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Unravelling transmission dynamics of influenza and its interaction with other respiratory viral pathogens in the population of Kamigoto island, Japan

SU MYAT HAN

Student number: 1901561 (LSHTM), 59719005 (NU)

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Department of Infectious Disease Epidemiology

Faculty of Epidemiology and Population Health

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Signed:

Date: 1 November 2024

Full Name: Su Myat Han

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Abstract

Respiratory viral infections such as influenza threaten public health. It is spread through infectious respiratory droplets containing influenza virus. Annually, prior to the COVID-19 pandemic, an estimated 500,000 influenza-related deaths occurred globally, with young children and older adults being the most vulnerable. Despite the availability of influenza vaccines and anti-viral, the ever-evolving nature of influenza strains, coupled with variations in transmission dynamics, presents significant challenges to the efficacy of prevention and control strategies. Very few studies are available to understand the influenza transmission dynamics in the local community setting, particularly in a semi-isolated community setting such as an island city. Moreover, the islands are the natural laboratory for studying infectious disease transmissions. Thus, it can help us better understand the role of different factors, such as virus-virus interference, on influenza transmission dynamics.

Therefore, the current study performed between the 2010 and 2018 influenza seasons in the population of Kamigoto Island, Japan, aims to

1. Examine the transmission dynamics of influenza virus by using longitudinal influenza surveillance data,
2. Identify transmission links and sources of outbreaks by constructing the phylogenetic tree of circulating influenza viruses, and
3. Explore the influence of virus-virus codetection on influenza transmission patterns.

To address the research questions:

1. A mathematical modeling approach was employed to understand the transmission patterns of the influenza virus.
2. Whole genome sequencing was performed on 198 influenza-confirmed human nasopharyngeal swab (NPS) samples to examine transmission links of the influenza clusters and the role of importation events.
3. Genetic characterization of 13 respiratory viruses was performed on 2,313 NPS samples, and the difference in the within-host diversity of influenza virus was studied.

To address the transmission dynamics of influenza within the small island city, a newly developed model, “o2geosocial,” an R package, was applied to analyze the fine-scale longitudinal influenzas surveillance data spanning eight influenza seasons. I chose this model because it allows the transmission tree reconstruction when sequence data are not available. Moreover, the model takes account of the probability of the connection between the different regions, which is particularly important for the current study in a small island city. The study found that preschool and school-aged children, high population density, low local vaccination coverage, and dominant strain of influenza play significant roles in shaping similar geographical transmission patterns across the seasons studied. Moreover, individual vaccination status did not show a significant association with onward transmissibility, suggesting that while vaccination may reduce the severity of infection, it may not prevent transmission.

Influenza-like illness (ILI) and/or rapid influenza diagnostic test (RIDT) diagnosed influenza data is insufficient to understand the transmission link of influenza. Genomic sequence data plays a crucial role in revealing the relatedness of the cases in the transmission

chains. Moreover, the genomic data can explain the relatedness of influenza strains in the island to mainland Japan or other parts of the world. The second part of this thesis aims to provide whole genome sequencing (WGS) data on influenza viruses by applying next-generation sequencing (NGS) technologies. Reversed reverse transcriptase polymerase chain reaction (RT-PCR) confirmed influenza samples from Kamigoto Island during the 2011/12 and 2012/13 seasons were sequenced. The web-based bioinformatic platform, "INSAFLU, " was used to conduct the phylogenetic study of influenza virus transmission patterns at the local community level. 229 NPS samples were successfully sequenced and identified as A/H3N2 subtypes. All these sequence data were deposited into the gene bank. During the study period, seasonal influenza A(H3N2) activities in the islands were marked by multiple introductions of influenza strains from outside the island and fuelled by local onward transmission. The circulating strains during the study periods were identified as Clade 3C.2 and 3C. At least five transmission clusters were observed during the study period. All the observed transmission clusters circulated simultaneously, which may be misinterpreted as part of the same cluster without sequenced data, highlighting the importance of genomic surveillance. The study also revealed that the first sequenced case and a large number of cases came from the busiest district of the island and spread to the other parts of the island. The epidemic was suggestive to be initiated in the adult working age group (19-64 years old) and spread to different age groups.

In an influenza season, other respiratory viruses, including but not limited to the human respiratory syncytial virus (RSV), human rhinovirus (hRV), and human metapneumovirus (MPV), also co-circulate. Despite evidence of virus-virus interactions, their influence on the within-host influenza viral diversity is unclear. In the last part of the Ph.D., 13 respiratory

viruses (influenza A and B, hRSV, hRV, hmpv, parainfluenza virus I-IV, adenovirus, bocavirus, human coronavirus (OC43, 229E) were identified in ILI samples using an in-house multiplex RT-PCR protocol. The ILI samples collected during the 2012/13 Influenza season were used for viral identification. Due to the low availability of WGS samples with high genome coverage, only 150 influenza WGS samples were available for variant calling to measure the within-host viral influenza. The study did not identify a significant difference in the influenza viral diversity within the host between those with only influenza-infected versus influenza-virus-infected cases. The within-host influenzas viral diversity is a random event, suggesting a minor or negligible contribution of these viral codetections to the evolution of influenza viruses. However, the sample size available is small, and thus, further study with larger sample sizes is needed.

In conclusion, this PhD research contributes to understanding influenza transmission dynamics in a unique community setting. The research demonstrates the importance of integrating surveillance and genetic data to study respiratory virus transmission. The current research also contributed to broader accessibility of the influenza sequence data from Japan, as there are limited whole genome sequences (WGS) available from Japan for that period (less than 10 in 2011/12 and zero in the 2012/13 influenza season). This research also explored virus-virus codetection on the influenza evolution with the host. However, given the low sample size, further studies are warranted for more in-depth investigations to conclusively determine the impact of virus-virus interactions on influenza virus genetic diversity.

Additional Publications

I contributed to other manuscripts which were not part of my PhD:

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List of Abbreviations

AdV	Adeno viruses
bp	base pair
BM2	Matrix Protein 2
Boca	Boca viruses
hCoV	Human coronaviruses
DNA	Deoxyribonucleic acid
HA	Haemagglutinin
hMPV	Human metapneumovirus
HRV	Human Rhino viruses
IAV	Influenza A viruses
IBV	Influenza B viruses
ICV	Influenza C viruses
ILI	Influenza-like illness
iSNVs	minor single nucleotide variants
M1	Matrix protein 1
M2	Membrane protein 2
ML	Maximum likelihood
MCMC	Markov Chain Monte Carlo
MoHLW	Ministry of Health, Labour, and Welfare
NA	Neuraminidase
NGS	Next generation sequencing
NIID	National Institute of Infectious Diseases
NP	Nucleoprotein
NPS	Nasopharyngeal swab
NS1	Non-structural protein
NEP	Nuclear export protein
PA	Polymerase Acidic protein
PB1	Polymerase Basic 1 protein
PB2	Polymerase Basic 2 protein
PIV	Parainfluenza viruses
R ₀	Basic reproduction number
Reff	Effective reproduction number

RIDT	Rapid influenza diagnostic test
RIR	Relative illness ratio
RNA	Ribonucleic acid
RSV	Respiratory syncytial viruses
RT-PCR	Reverse Transcriptive- polymerase chain reaction
WHO	World Health Organization
WGS	Whole Genome Sequencing

Chapter 1: Introduction

1.1. Motivation

Seasonal influenza as major public health burden

Respiratory viruses contribute significantly to the global burden of diseases. WHO estimated that 3,199,000 deaths were attributed to respiratory infections, a total of 5.7% of all-cause mortality per year.^[1] Influenza is a respiratory viral infection that causes yearly seasonal with a substantial economic and health care burden each year and remains as public health challenge.^[2] Seasonal influenza causes severe illness to approximately 3-5 million people each year. According to WHO, between 290,000 and 650,000 deaths occur yearly due to influenza-related infections.^[3]

Limited understanding of seasonal influenza dynamics at the local level

Influenza's transmission dynamics have been extensively examined in various contexts, including global, regional, and specialized settings like schools, universities, or military camps.^[4-11] Such studies illuminate the influence of age groups, environmental conditions (like humidity and temperature), human mobility, behaviors, and host immunity on influenza transmission. Insights gained from these discoveries can provide valuable guidance for public health interventions during seasonal outbreaks. However, it is important to note that the interaction of these factors can differ significantly based on the social structure and geographic location. Consequently, it's impractical to apply a one-size-fits-all approach to control measures across different settings. Moreover, there's a notable scarcity of research focused on local communities, particularly in geographies characterized by a heterogeneous population structure coupled with limited movement.

The increased role of next-generation sequencing (NGS) in infectious diseases

The advancement in Next-generation sequencing (NGS) has revolutionized the understanding of infectious disease transmission dynamics. Integrating genomic data with epidemiological information has proven to be a valuable tool in infectious disease surveillance. [12,13] It allows us to reconstruct transmission events, enabling us to infer who-infected-whom in the infectious disease outbreak. This helps us better understand the transmission dynamics and design better prevention and control measures. Yet, limited studies [14,15] exist due to scarcity of fine-scale epidemiological and genomic data.

