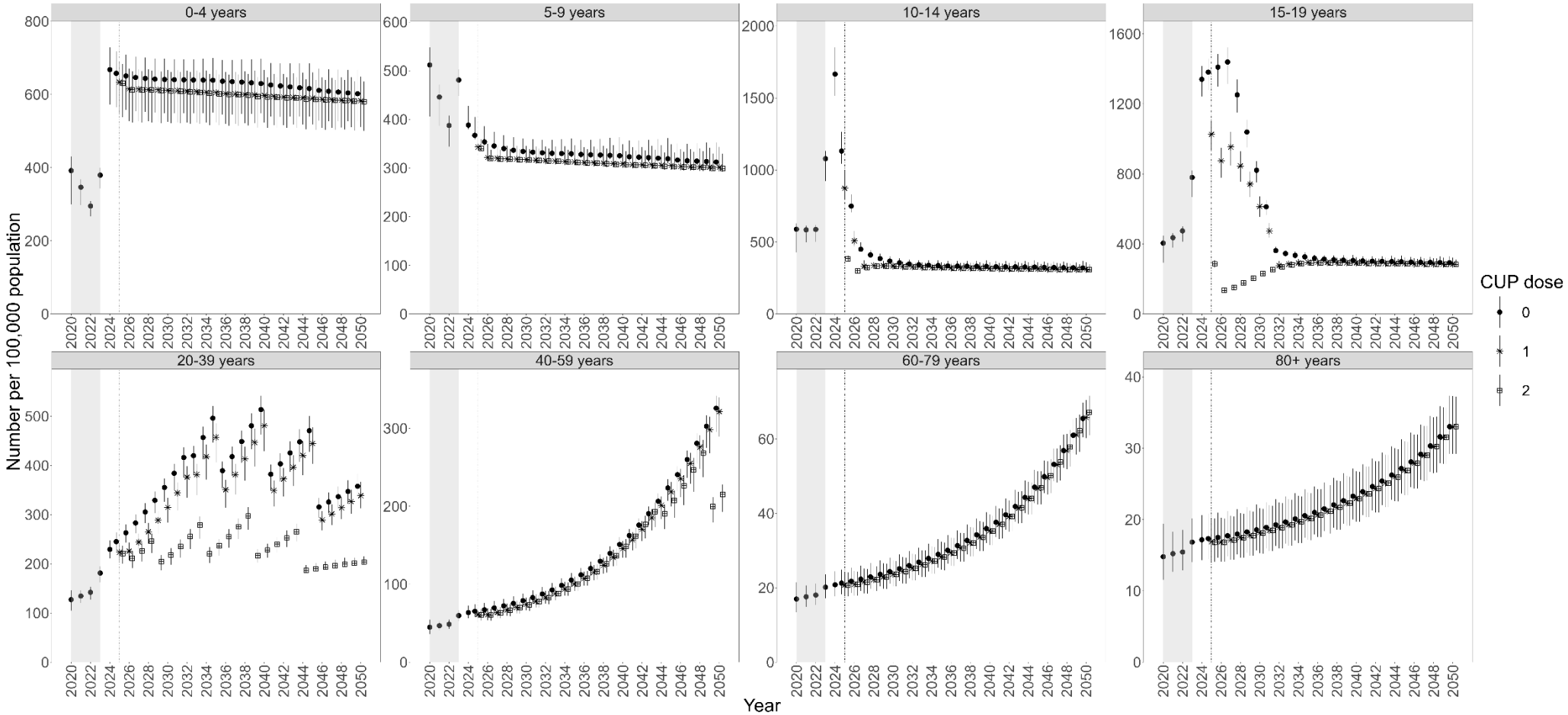
Figure S.5.11. Incidence rate ratio of cumulative incidence of simulated varicella infections under different catch-up programme by age and models, 2025 to 2050, Hong Kong.



Note: An incidence rate ratio (IRR) under one indicates a lower incidence rate compared to the baseline and vice versa.

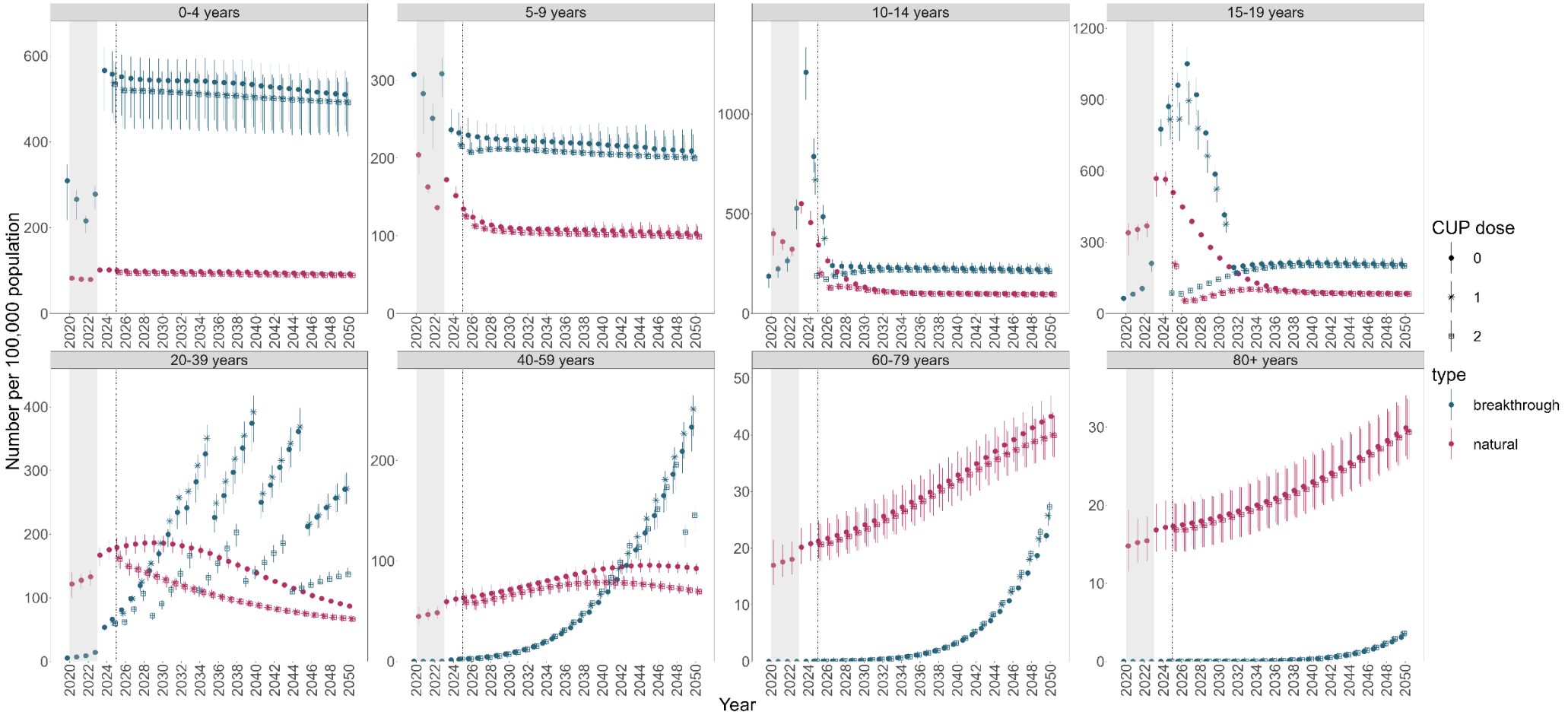
Figure S.5.12. Model 2a simulations of age-specific incidence of (a) all and (b) natural and breakthrough varicella infections per 100,000 with one- and two-dose catch-up programme, 2020 to 2050, Hong Kong.

(a) All varicella infections



Note: The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. The vertical dashed line represents CUP in 2025.