Evidence suggests an interaction of other respiratory viruses and influenza.

It's been observed that when one respiratory virus infects a host, it might alter the host's susceptibility to subsequent infections. [16-19] Given that respiratory viruses, including influenza, often circulate simultaneously, an infection from one can modify the transmission patterns of another. This alteration in susceptibility might arise from short-term general immunity against a different virus or more prolonged immunity against related strains. The primary evidence for such interactions includes observed shifts in flu epidemic patterns [20-23], experimental studies (in vitro and vivo) [16-19], and analysis of human serum samples [24-28]. Although these findings hint at the interplay between viruses, the role of co-infection/co-detection of respiratory viral pathogens on the genetic diversity of influenza virus (within and between the host) has not been studied yet. [3,29-31]

Within-host evolution of influenza virus

Like other RNA viruses, the influenza virus replicates by RNA-dependent RNA polymerase, which lacks the ability to proofread. [32,33] This leads to a high error rate, and RNA viruses' high evolution rate. Due to its large number of mutations, RNA viruses exist as the mutant swarms

“quasispecies” within the infected host. This within-host diversity of the viral population, particularly the low-frequency mutation, was hypothesized to have virulence factors or immune escape ability.^[34] Factors such as vaccination^[35], pregnancy^[3,4], transmission routes^[37], or presence of multiple genotypes or strains^[38] have been studied for their roles in shaping intra-host diversity during acute infections. However, very little evidence exists on the virus-influenzas codetection and its impact on the intra-host influenza dynamics during the acute infection. This knowledge gap is significant because co-infections could alter the evolutionary trajectory of the influenza virus by creating different selective pressures. For example, other viral pathogens might modulate the host immune response, potentially impacting the replication rate, mutation frequency, or selection of specific influenza strains.

Kamigoto island, Japan

Japan, an archipelago comprising 14,125 islands, includes Kamigoto Island off its western coast. This rural community is semi-isolated, with limited transportation to mainland Japan. An estimate of 22,599 people resides within the island (2011 census data). There is only one hospital, Kamigoto Hospital, covering the whole of Kamigoto town population. Kamigoto Hospital is part of the sentinel site for the influenza surveillance and influenza-like illness cases were systematically recorded. This semi-isolated island, distinguished by its diverse age demographics and relative isolation from the broader Japanese mainland due to its geographical nature, presents an ideal environment to study infectious disease spread. The availability of the longitudinal fine-scale datasets from the surveillance system is also an opportunity to study the influenza disease transmission dynamics.

Summary of motivation

Influenza stands out as a significant public health concern with wide-ranging global and local implications. While our understanding of its dynamics has grown, particularly with the advent of NGS technologies, gaps remain, especially concerning local transmission and the intricate interactions of respiratory viruses. Addressing these areas can pave the way for more effective and targeted interventions, safeguarding communities and potentially saving countless lives. Moreover, WGS by NGS technologies enable us to study the within-host viral dynamics and provides us the opportunities to study the virus-virus interaction at such level, which up to date has not yet existed.

What is in the thesis?

Inspired by Charles Darwin's insights into how remote islands can shed light on infectious disease propagation, this thesis delves into the spread of influenza in Kamigoto city, a semi-isolated island in southwestern Japan. The thesis has three main parts. I first use mathematical modeling to analyze influenza transmission dynamics on Kamigoto Island over eight seasons. Next, I employ phylogenetic analysis to discern relationships between influenza strains, focusing on importation and local transmission. Finally, I probe into the implications of viral co-detection on intra-host influenza dynamics through NGS. Throughout this endeavor, I executed all web-laboratory procedures, performed mathematical and genomic analyses with guidance from my supervisory team, and collaborated on the bioinformatics aspects.

1.2. Aim and Objectives

Aims

The aim of the research is to understand transmission dynamics of seasonal influenza in a semi-closed population setting: Kamigoto islands, Japan, and to inform the better prevention and control strategies at the local level.

Objectives

1. To reconstruct the epidemiological and spatial dynamics of seasonal influenza on Kamigoto island (paper I) and (paper II)
2. To investigate interactions of influenza with other viral respiratory pathogens and assess their impact on influenza transmission (paper III)

1.3. Outline of the thesis

This thesis comprised seven chapters. The present chapter offers a concise introduction to the PhD thesis. **Chapter 2** delves into the background knowledge and fundamental concepts underpinning the thesis. **Chapter 3** describes data sources and molecular methodologies employed. Within this chapter, I detailed the two primary data sources utilized. The first is a surveillance dataset collected over an eight-year period (2010-2018) as part of routine data collection procedures on the island. The second encompasses the web-laboratory methodologies and sequencing protocols I executed to generate data for subsequent analyses. Results from these methodologies are also presented in this chapter. **Chapter 4 (Paper 1)** investigates the transmission patterns of seasonal influenza and evaluates the driving factors within a semi-isolated island context, drawing from the surveillance dataset. Here, I reconstructed probabilistic transmission trees of influenza cases using Bayesian inference combined with the Markov-chain

Monte Carlo method. I then conducted a negative binomial regression on these inferred transmission trees to discern factors linked to onward transmission. For the transmission tree reconstruction, I employed the “o2geosocial package”, [46] an R tool developed by my colleague, Alexis Robert, during his PhD research. **Chapter 5 (Paper 2)** employs the phylogenetic analysis of influenza sequence data to uncover epidemic patterns within the Kamigoto island community. The sequence data generated through the methods outlined in Chapter 3 form the basis for this exploration. I scrutinized the phylogenetic relationships of the influenza strains of Kamigoto island to the mainland Japan and the global sequences. Subsequent analysis shed light on importation events to the islands and the spatio-temporal distribution of local onward transmission clusters. **Chapter 6 (Paper 3)** identifies co-circulating respiratory viral pathogens present during influenza seasons. It assesses how co-detection alongside other respiratory viruses might influence influenza’s genetic diversity and transmissibility. This chapter utilizes RT-PCR and sequence data derived as detailed in Chapter 3. **Chapter 7** synthesizes discussions and conclusions drawn across the thesis.

1.4. Impact of COVID-19 and Coup d'état in Myanmar on PhD progress

During the first year of my Ph.D., the COVID-19 pandemic unfolded. As a trainee in molecular diagnostic technology for virus characterization, I volunteered to be dispatched to San Lazaro Hospital in the Philippines, where my university has a long-standing history of collaboration. I was tasked with establishing the PCR diagnostic system for COVID-19 at the hospital. My deployment occurred at the peak of Manila's lockdown, when COVID-19 cases were surging. Upon arrival, I was taken aback by the complete silence that had replaced the once lively atmosphere of the city since the onset of the pandemic. As a member of the university team, my role centered around the laboratory, where I conducted COVID-19 diagnoses for healthcare

workers and patients at the hospital. My primary responsibility involved setting up the RT-PCR system at the NU-SLH laboratory, adapting the protocol from Japan NIID. Managing the workflow presented a challenge, necessitating tasks such as staff training, allocation, and coordinating with the ongoing provision of other laboratory services for hospitalized patients. Scheduling the turnaround time from sample collection to results provision was particularly challenging due to limited human resource capacity in our team. During the lockdown, public services such as taxis and buses were unavailable. Organizing sample collection was another challenge, particularly as we regularly swabbed healthcare workers for screening to support the SLH hospital. Staff concerns about potential infection, especially given the cultural context where many live with their families, prompted the need to arrange shifts and housing allowances for those staying away from home due to fears of spreading the infection to their families. After spending over a month there, I returned to my university to resume my doctoral studies. This collaboration led me to engage in COVID-19 research at San Lazaro Hospital and co-author four publications.^[39-42] Our collaboration team studied on the epidemiology and clinical characteristics of first few hundred COVID-19 cases admitted to the SLH hospital.^[39] This study was very useful as SLH received first COVID-19 cases in the country and was one of the main infectious disease hospitals receiving COVID-19 cases in the country. HCWs played a major role, as they were at the frontline, being susceptible population as well as source of transmission. To prevent, infection and transmission among HCWs and HCWs to non-COVID-19 patients, we regularly screened HCWs and shared the results as the publications.^[40] Vulnerable population to COVID-19 includes tuberculosis patients, and SLH had tuberculosis ward. We screened the admitted TB patients for COVID-19 and found none of them was infected.^[41] This proved the good infection control within the hospital, preventing the transmission from COVID-19 wards to the TB wards. Many respiratory viruses can co-circulate with COVID-19 and

thus we did the multiplex PCR to identify additional 13 respiratory viruses including influenza A, B and respiratory syncytial viruses, to all the HCWs tested for COVID-19.^[42] From this study, we found that only two percent of the symptomatic HCWs were positive for COVID-19. 13% of them were positive for other respiratory viruses mainly with rhino viruses. Initially, I considered integrating COVID-19 into my thesis. However, I decided to maintain my original focus on influenza for my Ph.D. project.

In my second year, a coup d'état occurred in Myanmar, which was shocking not only to me but to the entire Myanmar community both at home and abroad. I was deeply concerned for my family, who remained in the country; the heightened threats were particularly alarming as some of them are healthcare workers. My friends and I, coming from a medical background, were profoundly disturbed by these events. It took nearly seven months to regain the mental composure necessary to return to my studies, as I was actively participating in the movement against the dictatorship. Together with other Myanmar colleagues, we called on the international community to be aware of military coup impact on the Myanmar Health system.^[43] I also wrote op-ed to let international community about medical doctors and other health professionals within Myanmar.^[44,45] Coming from medical background and worked in humanitarian setting, it was irresistible for me to organize and run a medical program in remote areas with limited health resources. I applied different grants, and supported the volunteers HCWs who were unemployed due to CDM, to provide health care services to the population. My support included the supply of medicine, and salary for these volunteer HCWs. All these involvements took a toll on my mental health and subsequently delayed my Ph.D. progress. Although my doctoral journey did not unfold as planned, I had to conclude within the given time constraints. I have detailed the unfinished parts of my research as future opportunities in my thesis.

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Chapter 2: Literature review and fundamental concepts

2.1 Influenza viruses

Influenza viruses belong to the *orthomyxoviridae* family.^[1] Four types of influenza viruses exist (A, B, C, and D),^[1] with three of them, influenza A (IAV), influenza B (IBV), and influenza C (ICV), known to infect humans. Influenza viruses are enveloped by negative-strand RNA (negative sense, single-stranded), and their genomes are segmented with IAV and IBV genomes comprising eight segments (Figure 2.1).^[1] The genome segments, length, and function of influenza A and B viruses are described in (Table 2.1). The segment size of the influenza virus ranges from 890 to 2,341 nucleotides, with a total genomic length of approximately 13.5 kb.

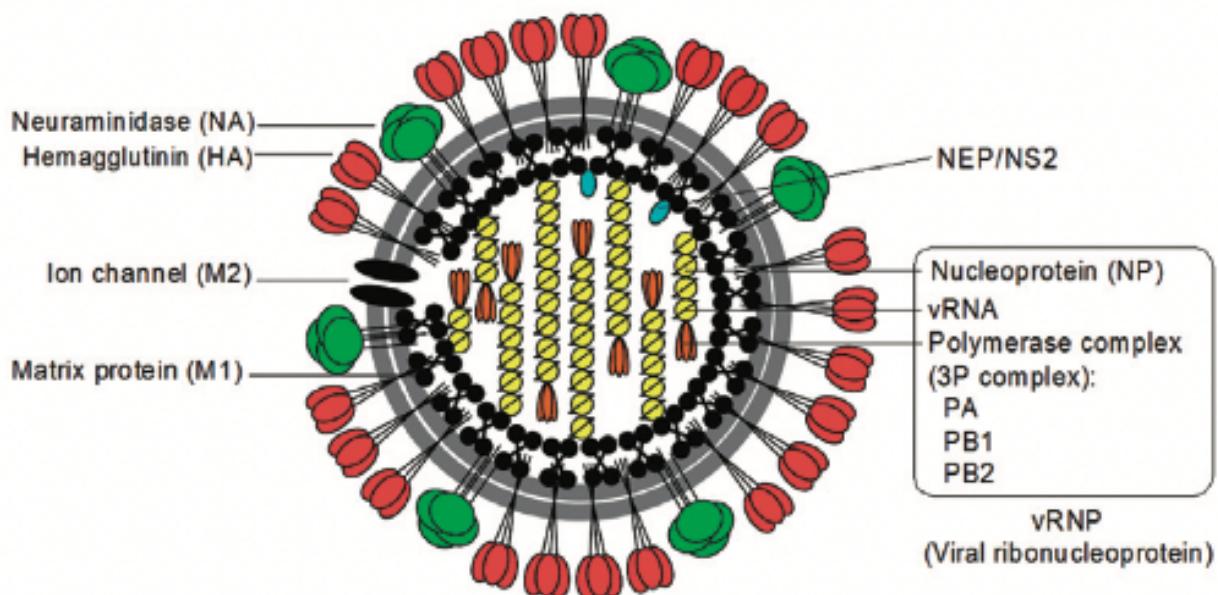


Figure 2.1: Genome of influenza, adapted from *Textbooks of influenza*^[2]

Table 2.1: Genome segments, their length, and function of influenza A and B viruses Influenza A virus (A/PR/8/34), Influenza B virus (B/Lee/40), Adapted from *Textbooks of influenza* [2] and published literatures [1, 3-5]

Segment	Length(bases)	Structure and protein Function
PB2	2341 (IAV)	The PB2 (Polymerase Basic 2) segment encodes the PB2 protein, which is a crucial component of the viral RNA-dependent RNA polymerase complex. The PB2 protein's primary functions include polymerase activity, cap snatching, viral replication and transcription, host-cell interactions, and nuclear localization. These functions are critical for viral RNA synthesis, replication, and pathogenesis, and PB2 plays a crucial role in the overall life cycle of influenza viruses.
	2369 (IBV)	
PB1	2341 (IAV)	The PB1 protein's primary function is to contribute to the viral polymerase complex's enzymatic activity
	2369 (IBV)	and also involved in viral RNA replication and transcription.
PA	2233 (IAV)	The PA protein's primary functions in both influenza A and B viruses are to facilitate the cap-snatching process, contribute to the polymerase activity of the viral RNA-dependent RNA polymerase complex,
	2245 (IBV)	and assist in the initiation of viral replication and transcription.
Haemagglutinin (HA)	1778 (IAV)	The HA (Hemagglutinin) segment encodes the HA protein, which plays an important part in viral entry
	1882 (IBV)	and host cell attachment. The HA protein's primary functions are host cell attachment, membrane fusion, and antigenicity. These processes are crucial for viral entry, commencement of infection, and escape of host immune responses.

Nucleocapsid protein (NP)	1565 (IAV) 1841 (IBV)	The NP protein is an essential component of the viral ribonucleoprotein complex (vRNP) and its primary functions include RNA binding and packaging, involvement in viral transcription and replication, nuclear localization, evasion of host immune responses, and contributing to antigenicity.
Neuraminidase (NA)	1413 (IAV) 1557 (IBV)	The NA (Neuraminidase) segment encodes the NA protein, a crucial component of the viral envelope. The NA protein's primary functions include receptor cleavage, viral spread and release, antigenicity, contribution to virulence and pathogenicity, and susceptibility to antiviral drugs.
Matrix protein M1 & M2 (IAV) M1 & BM2 (IBV)	1027 (IAV) 1180 (IBV)	The Matrix protein 1 (M1) and Matrix protein 2 (M2, IAV) or BM2 (IBV) are encoded by the matrix protein (M) segment. The M1 protein primarily functions in viral morphogenesis, budding, host-cell interactions, intracellular trafficking, and assembly processes. M2 or BM2, on the other hand, serves as an ion channel protein and contributes to viral assembly, budding, and susceptibility to certain antiviral drugs in influenza A viruses. The specific role of BM2 in influenza B viruses may share similarities with M2 but can have distinct characteristics due to the unique biology of influenza B viruses.
Non-structural protein (NS1) Nuclear export protein (NS2/NEP)	890 (IAV) 1096 (IBV)	The Non-structural protein 1 (NS1) and nuclear export protein (NS2/NEP) are encoded by the non-structural protein (NS) segment. NS1 primarily focuses on counteracting host immune responses and regulating viral RNA, while NS2/NEP plays a role in the export of viral ribonucleoprotein (vRNP) complexes out of the nucleus and contributes to viral assembly and budding processes.