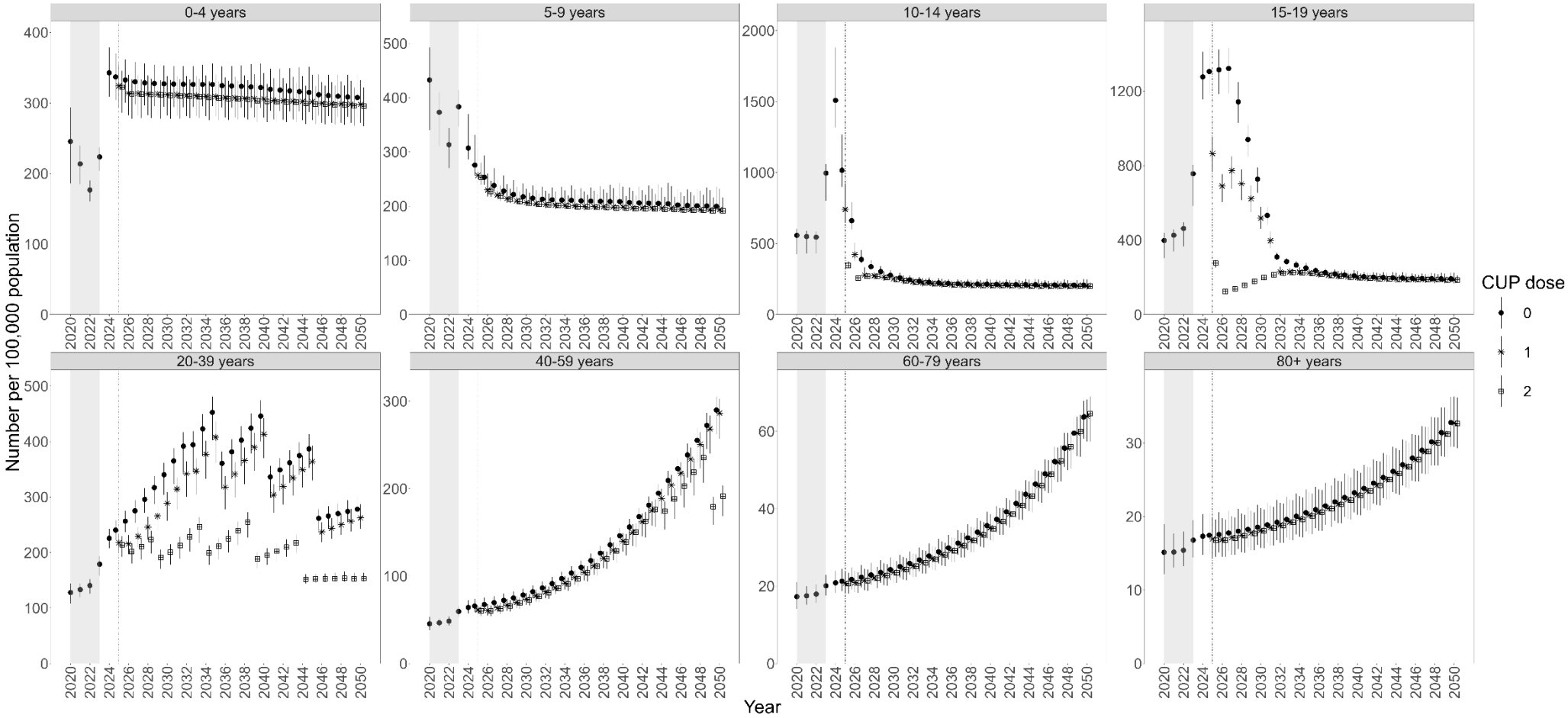
(b) Natural and breakthrough varicella infections



Note: The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. The vertical dashed line represents CUP in 2025.

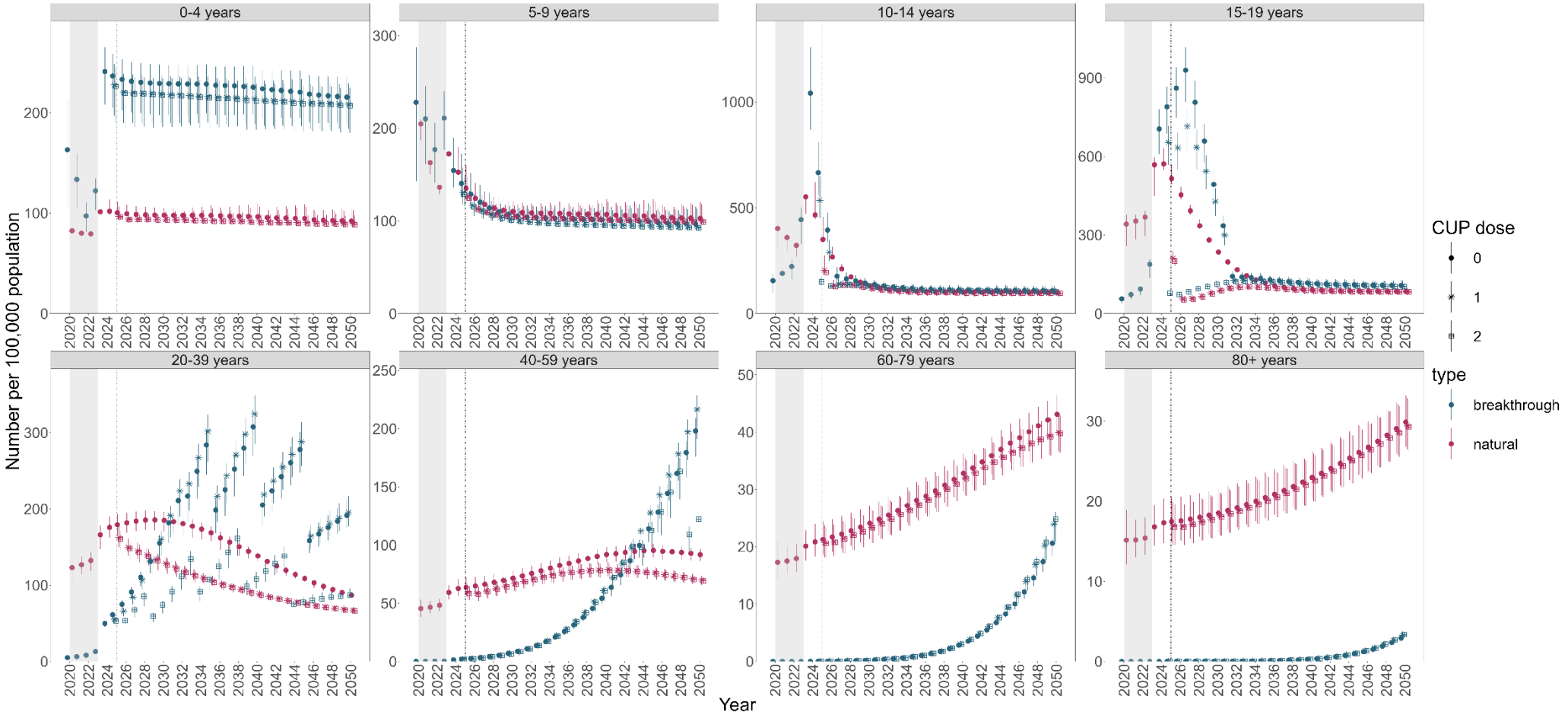
Figure S.5.13. Model 1a simulations of age-specific incidence of (a) all and (b) natural and breakthrough varicella infections per 100,000 with one- and two-dose catch-up programme, 2020 to 2050, Hong Kong.

(a) All varicella infections



Note: The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. The vertical dashed line represents CUP in 2025.