Influenza A viruses are well-known for their genetic and antigenic diversity.^[2, 3, 6] This is contributed by their broad host range, which includes natural reservoirs in wild birds and susceptibility in multiple species, including horses, dogs, poultry, and humans.^[1] The most antigenically variable segments are the HA and NA, the surface glycoproteins of influenza viruses. IAV is categorized into different subtypes based on the antigenic characteristics of their HA and NA proteins. Until now, 18 genetically different HA (HA 1-18) and 9 NA (NA 1-9) have been identified.^[4] Among the human populations, six HA subtypes (H1, H3, H2, H5, H7, and H9) and two NA subtypes (N1 and N2) have been found to circulate.^[4]

Influenza B viruses infect a more limited range of hosts and are known to infect only humans and seals. This limited range of hosts may explain the limited extent of virus recombination and diversity observed in IBV. IBV is subdivided into two lineages, namely Victoria and Yamagata.^[4]

The absence of a 'proofreading' mechanism in the viral RNA-dependent RNA polymerase causes a high mutation rate. This leads to the build-up of point mutations in the HA and NA segments of both IAV and IBV.^[6] This is known as antigenic drift, which permits the virus to escape the host immunity, resulting in regular seasonal influenza epidemics.^[6] Additionally, given the segmented nature of the influenza genome, the reassortment of gene segments can occur when cells are concurrently infected with several distinct influenza strains (antigenic shift). Antigenic shifts can generate novel strains to which population immunity is naive, leading to a pandemic outbreak. Antigenic shift is restricted to IAV, and throughout recent history, four pandemics have occurred: 1918 (A/H1N1), 1957 (A/H2N2), 1968 (A/H3N2), and 2009 (A/H1N1).^[1]

2.2 Clinical features of influenza infection

Influenza virus infection typically presents mild upper respiratory tract symptoms or common cold-like symptoms (sudden onset of fever, cough, headache, sore throat, fatigue,

muscle and joint pain, severe malaise (feeling unwell), and a runny nose. [4, 6, 7] However, it can cause severe or deadly illness to high-risk populations such as pregnant women, children under 59 months, elderly, immunosuppressed, and health care workers. [6] Yearly vaccination against influenza is advised for these high-risk populations. [8] Non-pharmaceutical interventions such as early case isolation, school closures, and social distancing are alternative strategies for vaccination to mitigate the epidemic. [1]

2.3 Epidemiology of seasonal influenza

IAV and IBV circulate and cause seasonal epidemics among the human population across all continents. Seasonal outbreaks happen in the winter in the northern hemisphere, in the autumn and winter in temperate areas, and year-round in tropical zones. [9, 10] Seasonal influenza is estimated to cause severe illness in approximately 3-5 million people, resulting in an annual death toll ranging from 290,000 to 650,000 (WHO). [11]

The typical transmission route of influenza between humans and humans is via droplets, aerosols, and direct contact. [6] The symptoms commonly present after an incubation period of 1-4 days. [4] However, viral shedding begins before the signs and symptoms and lasts about seven days. [4, 12] This implies that pre-symptomatic infections greatly influence the transmission patterns of influenza. Many studies also report the part of asymptomatic infections in the transmission dynamics. [13] It was estimated that 5-30% of influenza infections are attributed to symptomatic disease. [13]

2.4 Transmission dynamics of seasonal influenza

Studies have extensively examined the global circulation patterns of seasonal influenza. [14-19] East and Southeast Asia (E-SE Asia) have been identified as the primary hub for the emergence and circulation of new influenza A/(H3N2) variants. [15, 17, 18] A/H3N2 strains originating from E-SEA do not persist for long-term evolution; instead, new variants from E-SEA seed into temperate regions annually. [14] In contrast, global circulation of A/(H1N1), and

influenza B were found to vary substantially from that of A(H3N2). [18] The variants of A(H1N1), and influenza B were reported to be present for multiple seasons with the limited role of E-SE Asia as a source of new variants. The circulation patterns observed for A(H1N1) and influenza B reflect the findings of a slower evolutionary rate, increased susceptibility in younger individuals, and fewer epidemics compared to A(H3N2). [18] It was also found that temperature, humidity, and precipitation influence the dynamics of the seasonal epidemics across temperate and tropical climates region. [20] Owing to these findings, the establishment of a robust global influenza surveillance network and the optimization of influenza vaccination have become feasible.

Studies have also explored the dynamics at the continental, or country level, [21-25] with a focus on age-specific susceptibility and prevalence to different types or subtypes of influenza [25, 26], or the effect of environmental factors such as humidity [27] and temperature [28] or human mobility [22] or seasonality of the different types of influenza [29]. Some studies identified the regions of origin of each seasonal outbreak for the purpose of strengthening the control measures. [30, 31] Very few studies investigated the localized level or communities. [32, 33] I found two studies examining the spatial diffusion of pandemic influenza (A/H1N1, pdm09) within a single community: the university campuses. The first study from the US found a low level of intra-campus transmission, a lack of clustering of viruses, and no significant spatial clustering. Instead, the global genetic diversity of the samples revealed the multiple independent introductions of influenza (A/H1N1, pdm09) into the campus. [33] The second study from Singapore reported strong evidence of intra-campus transmission and evidence of multiple introductions from the community. [32] Studies of transmission dynamics in a more local community setting, such as in the city, [34, 35] revealed the extensive mixing of global strains with the local strains indicated by the repeated introduction events of influenza cases into the cities. The household [36, 37] transmission studies were valuable for elucidating the transmission

dynamics of infectious diseases, particularly in understanding patterns of virus spread, serial intervals and the identification of secondary attack rates within confined populations.

Given the above mentioned, the pattern, speed, and pathways of influenza viruses spread vary across geographical locations and seasons and are complicated by complex human movement patterns and behaviors. [22, 29, 32] A better understanding of transmission dynamics at the local level helps to identify fine-scale drivers of influenza transmission for more localized prevention and control interventions.

2.5 Influenza in Japan

In Japan, the prevalence of seasonal influenza endemic is estimated to be over 10% yearly. [38] The influenza season generally occurs between December and April. [39] Surveillance for Influenza-like Illness (ILI) and influenza has been systematically conducted since the enactment of the new infectious disease control law in April 1999. [40] An ILI case is defined by the sudden onset of fever exceeding 38°C, accompanied by respiratory symptoms and other systemic manifestations such as fatigue, headache, or myalgia. [40] Rapid influenza diagnostic tests (RIDTs) are widely used in Japan and as a proxy of the total symptomatic influenza cases in the population, and the sensitivity of the tests available in Japan is reported to be relatively high ranging from 72.9% to 96.4%. [41-44] In Japan, influenza vaccination is recommended annually between late October and December. Routine vaccination is recommended for those aged 65 and above and high-risk populations aged 60 and above. For children, influenza vaccination is not compulsory according to the national immunization schedule of Japan. [11]

Influenza surveillance is carried out nationwide through the collaboration of local health centers, public health institutes, and infectious disease surveillance centers operated by prefectural governments, all following the guidelines set by the Ministry of Health, Labour, and Welfare (MoHLW), Japan. [45] Since the 1980s, surveillance efforts have significantly expanded, leading to more sentinel clinics that provide weekly reports on the incidence of

outpatient influenza cases.^[46] National Institute of Infectious Diseases (NIID), Japan releases an annual influenza report on its website. Furthermore, comprehensive influenza surveillance studies including but not limited to epidemiology^[26, 47, 48], prevalence^[26, 49], drug resistance, vaccination rate^[50-54], or vaccine effectiveness^[55-59] are conducted throughout various regions of Japan. However, there needs to be more research utilizing both genomic data and surveillance data to reconstruct local-level transmission dynamics to inform prevention and control strategies.^[60-63]

2.6 Role of mathematical modelling in infectious disease transmission studies

Mathematical modeling techniques have been proven helpful in understanding the complexities of infectious disease transmission dynamics. These models help examine various factors that affect transmission, such as seasonality, vaccination strategies, human mobility, and age-group mixing.^[60-63] Mathematical models serve as hypotheses about the spread of infections and undergo continuous refinement and evaluation based on specific disease data. They are integral to public health strategies, as they help propose, test, and implement theories and plan, execute, and evaluate detection, prevention, and control programs. Some noteworthy findings from mathematical modelling includes examining rotavirus dynamics in the United States,^[63] which emphasized the influence of birth rates on seasonal patterns; utilizing contact data to parameterize a model, underscoring the significance of contact patterns in identifying vulnerable groups;^[62] and estimating the basic reproductive number during an Ebola outbreak,^[60] emphasizing the necessity for enhanced bed capacity and case identification to control the spread effectively.

While modelling disease transmission dynamics, the estimation of regional connectivity plays a crucial role in understanding population movements, which is often neglected. Traditional data sources like commuting data^[64] or mobile phone GPS^[65] are used in infectious disease modelling, however, these may not capture the specific mobility patterns of age groups

affected by the virus, such as school-aged children since they may not have mobile phone. Moreover, the infected individuals may exhibit different movement behaviour, for those with symptoms may not travel to work, or control measures during the outbreak to control the spread of infection may impact mobility. Mobility models are integrated into virus spread modeling to account for disease-related mobility specifics. Among these models, gravity models [64, 66, 67] are commonly used, where connectivity between regions depends on population size and distance. However, a limitation of gravity models is their inability to account for the influence of neighboring regions on connectivity. Stouffer's "law of intervening opportunity" suggests that the connectivity between regions depends on the number of intervening opportunities, rather than just geographic distance. [68, 69] Alternative models like the radiation model [70] and Fotheringham's competing destinations model [71] offer different perspectives on human movement patterns. Comparison studies between these models have shown varying performance depending on data sources and distances. For instance, Stouffer's rank models have outperformed gravity models in some cases, while the exponential gravity model was more suitable for fitting commuting flows over short distances. Thus, different mathematical models are employed to analyze regional connectivity and its implications for diseases like measles.