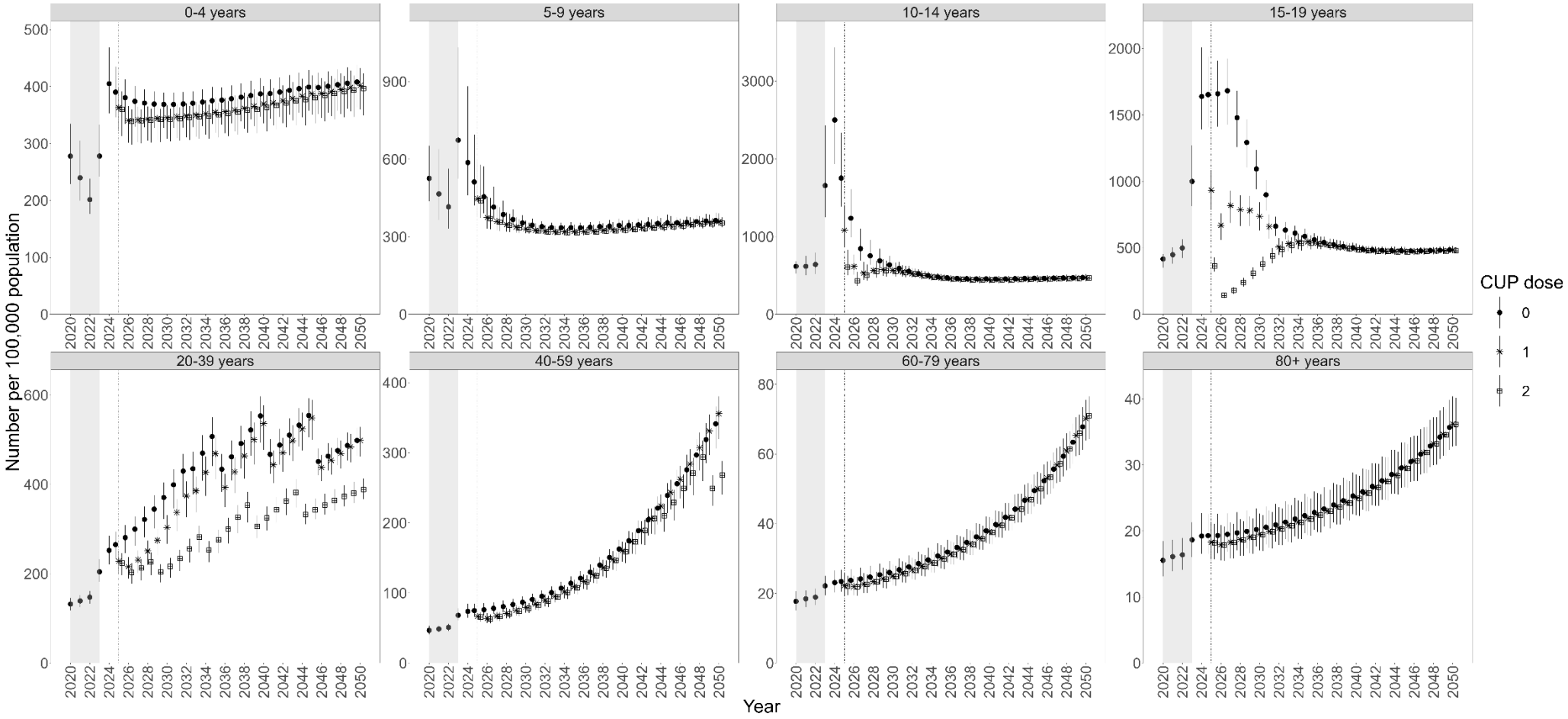
(b) Natural and breakthrough varicella infections



Note: The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic. The vertical dashed line represents CUP in 2025.

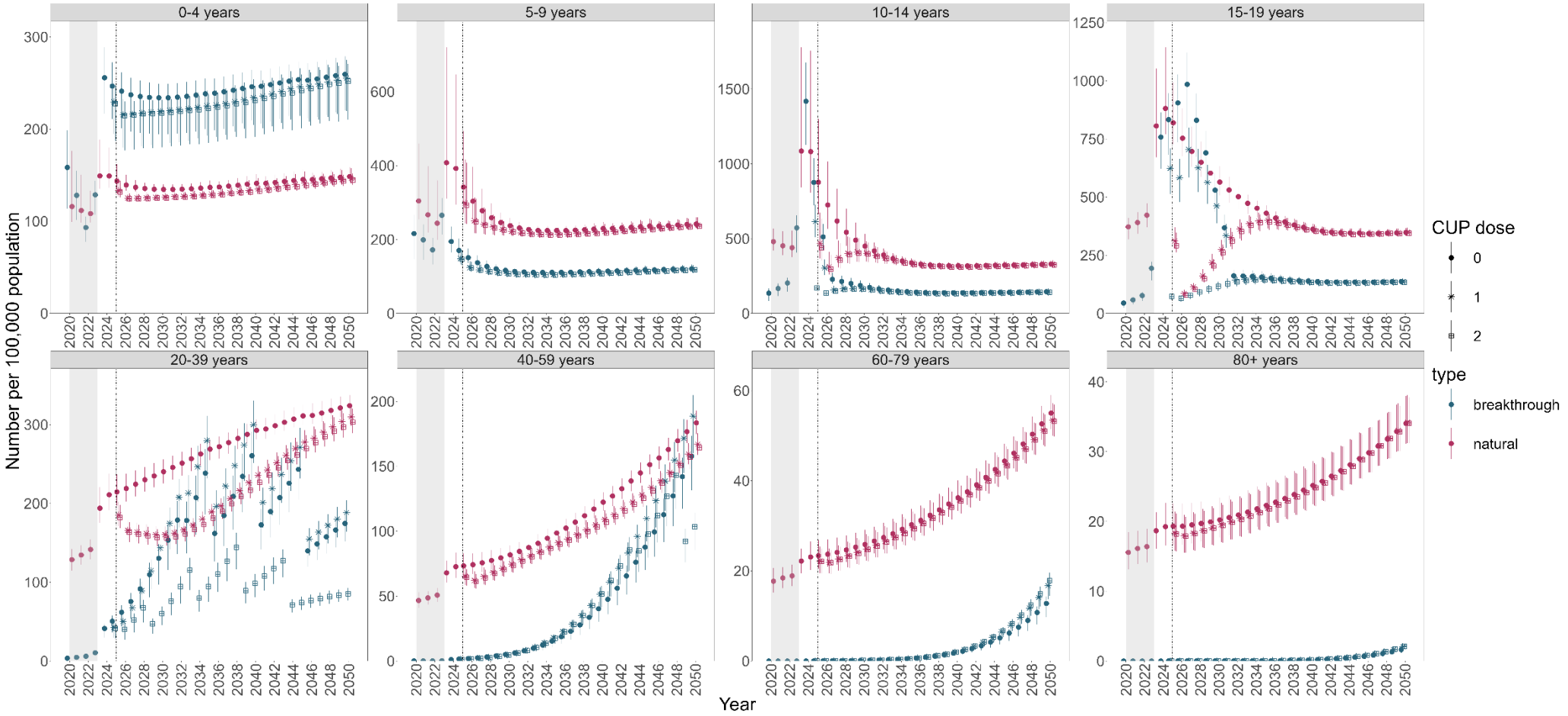
Figure S.5.14. Model 1b simulations of age-specific incidence of (a) all and (b) natural and breakthrough varicella infections per 100,000 with one- and two-dose catch-up programme, 2020 to 2050, Hong Kong.

(a) All varicella infections



Note: The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic.

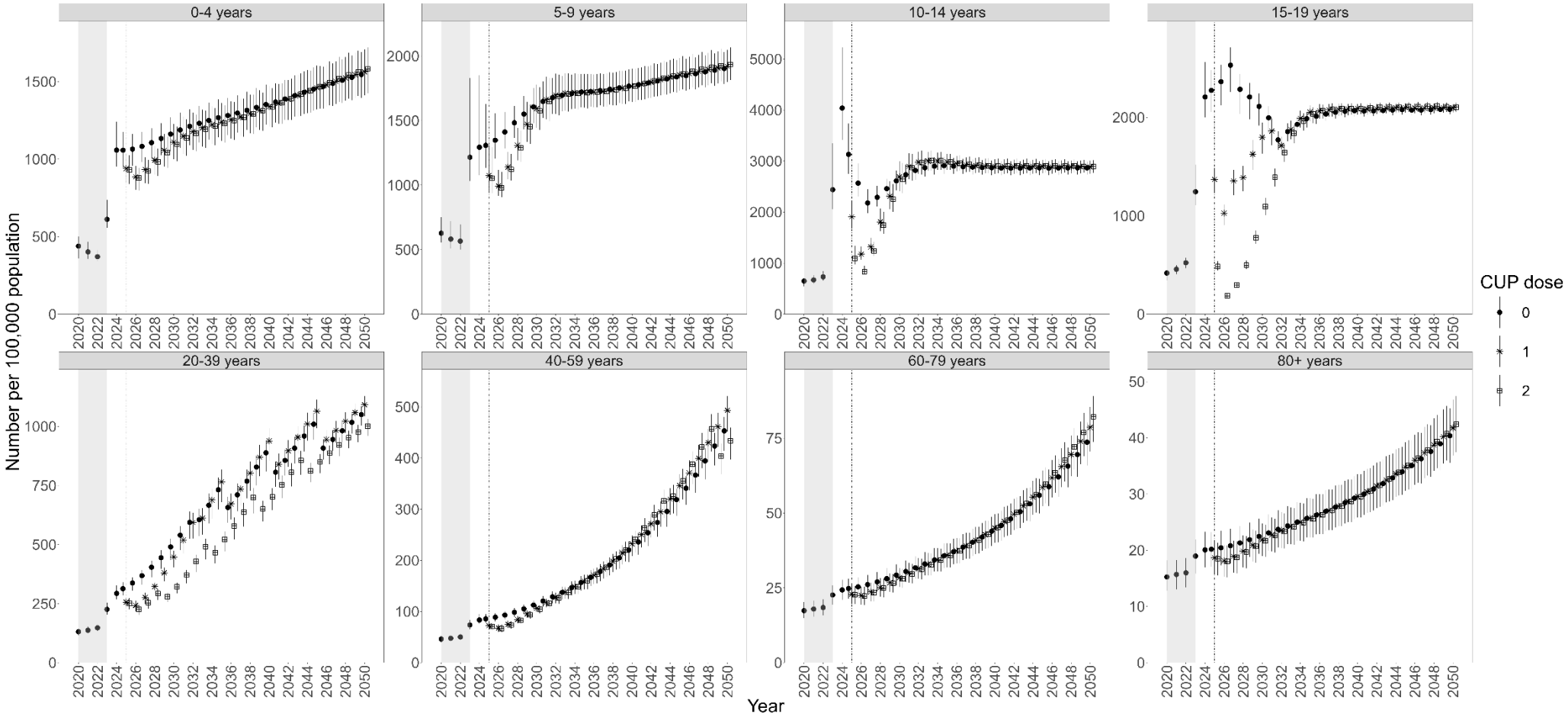
(b) Natural and breakthrough varicella infections