Understanding the transmission dynamics of a virus within a community requires reconstructing transmission trees to determine who infected whom. This information is crucial for calculating the effective reproduction number, which indicates the virus's ability to spread. Transmission trees are reconstructed using patient interviews and statistical methods, but they have limitations such as underreporting and the inability to account for missed transmission opportunities. Statistical methods like the Wallinga-Teunis algorithm [72-74] use onset dates to estimate transmission probabilities between cases and calculate individual reproduction numbers. These methods have been adapted to incorporate additional data sources like genetic

sequences, which can improve the accuracy of transmission tree reconstruction.^[75-78] However, genetic sequences may not always provide conclusive evidence of transmission links. Social contact data, particularly age mixing patterns, also play a crucial role in transmission tree reconstruction, as mixing between different age groups influences transmission dynamics.^[62,79,80] By integrating variables like onset dates, age groups, and locations of cases, routine surveillance data can be maximized to reconstruct transmission trees and identify regions or settings where targeted interventions are needed to control disease spread.

2.7 Role of Generation Sequencing in infectious disease transmission studies

The advancement in Next-generation sequencing (NGS) has revolutionized the understanding infectious disease transmission dynamics. NGS enables us to characterize the complete DNA sequence of organisms of interest, surpassing the traditional Sanger sequencing. Several NGS platforms have been developed, including Illumina^[81], and Ion Torrent^[82]. They rely on fragmenting the DNA/genome into smaller pieces and sequencing them parallel to generate overlapping sequences or reads. These reads are aligned to a reference genome or assembled de novo to reconstruct the sequenced DNA. NGS provides significant advantages over Sanger sequencing regarding cost, throughput, and accuracy. NGS can efficiently perform whole-genome sequencing (WGS) for viruses, enabling comprehensive genomic characterization of viral pathogens. The wide availability of whole-genome sequencing (WGS) technology in the past decade has increased. On the other hand, the cost of the WGS has been reduced.

The basic steps of next-generation sequencing technologies are 1) DNA fragmentation and denaturation resulting in the sections of single-stranded DNA, 2) adding adaptors to the ends of the fragments, 3) amplification of the DNA, creating multiples copies to be sequenced in parallel and 4) sequence by synthesis with either DNA polymerase or DNA ligase. The fluorescent-labeled nucleotides are incorporated and detected in real-time during synthesis.

Illumina is a widely used WGS technology; the Illumina platform with over 90% of sequencing data globally.

Integrating genomic data with epidemiological information has proven to be a valuable tool in infectious disease surveillance. It allows us to reconstruct transmission events and infer who-infected-whom in the infectious disease outbreak. This helps us better understand the transmission dynamics and design prevention and control measures.

NGS enables us to perform detailed studies of the viral diversity within the infected host. [83-85] The type and frequency of mutations within a population are easily obtained from NGS. Viral diversity can be measured and compared by different methodologies (richness, abundance and evenness, Shannon entropy, pairwise nucleotide diversity). These methods capture the varying impact of mutations present at different frequencies. Differences in variety across tissues (respiratory, gastrointestinal) or changes over time (within days to weeks) can be used to model within-host viral dynamics due to selection and genetic drift. These studies shed light on the within-host viral evolutionary dynamics and offer insight into their relationship to the epidemiology and evolution at broader scales.

2.8 Intra-host or within-host evolution of influenza virus

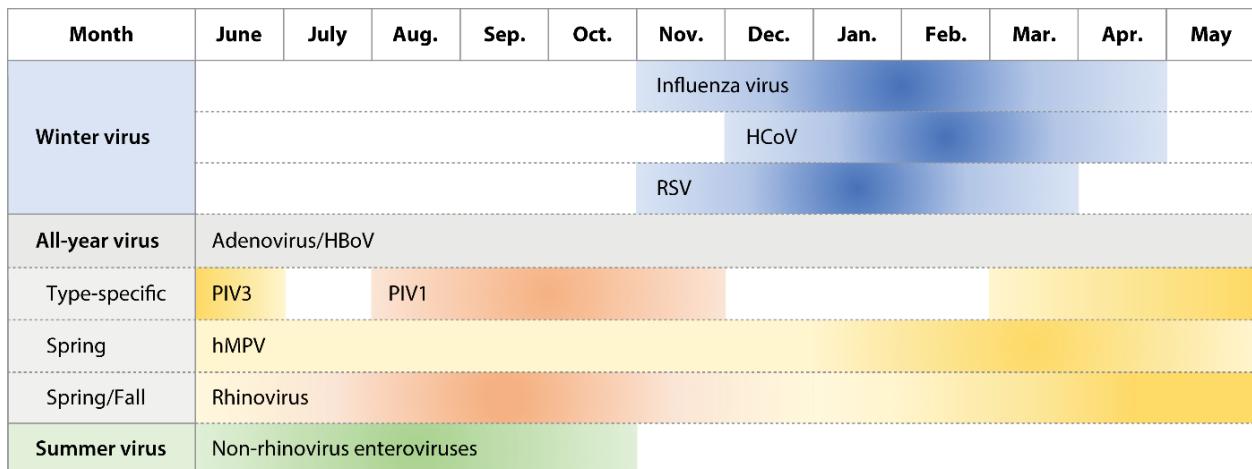
Like other RNA viruses, the influenza virus replicates by RNA-dependent RNA polymerase, which lacks the proofreading ability. [1, 6] This leads to a high error rate and the RNA viruses' evolution rate. Due to its many mutations, RNA viruses exist as the mutant swarms "quasispecies" within the infected host. This within-host diversity of the viral population, particularly the low-frequency mutation, was hypothesized to have virulence factors or immune escape ability. Understanding the evolution of viruses, especially influenza, is crucial because these mutations and resultant viral diversity can significantly impact viral virulence, transmissibility, and susceptibility to immune responses, shaping the trajectory and severity of outbreaks and influencing vaccine effectiveness. [86-90]

Influenza infections usually last a week, and it is challenging to have enough samples to study the within-host dynamics. The existing studies of within-host dynamics were mainly based on animal models, human challenge studies, or immunocompromised patients. These studies have documented that the intra-host populations of influenza viruses were diverse, dynamic, and characterized by incomplete purifying selection.^[91-99] Experiment studies with horses^[91] and swine^[92] reported the rapid turnover of the intra-host population and quick fixation of the synonymous mutations throughout the infection. However, contradictory results were reported in equine models, which stated that the mutations accumulate over time.^[93]

In recent years, intra-host diversity of the influenza viruses was studied in naturally occurring acute infections in the human population.^[94-98] Deep sequencing of influenza viruses from the infected human samples found that the mutations were present in only a few cases and at a shallow frequency.^[99] This suggests that intra-host minor variants do not reach fixation or higher frequencies than the significant variants.^[99] The presence of multiple genotypes of cellular co-infections were reported as driving factors on the intra-host viral diversity in HIV, CMV, and RSV viruses.^[100] Debbink et al.^[94] studied the impact of vaccination on the intra-host viral diversity of influenzas viruses and found no difference in within-host viral dynamics between the vaccinated and non-vaccinated patients.^[94,97] A recent study explored the impact of pregnancy on intra-host viral diversity and reported that modulation of the immune system during pregnancy does not affect the intra-host influenza viral diversity.^[95] Other studies explored the within-host diversity of influenza viruses in upper and lower respiratory tracts^[96, 101] and concluded that viral diversity is not site-specific. However, the impact of virus-virus codetection on the intra-host diversity of influenza has yet to be well-studied.

2.9 Viral interference on influenza transmission dynamics

Most respiratory viruses show seasonality patterns and thus can be classified according to their seasonal epidemics (Figure 2.2).



 Moriyama M, et al. 2020.
Annu. Rev. Virol. 7:83–101

Figure 2.2: Seasonality respiratory viral pathogen, adapted from Moriyama M. et al. 2020^[102]

Many respiratory virus infections may present as influenza-like illness (ILI), and studies reported the presence of more than single respiratory pathogens (viruses and bacteria) in the same patients. ^{[103-105] [106]} The incidence rate of these respiratory viruses responsible for ILI varies by location, age group, or season. ^[102-104, 107, 108] The respiratory viruses' structure, type, and seasonality are discussed more in Table 2.

Common viral pathogens co-circulating with influenza

Table 2.2: Common respiratory viral pathogen cocirculating with influenza virus (adapted from Thorburn, Fiona (2016)^[109] and review article [110])

Virus Name	Structure, type and seasonality of the virus
Respiratory Syncytial Virus (RSV)	<p>RSV is part of the <i>Paramyxoviridae</i> family, the sub-family <i>Pneumonviridae</i>, and the genus <i>Orthopneumovirus</i>. RSV is an enveloped, negative-sense, single-stranded RNA virus with a length of approximately 15 kilobases (15kb).</p> <p>RSV can be divided into two main groups, RSV-A and RSV-B, based on their serological differences. Each group has multiple genotypes that may have slight differences in their genetic sequences and antigenic properties.</p> <p>RSV infections are common during winter. RSV is often detected alongside influenza viruses.</p>
Human Metapneumovirus (hMPV)	<p>hMPV belongs to the <i>Paramyxoviridae</i> family, the sub-family <i>Pneumonviridae</i>. It is classified under the genus <i>Metapneumovirus</i>.</p> <p>hMPV is a non-segmented, negative-sense, single-stranded RNA virus. Its genome has a length of approximately 13 kilobases (13kb).</p> <p>hMPV is categorized into two main subtypes: A and B. Each subtype consists of minor subgroups, including A1, A2, B1, and B2.</p> <p>hMPV infections can be detected throughout the year and are considered an all-year virus. hMPV infections commonly occur in young children, older adults, and individuals with weakened immune systems. It is reported to be co-detected with influenza viruses.</p>
Human Parainfluenza Viruses (PIV)	<p>PIVs are a group of respiratory viruses that belong to the <i>Paramyxoviridae</i> family.</p> <p>PIVs are enveloped viruses with a non-segmented, negative-sense, single-stranded RNA genome.</p> <p>There are four major types of PIVs: PIV-1, PIV-2, PIV-3, and PIV-4. Each type can cause respiratory infections, particularly in young children, but they vary in terms of disease severity and symptoms. Outbreaks of HPIV infections can occur throughout the year, but they are more common in the fall and winter months.</p>

Human Rhinovirus (HRV)	<p>HRV belongs to the <i>Picornaviridae</i> family. It is a non-segmented, positive-sense, single-stranded RNA virus. The genome of HRV is approximately 7.3 kilobases (7.3kb) in length.</p> <p>HRV is classified into three main groups: Rhinovirus A, B, and C. These groups are based on genetic differences, with each group containing multiple distinct strains. Rhinovirus A and B are more common and well-known, while Rhinovirus C was discovered more recently.</p> <p>HRV infections can occur throughout the year, earning the classification of all-year viruses. They are a leading cause of the common cold, accounting for a significant proportion of respiratory infections in both children and adults.</p>
Human Coronaviruses (hCoV)	<p>hCoV belongs to <i>Coronaviridae</i> family. It is an enveloped virus, a single-stranded positive sense RNA virus. The genome length is approximately 27-33 kb, the longest of the RNA viruses.</p> <p>hCoV is classified into two genera: alpha and beta coronaviruses. (HCoV 229E, HKU1, OC43, NL63, SARS, MERS, SARS-CoV2 cause human infections). hCoV is known as winter virus.</p>
Adenoviruses (hAdV)	<p>hAdV belongs to the <i>Adenoviridae</i> family. It is under the genus <i>Mastadenovirus</i>. hAdV is a double stranded DNA virus, with a genome length of about 32kb.</p> <p>hAdV are divided into subgroups A to G with at least 52 serotypes (Subgroups C and E are common). hAdV can be detected throughout the year.</p>
Bocaviruses (hBoV)	<p>hBoV are belonged to the <i>Parvoviridae</i> family. It is a non-enveloped, single stranded DNA virus with a genome length of about 5.3kb.</p>

Virus-virus interaction at population level

The attention towards the role and interplay of virus-virus codetection has gained momentum in recent years. The presence of multiple viruses codetection was reported; the commonly reported cocirculating respiratory viral pathogens include RSV, hCoV, hMPV, and hRV. [102, 106, 111-113] From the existing studies, the virus's co-detection rate ranges from 11.6% to 15.7%. [103, 114, 115] Virus-virus cocirculation or co-detection within the patients may influence the circulation and transmission of influenza and other factors, such as host and environmental factors. However, the role of co-infection/co-detection of respiratory viral pathogens and their interactions at different scales (cellular, host, community, and global) are complex and unclear. [106, 108, 116, 117] Very few studies of influenza transmission dynamics account for the viral-viral pathogen interactions. [113, 118]

Some studies hypothesized that competitive viral-viral interaction impacts the outbreaks of respiratory viruses (mainly influenza viruses, RSV, and RV). [19, 119, 120] For example, the early occurrence of seasonal IAV outbreaks shifted the timing of seasonal epidemics of IBV, RSV, and hCoV.[119] Alternatively, the HRV epidemic delayed the second wave of 2009 influenza pandemic in European countries and China. [120-122] The recent COVID-19 outbreaks have diminished the other seasonal respiratory pathogens circulation. [123, 124] Though the non-pharmaceutical measures may contribute to this, the effect of virus-virus interaction is less known.

Virus-virus interaction at host level

In clinical settings or at the individual level, respiratory illness co-infected with a virus and a bacterial pathogen has proven to be associated with increased disease severity. [125] Regarding virus-virus co-infection, inconsistent findings were reported: association with increased or decreased disease risk or no associations. [126-130] The human rhinovirus (HRV) infection was found

to be associated with a reduced probability of infecting with certain other respiratory viruses such as RSV and inf A.^[131, 132] Still, it increases the morbidity in infants with bronchiolitis or pneumonia once co-infection with other respiratory viruses occurs.^[126, 129] Other viral pathogens such as hMPV, hCoV (HCoV; 229E, OC43, NL63, HKU1), AdV, BoV, and PIV 1-4) were reported to have lower rates of co-detection.^[131-133]

Virus-virus interaction at cellular level

At the cellular level, it was found that competition for resources among viruses; the virus that infects the host cell earlier can block the entry of other viruses or the dominant virus interferes with the replication of the co-existing viruses.^[88] A clinical analysis and experimental infection study of viral interference between rhinovirus and influenza.^[89] In that study,^[89] it was found that one respiratory virus can prevent the infection of another by triggering antiviral responses in the airway mucosa through the activation of interferon-stimulated gene (ISG) expression. In their vivo study, RV infection protects against subsequent IAV for up to 3 days. It was also found that day-5 post-rhinovirus infection reduces approximately 50 000-fold IAV H1N1pdm09 viral RNA.^[89] Another in vitro experiment suggested that hRV may downregulate the genes related to the processing of viral mRNA, ribosomal proteins, translation, and influenza infection.^[134]

2.10 Contribution of the Proposed Study to Knowledge

There are very few studies looking at the transmission patterns of seasonal influenza at the local level or community, while control measures put in place are important at such a level. Moreover, islands are the natural laboratory for studying infectious diseases, including influenza viruses, given their heterogeneous population (different age groups, work or household sizes) yet semi-isolated from the urban or mobilized communities. The availability of the fine-scale

longitudinal surveillance dataset provides the opportunity to study the transmission dynamics of influenza in such a setting.

Many respiratory viruses circulate at the same time, and yet very little is known on how these influence on influenza transmission at the population level, host level or cellular level. Therefore, there is also a need to assess the role of virus-virus interaction on the impact of influenza transmission patterns.

In this thesis, I first explored the transmission dynamics of seasonal influenza in the island community setting by using surveillance datasets as well as genomic data. Then I studied the differences in the within-host diversity of influenza viruses between only-influenza-infected patients versus virus-influenza co-detected/co-infected cases. The Figure 2.3 captures the PhD workflow overview.

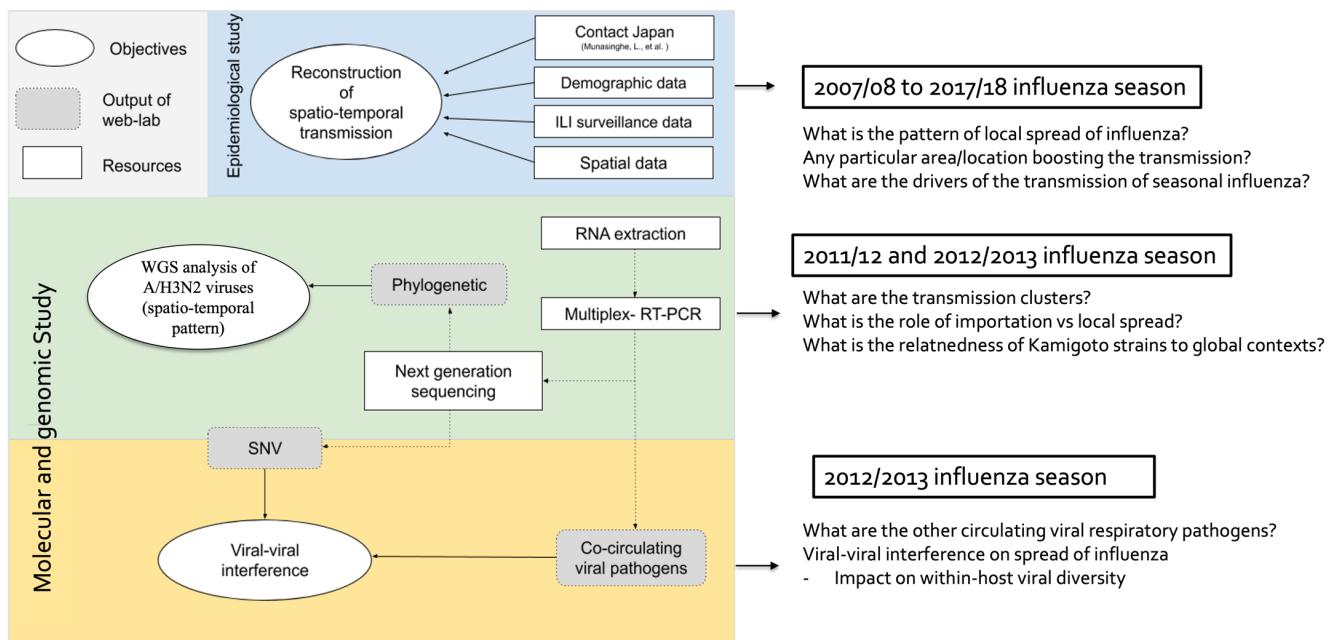


Figure 2.3: PhD workflow overview

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Chapter 3: Data source, Molecular diagnostic methods and data results