Note: The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic.

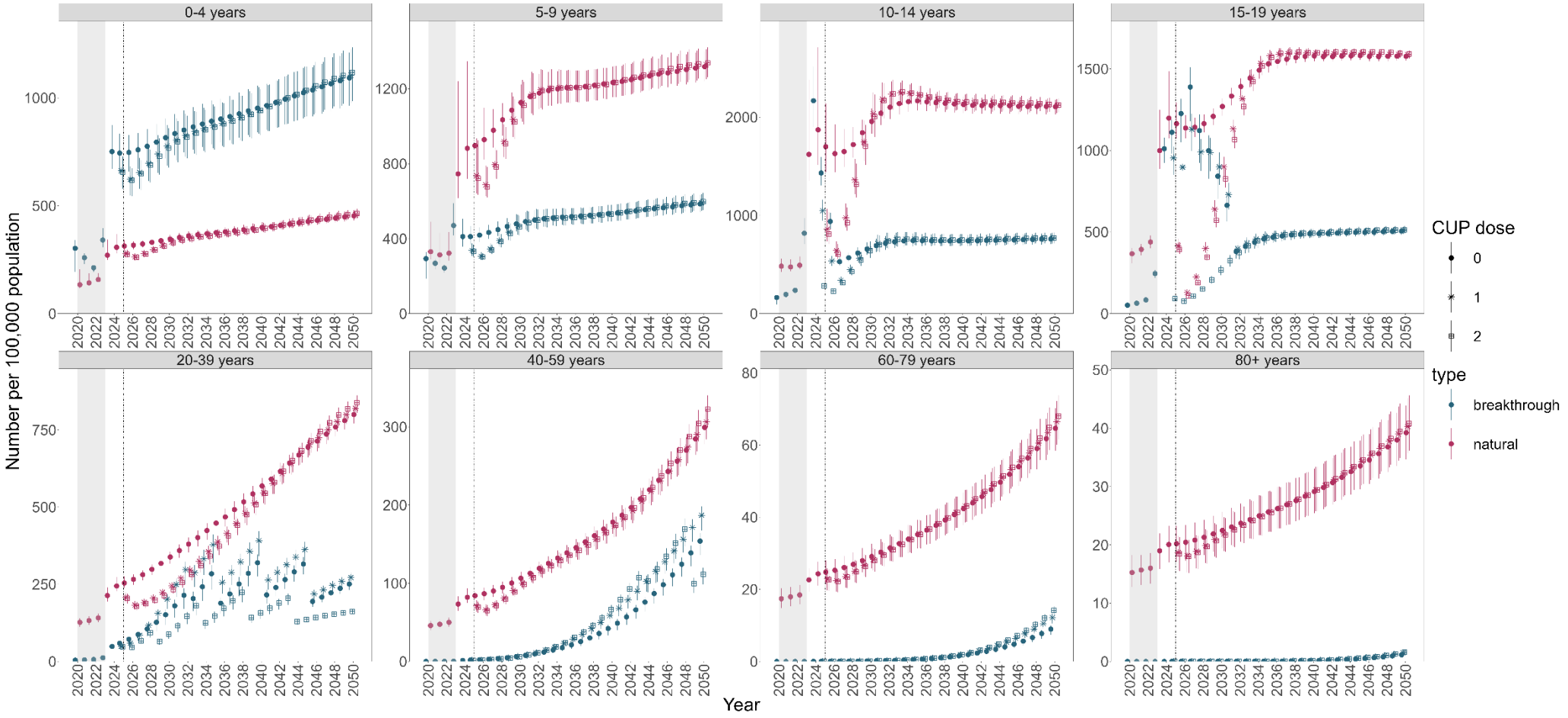
Figure S.5.15. Model 2b simulations of age-specific incidence of (a) all and (b) natural and breakthrough varicella infections per 100,000 with one- and two-dose catch-up programme, 2020 to 2050, Hong Kong.

(a) All varicella infections



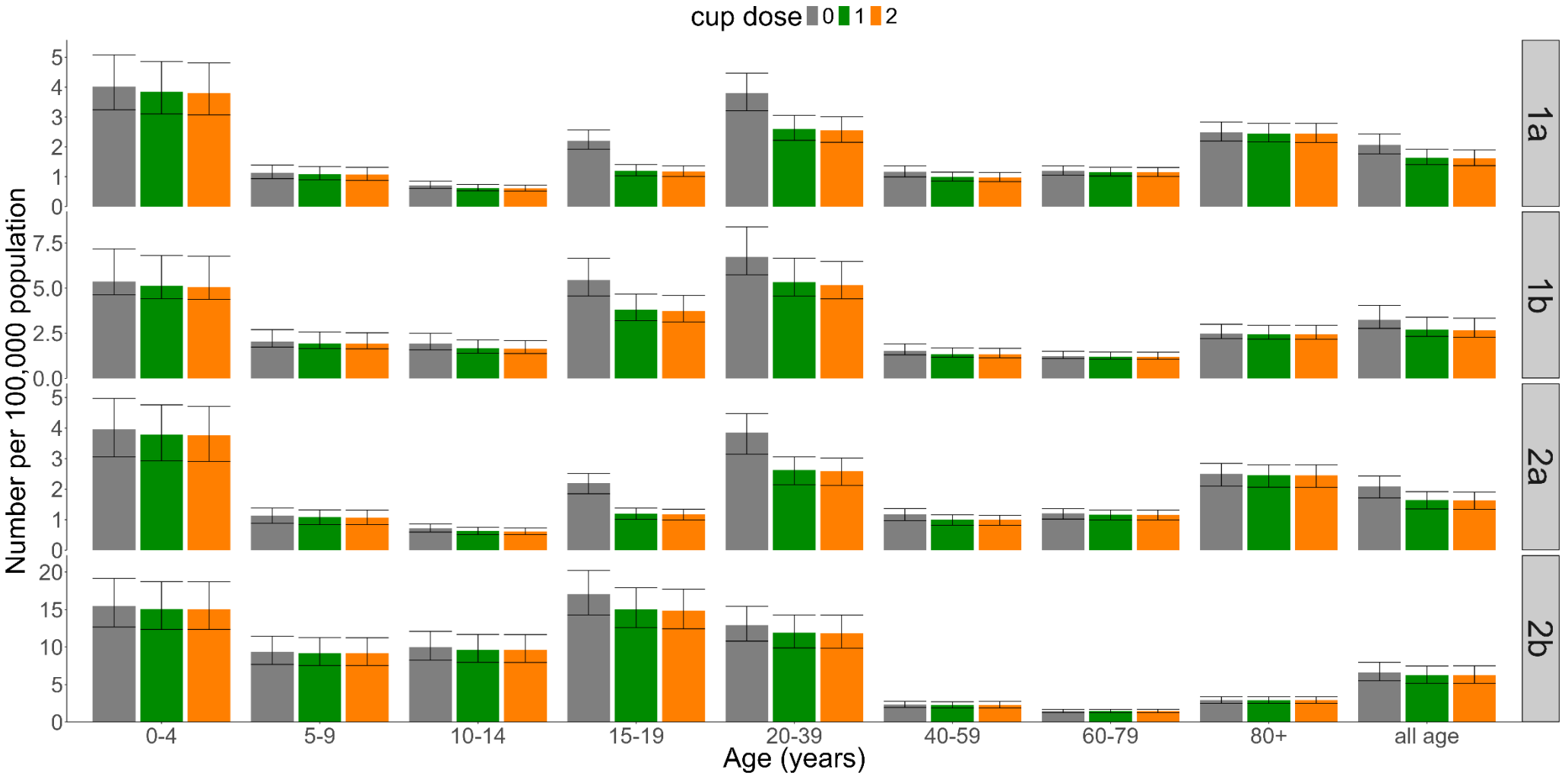
Note: The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic.