3.1 Study setting and data source.

This joint Ph.D. project was motivated due to the availability of detailed epidemiological data collected over ten seasonal/years (2007/2008 - 2017/2018) in primary care surveillance and collection of nasopharyngeal swab samples for specific years (2011/12 and 2013/14) from the Kamigoto islands, Nagasaki prefecture, Japan. Kamigoto is a rural town with one main island, surrounded by several small islands located along Japan's western coast (Figure 3.1A). The transportation to the mainland island is limited, and the island is a semi-closed community. The island has a single hospital, named Kamigoto Hospital, and six clinics. Kamigoto Hospital is 186 bedded hospital, providing primary, secondary, and tertiary care; it is the only health facility with a pediatrician on the island. As of 2010 census data, Kamigoto Island had a population of 22,630 individuals. The demographic characteristics of the people of Kamigoto Island are described in the below table (Table 1) and Figure (1B).

(i) Surveillance dataset

Chapter four of this Ph.D. thesis uses surveillance data, which collects data on patients with ILI visiting at the outpatient department of Kamigoto Hospital between October 2010 and May 2018. Since 2007, Kamigoto Hospital has systematically registered all ILI cases. Individuals with influenza-like illness (ILI) symptoms visiting the hospital during the study period were tested with a commercial rapid diagnostic test (RIDT; Esplini Influenza A and B®, Fujirebio Inc, Japan) to diagnose influenza A- and B-positive cases as a routine practice. Rapid influenza diagnostic test kits (RIDTs) are widely used to diagnose influenza in Japan. The globally estimated sensitivity and specificity of RIDTs range between 50-70% and 98-99%, respectively. [8, 9] Sensitivity of RIDTs in Japan is relatively high, with 72.9–96.4% sensitivity across the studies restricted to Japan. [12, 13] Additional sociodemographic and clinical

information for these ILI patients was collected from the hospital database. Information about current and past influenza vaccination status (2008 – 2013) was retrieved from the local government's vaccine registry system. Vaccine status was defined as ‘vaccinated’ 14 days after vaccine administration.

(ii) Samples available for molecular characterization and genomic analysis

In the Kamigoto setting, the residual nasopharyngeal swabs (NPS) from the RIDTs were temporarily stored at -20°C in the laboratory department of the hospital after being used for the RIDTs. Within a week, the samples were transported to the Institute of Tropical Medicine, Nagasaki University for storage in a deep freezer (-80°C).

For this study, I used the samples collected during the 2011/12 and 2012/2013 influenza seasons for molecular characterizing and genomic analysis. In this chapter, I describe the molecular characterization and genomic analysis methods in detail with a summary of the data output results. **Chapter 5 and Chapter 6** of the thesis utilize these output data, and the detailed analysis and results are discussed in each chapter.

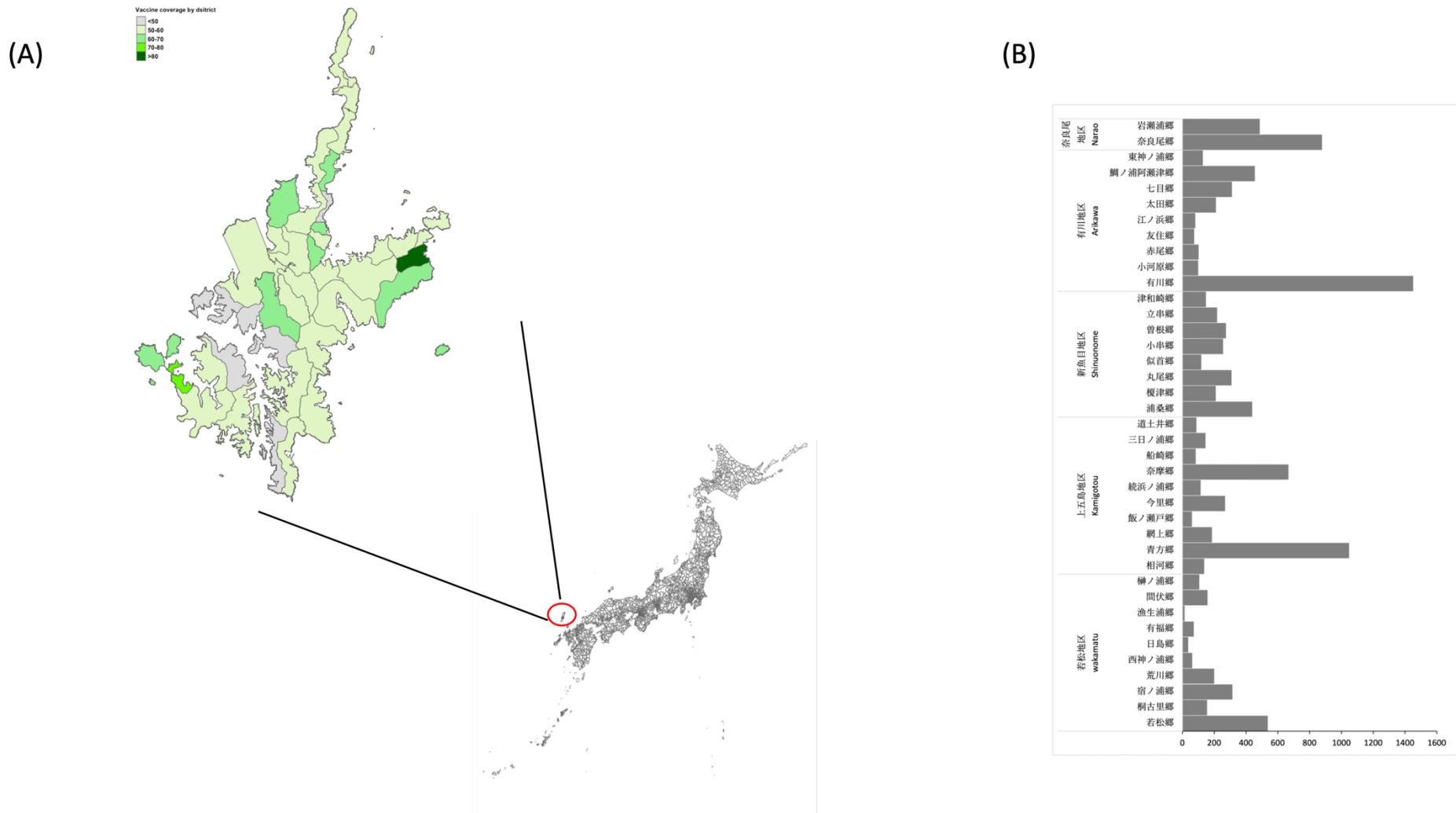


Figure 3.1: Map of Kamigoto island (study site) with vaccination coverage by district (A) and population distribution by districts (B)

Table 3.1: Demographic characteristics of population in Kamigoto Island (2007/2008 – 2017/2018 influenza season)

Characteristics	Year										
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Population	24,320	23,718	23,213	22,796	22,305	21,846	21,262	20,294	20,813	19,921	19,456
Sex*											
Male	11,402	11,094	10,865	10,677	10,431	10,212	9,947	9,554	9,746	9,409	9,189
Female	12,918	12,624	12,348	12,119	11,874	11,634	11,315	10,740	11,067	10,512	10,267
Age group, years											
<4	634	574	540	530	495	477	425	380	419	403	499
4-6	575	553	491	459	449	432	405	375	381	338	315
7-12	1,400	1,333	1,319	1,216	1,146	1,075	999	875	963	848	783
13-18	1,597	1,498	1,420	1,366	1,301	1,227	1,189	1,101	1,121	1,038	976
19- 64	12,488	12,135	11,841	11,754	1,1437	11,099	1,0691	9,917	10,317	9,591	9,242
65-74	3,651	3,534	3,443	3,213	3,170	3,166	3,181	3,278	3,243	3,282	3,390
≥ 75	3,975	4,091	4,159	4,258	4,307	4,370	4,372	4,368	4,369	4,421	4,344
Vaccine coverage (%)	59.1	58.4	56.0	58.0	56.3	56.4	58.6	58.6	62.1	60.0	61.1

*<https://official.shinkamigoto.net/jinko.php?pageno=3&details=of>

3.2 Molecular Diagnostic Methods

I used the NPS samples collected during the 2011/12 and 2012/2013 influenza seasons in this part. ILI cases presented to the Kamigoto Hospital, Nagasaki, Japan during the influenza season were tested with the RIDT as part of the routine influenza surveillance system. The residuals of NPS used for RIDT were kept in viral transport media (VTM) and stored at -80°C for long-term storage. These stored NPS samples used in this samples were collected as part of a vaccine effectiveness study conducted.^[17, 18]

RNA extraction and respiratory virus detection by RT-PCR

Frozen samples were thawed on an icetray, spun down at **1800 rpm for 1 min**, and were centrifuged briefly at 1500 x g. The liquid above the sediment was carefully moved to a sterile 1.5 ml tube. Viral nucleic acid was isolated utilizing a QIAamp Viral RNA Mini Kit (QIAGEN Inc., Valencia, CA) in accordance with the provided guidelines from the manufacturer. The detail of the procedure is written in appendix.