(b) Natural and breakthrough varicella infections



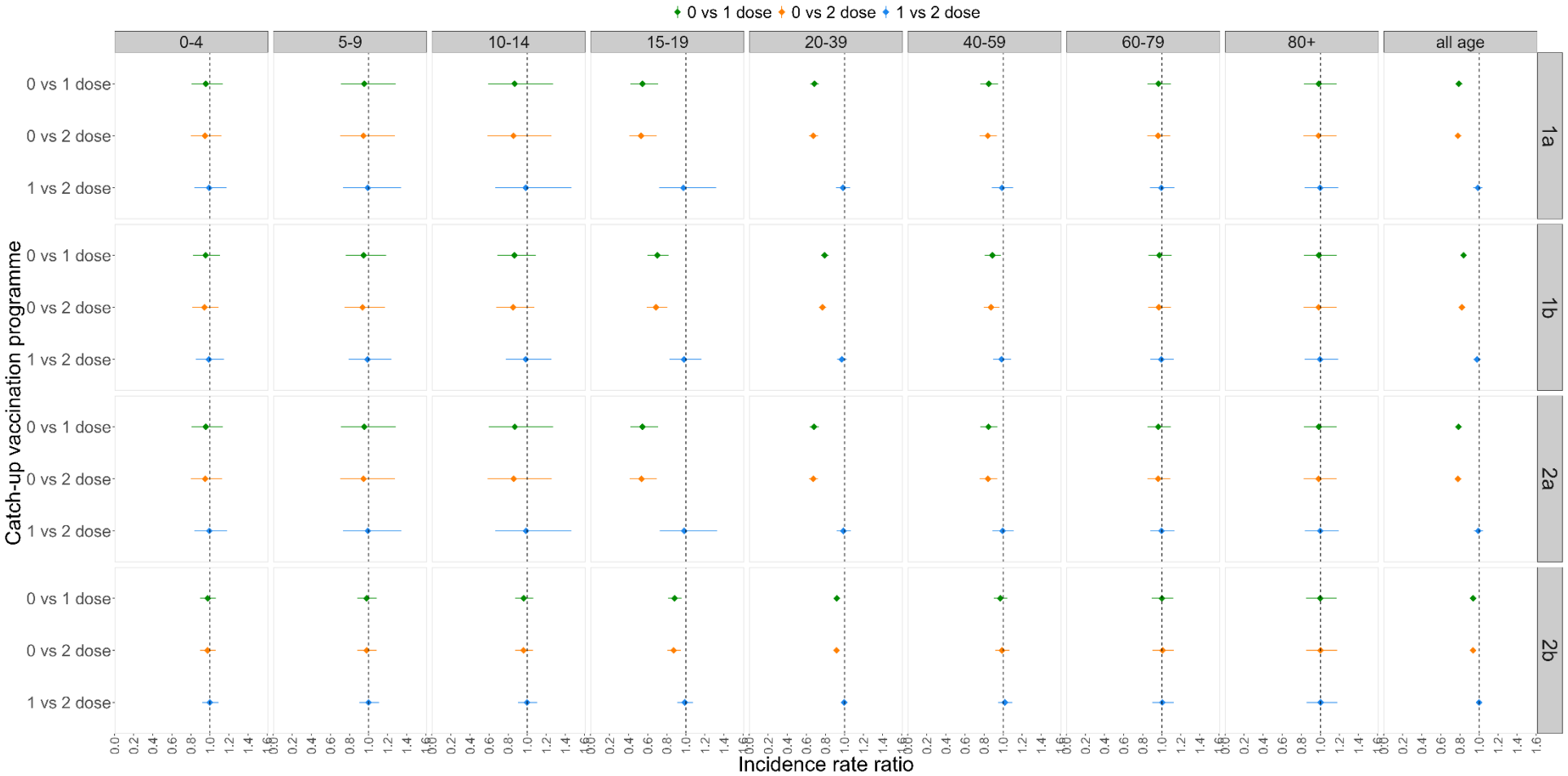
Note: The vertical dashed line indicates the launch of UVV in 2014. The grey rectangle highlights the period between 2020 and 2023, when non-pharmaceutical interventions were implemented in Hong Kong against the COVID-19 pandemic.

Figure S.5.16. Cumulative incidence of simulated varicella hospitalisations per 100,000 with one- and two-dose catch-up programme for different models, 2025 to 2050, Hong Kong.



Note: Scales of y-axis differ by models. Only natural varicella was assumed to result in hospitalisations.

Figure S.5.17. Incidence rate ratio of cumulative incidence of simulated varicella hospitalisations under different catch-up programme by age and models, 2025 to 2050, Hong Kong.



Note: An incidence rate ratio (IRR) under one indicates a lower incidence rate compared to the baseline and vice versa. Only natural varicella was assumed to result in hospitalisations.

Chapter 6. Discussion

6.1 Summary of findings

This PhD consists of epidemiological analyses pre- and post-UVV, vaccine effectiveness estimation and mathematical modelling. Varicella vaccination in Hong Kong provided a compelling opportunity to add to the collective evidence on the vaccine effects on the epidemiology of both varicella and herpes zoster. Before the initial discussion of implementing UVV in the early 2000s, the Department of Health Hong Kong started the first 5-yearly seroprevalence study in 1995 and varicella notifications in 1999. Data on public hospital A&E attendance and hospital admissions related to varicella and herpes zoster have also been available since 2004. Varicella vaccination in the private market has been ongoing since the 1990s, and the vaccine uptake in preschool children has been monitored in regular cross-sectional surveys since 2001. With the wealth of both seroprevalence and surveillance data the impact of varicella vaccination in the private market and the early effect of UVV since 2014 can be studied in detail. In addition to epidemiological analyses, a mathematical model was developed to integrate these data, re-establish and project varicella infections, with the aim to evaluate the benefit of offering catch-up vaccination to less exposed and under-unvaccinated older children. On top of vaccine effectiveness estimated in observational studies, the mode of varicella vaccine action was also studied through calibrating the model with data collected after vaccination started.

Changing epidemiology of varicella and herpes zoster during the private vaccination era (Chapter 2)

I first analysed surveillance data up to 2014, when the introduction of UVV had just started [Chapter 2]. The vaccine uptake increased from under 10% for preschool children born before 2000 to 50% for those born in 2012, the youngest cohort not included in UVV. Less than 10% of the vaccinated preschool children received a second dose. Therefore, a low to medium level of 1-dose varicella vaccination affected the population immunity and disease epidemiology before UVV. Both varicella and herpes zoster cause substantial health burdens in the public sector, with varicella primarily affecting children under 10 years and herpes zoster mainly affecting adults 60 years or older. For varicella, I found a shift in the burden of notified cases, AED attendance and hospitalisation from very young children to slightly older age groups. Seroprevalence for those aged between five and 19 years had decreased between 1995 and 2010. Catalytic models fitted to the seroprevalence data showed a decrease in the overall force-of-infection and increase in the average age of infection. This reduction in FOI and shift of burden of varicella infection during the private vaccine era was confirmed by the age-structured deterministic compartmental model developed in Chapter 5. For herpes zoster, a rise in AED attendance and hospital admission was found for those aged 10 to 59 years. The fact that these changes started shortly after vaccine licensure may indicate factors additional to varicella vaccination, such as reduction in newborns and smaller school and class sizes, which might result in less frequent contacts among children and contribute to these observations.

Early post-UVV data showed direct and indirect vaccine effects under near universal one dose uptake (Chapter 4)

The epidemiological analyses were extended to include data between 2015 and 2020, a period consisting of six years after UVV introduction in 2014 [Chapter 4]. The 2-dose UVV initially scheduled at 1 year of age and primary one (about six years of age) was later amended in 2018 to bring forward the second dose to 18 months, which became effective in 2020. Further cross-sectional surveys showed that the implementation of UVV was successful, as first-dose uptake reached 98% for all eligible children (born 2013 and after), though these children remained protected only from one dose of vaccination before 2020 [Chapter 4.1]. Sampled in 2015 and 2020, seroprevalence for very young children aged 4 years or below had increased considerably (45% in 1995 vs 82% in 2020) but seroprevalence in those aged between five and 24 years continued to decrease (overall ≥ 80% in 1995 vs ≥ 66% in 2020, with reductions in all 5-year age bands). This has resulted in an increasing number of susceptible older children, adolescents and young adults, who were not included in UVV and would be at higher risk of complications if infected with varicella. It should be noted that the analyses on seroprevalence showed that there were issues in low sensitivity of EIA assays to detect vaccine-induced immunity, which might have led to under-estimation of the observed seroprevalence in cohorts with higher vaccine uptake.

Surveillance data indicated that the reduction in varicella notifications, A&E attendance and hospitalisations among children aged under five years became more substantial between 2015 and 2020, which was likely related to the successful implementation of UVV [Chapter 4.3]. However, a relatively low level of varicella notifications remained in this age group (278 per 100,000 in 2019), indicating varicella persisting despite a nearly universal one dose uptake. A less substantial

reduction in varicella notifications and AED attendance was also found among those aged 5 to 9 years in the same period. The early impact of UVV in reducing varicella burden in young children should be balanced against a worrying trend of increase in notifications for those aged 10 to 19 years, whose vaccine uptake were only 11% to 38%. This continuous increase in varicella incidence in adolescents and young adults demonstrated the indirect effect of varicella vaccination. It should be noted that increases in varicella notifications were also observed for adults aged 40 years or above, whom should be mostly immune due to natural infections in childhood when varicella vaccine was not yet registered. For herpes zoster, an increase in herpes zoster AED attendance for those aged 20 to 59 years and hospitalisation for those aged 20 years or above was noted. During the COVID-19 pandemic, all varicella surveillance data decreased to very low levels. A smaller reduction in herpes zoster was also noted.

Modelling the impact of varicella vaccination (Chapter 5)

The analyses of the surveillance data in Chapters 2 and 4 suggested that under a prolonged period of one-dose varicella vaccination, varicella incidence decreased substantially in very young children and the burden shifted to older children and adolescents. These included particularly cohorts born before 2013, who were not eligible for UVV nor offered catch-up vaccination (CUP), despite only having moderate levels of previous vaccine uptake. Nevertheless, there were challenges in the interpretation of these post-UVV data. For instance, serosurveys in 2015 and 2020 indicated no or very low levels of infection for young children, which did not concur with the burden of varicella in these children as reflected by the notification data [Chapter 4.2]. Also, seroprevalence in adults aged 40 years or above has been consistently high at 90% or above, whereas notifications in adults have been increasing since mandatory reporting started, as both the

analysis based on the catalytic model of seroprevalence data in Chapter 2 and model calibration in Chapter 5 showed increase in notification sensitivity over the years. Furthermore, assuming a high vaccine uptake will be maintained and the UVV progresses with more children receiving two doses, VZV transmission is expected to further reduce but is unlikely to be eliminated, as adults will be a source of varicella infection when they develop herpes zoster. Hence, the projection of varicella incidence will inform risk assessment of varicella outbreaks in adolescents and adults and planning for appropriate public health measures.

These remaining questions were addressed in the Chapter 5 of the PhD. A mathematical model was developed to understand how varicella vaccination has affected the epidemiology of varicella over the years. Varicella incidence was also projected and compared with different CUP scenarios. Four candidate models were developed and calibrated with the seroprevalence data between 1995 and 2020 as well as notification data between 1999 and 2019. Several vaccine efficacy related parameters were included in model calibration to better understand the mechanistic action of the vaccine. I found that the simplest model without a temporary protection compartment (model 2a) fitted the data as well as the one with such a compartment (model 1a), indicating that there was no compelling evidence in the data used for calibration supporting such temporary complete protection against acquisition (in fact 1-dose protection against acquisition was found to be rather low generally with the vaccine providing mainly protection against progression to disease and onward transmission). The simpler model (with fewer parameters) was chosen as the main model with other models retained as sensitivity analyses. The abundance of notification and low seroprevalence among vaccinated cohorts signified that partial immunity might be the predominant outcome after one-dose vaccination.

The calibrated model showed significant reductions in both varicella infections and notifications for children under ten years of age before the pandemic, with a greater reduction in infections. The reduction consisted of a considerable decrease of natural infections, offset by an increase in breakthrough infections concomitant with the rise in vaccine uptake. The annual force-of-infection decreased over the years for all age groups, indicating a continuous drop in VZV transmission in the community, which is consistent with the estimations from the catalytic model on seroprevalence data between 1995 and 2010 [Chapter 2]. Consistent with the seroprevalence data, non-immune and partially immune older children and adolescents slowly accumulated over the years. The model fitting showed observed seroprevalence in older children and adolescents were likely under-estimated due to low sensitivity of the IgG assays to vaccine-induced immunity and potentially sampling issues, which was also inferred from the analysis of the seroprevalence data in Chapter 4.2. Also, increases in notifications throughout the study period for adults aged over 40 years, who should be mostly immune from infection in childhood, was likely driven by a general increase in surveillance sensitivity. Non-pharmaceutical interventions (NPIs) against COVID-19 greatly suppressed VZV infections during the pandemic. After the relaxation of NPIs, the model predicted an upsurge of both natural and breakthrough varicella that would primarily affect adolescents and young adults aged 10 to 39 years. The upsurge for adults aged 20 to 39 years is expected to last longer and be dominated by infections in non-UVV eligible cohorts. This model prediction highlighted that the accumulation of susceptibles through a prolonged period of one-dose varicella vaccination with moderate vaccine uptake can linger on if VZV transmission is heavily suppressed by a successful vaccination programme without addressing the cohorts with low immunity. These pre-UVV cohorts consist of up to half being mostly one-dose vaccinees that are susceptible to breakthrough infections and a smaller proportion who remain fully susceptible to natural infections. The model further suggested that providing a CUP to these older children and

adolescents would significantly reduce the projected post-pandemic upsurge, with a higher impact on reducing varicella incidence through a two-dose CUP. Although one- and two-dose CUP would effectively reduce the burden of varicella hospitalisations in adolescents and young adults, the absolute reduction is expected to be low (less than 1 per 100,000 between 2025 and 2035).

Estimation of varicella vaccine effectiveness and understanding its mode of action using observational data and a modelling study (Chapters 3 and 5)

In this PhD I estimated the varicella vaccine effectiveness in Hong Kong using both an observational study [Chapter 3] and the model developed in Chapter 5. After digitalising the dose number and date of varicella vaccination of over 10,000 immunisation records collected in the 2009 and 2012 immunisation coverage surveys, as well as validation of all varicella notification data included in the VE estimation, varicella VE of preschool children was estimated using the screening method in Chapter 3. The proportion of cases vaccinated (PCV) derived from the notification data was compared with the proportion of the population vaccinated (PPV) derived from the 3-yearly immunisation coverage surveys in 2009, 2012 and 2015. The VE was estimated by dosage (1- or 2-dose) and by severity of outcomes (all notification, hospitalised cases and cases with complications). One- and 2-dose varicella vaccination was found to be moderately and highly effective in preventing notified varicella cases (1-dose VE: 69.4% [95%CI: 67.5 to 71.2%] and 2-dose VE: 93.4% [95%CI: 91.7 to 94.7%]). One dose of the vaccine was more effective against complications (86.0% [95%CI: 48.8 to 95.8%]) and hospitalisations (75.2% [95%CI: 53.4 to 86.8%]). The VE estimates in Hong Kong are comparable to other global VE estimates, though the 1-dose VE in Hong Kong is relatively low (57, 269). The lower VE indicated breakthrough varicella would be fairly common among one dose vaccinees, and VZV will continue to circulate

in the community in the one-dose era. There was no significant difference in VE estimates in the first four years since vaccination, indicating no sign of waning shortly after vaccination when VZV remained circulating in the community.

While the VE estimation in Chapter 3 provided evidence on the degree of protection of varicella vaccines against different disease outcomes, the mode of vaccine action remains uncertain. In Chapter 5, the main model (model 2a) suggested that 1-dose varicella vaccine was ineffective in preventing breakthrough infections (*VE_infection*$_1$: 14.1% [95%CI: 5.1 to 27.9%]), moderately effective in preventing the development of notifiable and notified disease after contracting infection (*VE_progression*: 59.6% [95%CI: 19.3 to 84.4%]) and highly effective against onward transmission (*VE_transmission*$_1$: 98.1% [95%CI: 89.8 to 99.9%]). This estimation showed that the partial immunity acquired via one dose of varicella vaccination is ineffective in protecting vaccinees from being infected, but still confers sufficient immunity to protect the vaccinees from developing severe diseases and transmitting the viruses to their contacts. The low *VE_infection*$_1$ estimated is similar to those estimated in Gao *et al.* (123) and Brisson *et al*.'s studies (106) of which post-UVV surveillance data from the US and clinical trial data of MSD mVV were being fitted to. There are no directly comparable estimates of *VE_progression*, which is more specific to the protection against varicella notification, but the combined effect of *VE_infection*$_1$ and *VE_progression* (64%) are comparable to the estimated 1-dose VE against varicella notification (69%) in Chapter 3 [refer to the discussion on '*Characteristics of varicella vaccine effects*']. The estimated *VE_transmission*$_1$ is generally higher than those assumed in other models that inferred this effect from other observational studies (61, 65, 118), and comparable estimates are not available.

6.2 Generalisibility of the research

The WHO recommended countries introducing varicella vaccine into their routine vaccination to maintain an uptake of 80% or above (251). The analyses contained within this PhD have illustrated the experience of varicella vaccination in Hong Kong, which consists of over 15 years of low to moderate vaccine uptake in the private market, followed by a rapid attainment of near universal vaccination. The predominantly one-dose vaccination at sub-optimal uptake for over 15 years resulted in a reduction of the overall disease burden, with some increase in disease burden in older children and adolescents, as well as an increasing number of susceptible individuals moving into adolescence and adulthood. This is an important reference for countries who plan to introduce universal varicella vaccination, or those who have low or moderate varicella vaccine uptake from private and/ or funded vaccination. For instance, similar trajectory of low to moderate one-dose uptake in the private market, followed by a high uptake of two dose UVV, was reported in Japan (96). In China, subsidy in varicella vaccination is only available in certain areas (88, 270). This study has also highlighted the benefit for countries to monitor non-routine vaccine uptake, in particular if parents tend to bring their children for vaccination not included in the funded programme, as disease epidemiology may have already changed under sub-optimal vaccination.

From a surveillance perspective, the collection of long-standing data is immensely valuable in planning and evaluating vaccination programmes. In conjunction with these surveillance data, the availability of regular varicella seroprevalence data starting before private vaccination allows the monitoring of change in population immunity and age of infection. Despite the extended scope of varicella surveillance data available in Hong Kong, the post-vaccination analyses showed countries should adjust their surveillance strategies with major interventions such as the

vaccination programme changing the disease epidemiology. This PhD also showed the value of using mathematical models to evaluate existing vaccination programmes. Although mathematical models and cost-effectiveness analyses have been providing crucial evidence for policy-makers at the stage of programme planning, they are not as often deployed to understand the impact after the launch of vaccination programmes [Chapter 1]. Countries should consider allocating modelling resources to evaluate the effect of vaccination programmes and assess the need to adjust vaccination policy, such as Gao *et al*'s modelling study to project the effect of stopping a catch-up programme (118). Mathematical models calibrated with data collected in the post-vaccine era can also inform the mode of vaccine action to supplement the VE estimated in observational studies.

6.3 Limitations

Although this PhD has added to the collective evidence of varicella vaccination and epidemiology, there are several limitations arising from the data collected and/ or methodologies adopted.

Lack of data in primary care on the burden of herpes zoster

While the epidemiological and modelling analyses of varicella in this PhD encompassed both outpatient and inpatient data, there is a lack of data on the burden and trend of herpes zoster in outpatient settings. In Hong Kong, electronic data readily available to the Department of Health include only secondary care utilisation (AED attendance and hospital admissions) in public hospitals. Therefore, the incidence of herpes zoster presented in Chapters 2 and 4 were limited to secondary care, which is more representative of severe or complicated herpes zoster. Data on primary care consultations for herpes zoster would be more representative of the burden in the

population and more sensitive to any changes.

Biases in surveillance data collected after increasing vaccine uptake

Despite the effort in addressing the biases identified in the surveillance data during the model fitting, there are other potential factors that were not taken care of. First, although a good posterior estimate was obtained for the sensitivity of the IgG assays towards vaccine-induced immunity, different combinations of IgG assays were used across the study period and their sensitivity likely differed. With only aggregate data available, I was also unable to adjust the seroprevalence data even if there appeared to be a sampling issue in some age groups. Similarly, the fitting to notification data was improved by inclusion of a parameter of annual change in notification sensitivity, which was generalised across different age groups. Such changes might also be affected by other factors such as health-seeking behaviour and diagnostic accuracy. However, there was no relevant empirical data that could guide further adjustment.

Simplification of model compartments and age structure limits precision for forward simulation

The models were designed with the aim to represent childhood varicella vaccination in Hong Kong up to 2020, when one-dose vaccination predominated. Thus, the models only consist of one-dose vaccination compartments and have single year age groups up to 20 years of age. This framework served the purpose of modelling the vaccination scenarios while reducing the computation time, and it provided an approximation of the future trajectory of varicella vaccination when an increasing number of cohorts will be receiving two doses of vaccination. It should be noted that the forward simulation is less precise when UVV cohorts enter adulthood, as the age grouping

change from a single year age band to a five-year age band. The five-year age band will include cohorts eligible for different vaccine regimen in certain years.

Uncertainty of pandemic effects on VZV transmission and other behaviour

While some of the NPI effects such as reduction in contacts and the protective effect of face masking were adjusted on an annual basis in the model, variations likely existed within each year and across different sectors of Hong Kong society. Cross-sectional surveys in 2020 showed adherence to COVID-19 risk reduction behaviour fluctuated within different months of the year (268), while another survey in 2022 showed that work and social pattern had also been evolving after the Omicron wave (267). Also, there were likely unadjusted effects after the pandemic measures, especially in health-seeking behaviour and risk reduction measures. Avoidance of medical consultations due to fear of COVID-19 might have reduced the sensitivity of notifications especially for those with relatively mild disease (172, 173). Increases in physical distancing such as remote working and/ or face masking may persist after the pandemic (244). These changes may reduce VZV circulation, varicella notification and healthcare utilisation post-pandemic.

6.4 Future work

Based on the experience of this PhD, I suggest the following subsequent work specific to Hong Kong and more general to the study of varicella vaccination.

Modifying surveillance of notification and seroprevalence for the post-UVV era

As shown in Chapter 2 and Chapter 4, varicella surveillance, including notifications and seroprevalence studies should be fine-tuned to minimise biases in monitoring disease activity and sero-immunity when a high proportion of children acquire partial immunity via vaccination and remain largely susceptible to breakthrough infections. Periodic evaluation of the notification system should be undertaken, as disease severity and likely health-seeking behaviour may differ following large-scale vaccination programmes. Surveillance based at sentinel schools can also be used to supplement and understand the performance of mandatory notification (271, 272). This will allow adjustment to the observed data and ensure a more accurate assessment of the impact of vaccination programmes. Varicella notification is usually based on clinical diagnosis and rarely confirmed with laboratory testing (178, 273). A small representative sample of notified cases may be selected for laboratory testing, especially for breakthrough infections presented as milder and modified varicella. Research in rapid tests on oral fluid can improve accessibility of laboratory confirmation and is currently underway (206).

To reliably assess varicella seroprevalence in a highly vaccinated population, an IgG assay sensitive enough for vaccine-induced immunity, for instance glycoprotein (gc)-based should be used (35). Before carrying out the main study, the assay should be evaluated against samples with known vaccination and/ or infection history, allowing a more sensitive threshold to be determined using mixture modelling (176, 274). If vaccine uptake changes rapidly by cohorts, the samples should be collected by single age group to avoid mixing cohorts of different vaccine eligibility and vastly different vaccine uptake.

Monitoring varicella vaccine effectiveness through outbreak studies

Varicella vaccine effectiveness for preschool children was estimated in this PhD by using the screening method [Chapter 3]. The estimation involved children not eligible for UVV and their vaccine uptake was low to moderate (between 24% and 51%). The screening method is less suitable when the population uptake becomes high (275). Therefore, alternative observational studies, such as case-control study with controls identified during outbreaks (276, 277), would need to be considered for VE estimation post-UVV. VE estimation using cohort or case-control studies in primary care settings is difficult to be carried out as Hong Kong's residents are not registered to designated healthcare providers. As outbreaks in households, schools and other institutional settings are routinely followed up by DH Hong Kong, it provides a good opportunity to study the effect of vaccine in these settings (276, 277). The study would allow estimating the vaccine effect by doses and duration since vaccination in protecting vaccinees from acquiring infections and potentially even effectiveness against transmission. Laboratory testing such as polymerase chain reaction (PCR) of outbreak cases could help ascertain case status and provide quantitative estimates of viral load by vaccination status. Transmission chains can also be studied in well-defined outbreaks and important biological parameters such as serial intervals can be estimated. Further VE estimation should also include comparison of second dose VE of different schedules (18 months vs Primary 1).

Assessing the burden of herpes zoster in primary care settings

With a rapidly ageing population in Hong Kong, prevention of herpes zoster, potentially through vaccination, should be a priority in the overall strategy to reduce VZV disease burden. While AED

attendance and hospital admission data related to herpes zoster are available from the public hospitals, data on outpatient consultation, where most of the cases are being managed, are not available. A systematic literature review of the epidemiology and burden of herpes zoster between 2000 and 2020 in the Asia Pacific affirmed that the data on herpes zoster in Hong Kong are mostly limited to secondary care (278). The private sector accounts for over 70% of outpatient primary care in Hong Kong (279) and these data are important to support formulation of shingles prevention strategies. Without local primary care data, recent economic analyses of herpes zoster vaccination in Hong Kong relied either on relevant estimates in Taiwan (280) or data from a single hospital in Hong Kong (280).

Expanding the varicella vaccination model

The model developed in this PhD was tailored to enhance our understanding for a period of largely one-dose varicella vaccination scenario. As discussed in the limitations section; to understand the impact of UVV in Hong Kong with more children receiving second doses of varicella vaccine, the model should include compartments corresponding to two-dose vaccination and be calibrated with data collected when the second dose uptake increases. Model predictions could also be expanded to include primary care consultations and severe varicella, such as varicella in pregnancy and neonatal and congenital varicella. To assess the joint effect of varicella and herpes zoster vaccination, compartments representing herpes zoster disease and vaccination should also be included. Similar to Chapter 5 in this PhD, 2-dose varicella VE parameters related to susceptibility, transmission and disease severity should be included in the estimation. The effect of large-scale varicella vaccination programmes on the magnitude and duration of exogenous boosting of immunity against development of herpes zoster remains unclear (29, 30), though the US

observational data appeared to signal a shorter effect on the duration of protection, contributing to the UK's recent decision in introducing varicella vaccination (150). Exogenous boosting on CMI is another important parameter to be included in the calibration, and surveillance data on varicella and herpes zoster in other countries collected after UVV implementation should also be explored. The current and updated model should inform cost-effective analysis to understand the best combined varicella and herpes zoster vaccination strategies. Previous economic analyses on zoster vaccination in Hong Kong were based on static models which assumed the risk of herpes zoster would not be affected by the reduced exogenous boosting due to varicella vaccination (220, 280, 281).

Understanding the implication of population movements between Hong Kong and mainland China on control of varicella

There are high cross-border population movements between Hong Kong and mainland China, including both short-term cross-border travel for work, business, leisure and education, as well as migration. A survey in 2017 showed the average daily number of passengers between Hong Kong and mainland China reaching 666,700, compared to 275,400 in 2001 (282). 319,800 (48%) were Hong Kong residents travelling to mainland China, which approximated 4.3% of the Hong Kong population (282, 283).

This consistent population movements between Hong Kong and mainland China may pose challenges in controlling varicella in Hong Kong. Infectious disease transmission between mainland China and Hong Kong has been frequently documented. One of the more prominent examples was the outbreak of severe acute respiratory syndrome (SARS) in Hong Kong in 2003,

which was originated from an index patient travelling from Guangdong province, China (284). A meta-population model studying the early transmission of COVID-19 first identified in Wuhan, China found that the exportation of cases before travel restrictions was driven by human mobility between late 2019 and early 2020 (285). Varicella vaccination has not yet been included in the national immunisation programme of mainland China (286). Subsidy on varicella vaccination is only available at sub-national level, leading to diverse varicella vaccination strategies across different geographic regions (87). As a result, there are substantial differences in vaccine uptake in different provinces, as reflected by wide range of estimates in 2019 (from 27% in Gansu where funded varicella vaccination was not available to 95% in Shanghai and Tianjin which have free varicella vaccination provision) (87). Moreover, varicella vaccine uptake was only estimated to be 61% in Guangdong, the province that directly borders Hong Kong (87). Therefore, varicella infections in mainland China will likely remain at a higher level than that of Hong Kong, which will be an increasingly important source of wild-type VZV infection as endemic transmission in Hong Kong is modelled to further reduce with sustained near universal vaccine uptake [Chapter 5]. As varicella notification in Hong Kong has now decreased to very low levels (annually 1,396 to 1,686 reports in 2023 and 2024), additional information such as travel history, place of birth and usual place of residence in childhood can be collected to study the influence of varicella importations from mainland China.

In addition to the high level of daily cross-border travel, there are also consistent immigrations from mainland China. Between 2011 to 2019, there were 54,300 to 76,800 mainland China immigrants, accounting for 0.8 to 1.1% of the average population of Hong Kong in the corresponding period (283, 287). The net immigration between 2016 and 2021 was highest in females aged 25 to 49 years, with 5,000 to 20,000 per 5-year age cohort (288). Before the COVID-

19 pandemic, mothers born in mainland China accounted for about 40% of total births in Hong Kong between 2015 and 2021, of which more than half resided in Hong Kong 7 years or less before giving births (289). Seroprevalence among immigrants may differ from local residents, as they experience different vaccination programme and transmission intensity during their childhood. This is especially important if female immigrants remain susceptible during their pregnancy, as they would still be susceptible for maternal varicella and potentially transmitting the virus to the fetuses. Demographic information on place of birth and usual place of residence during childhood can be collected in future seroprevalence studies in the general population [Chapter 4.2] and in pregnant women (290) to understand the need for health education on varicella prevention for different population sub-groups.

6.5 Conclusion

In summary, this PhD demonstrated how mathematical models can integrate with routine surveillance data to study the effect of varicella vaccination. The model showed that a prolonged period of low to moderate one-dose vaccination reduced varicella transmission and led to a partial shift of disease burden to older children and adolescents. Estimation of varicella vaccine effectiveness through an observational study showed that one-dose of vaccine was moderately effective against notified varicella disease. This is largely comparable to the estimation of vaccine effectiveness through calibration of the full transmission dynamic model, which showed that one-dose varicella vaccine was ineffective against acquiring breakthrough infections but was moderately effective against developing notified disease and highly effective against onward transmission. Varicella vaccination in the private market led to health inequality as those unvaccinated have a diminished opportunity to acquire immunity via natural infections at a

younger age leaving them at increased risk of complications if infected in adolescence and adulthood. Hence, countries should carefully assess the baseline epidemiology including vaccine uptake in the private market and the potential impact before launching universal vaccination. Continuous monitoring of changes in disease epidemiology and population immunity, supplemented with appropriately parameterised mathematical models, allows for timely evaluation of the vaccination programme and can inform decision-makers on the need to refine the vaccination strategy.

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