Infecting viral pathogens were identified using multiplex RT-PCR resulting in the identification of 13 main pathogens: influenza A/B, respiratory syncytial virus (RSV), human metapneumovirus (hMPV); human parainfluenza virus (hPIV) types 1–4; human rhinovirus (hRV), human coronavirus OC43/229E (hCoV); human adenovirus (hAdV) and human bocavirus (hBoV). In-house four multiplex PCR assays were used to detect 13 respiratory viruses (RVs) for each sample using the one-step RT-PCR kit from QIAGEN. The details of the assays are published elsewhere^[19] and can also be found in appendix Table 1-4. Briefly, each multiplex assay identifies the following viruses.

- Multiplex PCR-1: influenza A/B, respiratory syncytial virus (RSV), and human metapneumovirus (HMPV).
- Multiplex PCR-2: human parainfluenza virus (HPIV) types 1–4.

- Multiplex PCR-3: human rhinovirus (HRV) and human coronavirus OC43/229E (HCoV); and
- Multiplex PCR-4: human adenovirus (HAdV) and human bocavirus (HBoV)

Positive RT-PCR products from multiplex assays (checked by agarose gel electrophoresis, described below) were confirmed by performing a hemi-nested PCR assay (Appendix Table 5-9). Samples were defined as confirmed positive if both multiplex and hemi-nested PCRs showed positive results. The details step-by-step procedure of performing multiplex RT-PCR methodology is written in Appendix.

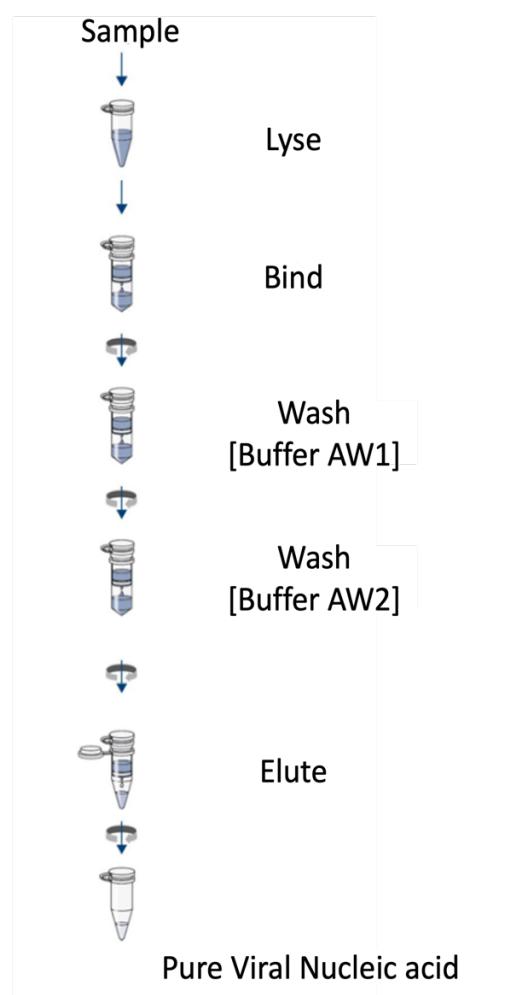


Figure 3.2: An illustration of QIAamp Viral RNA workflow (Mini Spin procedure)

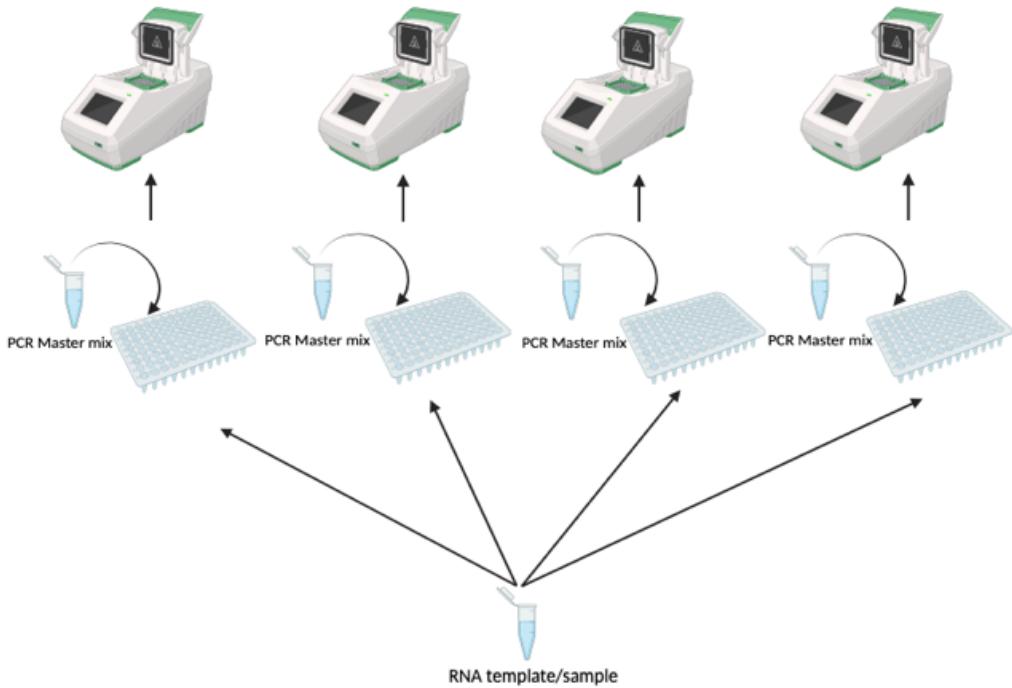


Figure 3.3 : An illustration of multiplex RT-PCR procedure

Agarose Gel Electrophoresis

PCR product presence, potentially indicating viral presence, was assessed through agarose gel electrophoresis. Gel preparation involved the creation of 2% agarose gels using 1x TAE buffer and an ethidium bromide concentration of 0.4 µg/ml. Following gel casting, the gels were submerged in 1x TAE buffer, and PCR samples were loaded with a 6:2 volume loading dye. To determine fragment sizes, a 1kbp ladder was included alongside the samples. Gel electrophoresis was conducted at 100V until satisfactory separation of fragments was achieved. Visualization and imaging were carried out using a UV transilluminator. An example of multiplex RT-PCR positive samples visualized using a UV transilluminator is illustrated in Figure 3.4.

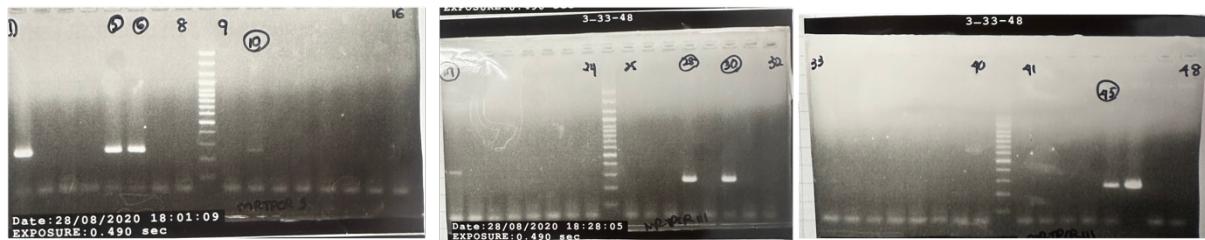


Figure 3.4: An example of the gel electrophoresis output following a multiplex RT-PCR reaction. The bands containing samples show a positive RT-PCR results, the middle lanes is the ladder for target amplicon size to compare.

RT-PCR amplification, purification, library preparation, and next-generation sequencing

All 8 segments of RT-PCR confirmed influenza samples are amplified following the protocols of Zhou, B., et al. (2009)^[20] and (2014)^[21] for influenza A. The primers used for the RT-PCR reactions were described in Appendix Table (10). The RT-PCR assay is shown in Appendix Table (11).

Each PCR product underwent an additional purification step using Ampure XP beads (Beckman Coulter) following the provided protocol from the manufacturer. Subsequently, the purity of the purified products was evaluated using an Agilent Technology 2100 Bioanalyzer equipped with a High Sensitivity DNA chip, alongside the Qubit dsDNA HS Assay Kit from Life Technology. 1 ng of the DNA is used for library preparation (Nextera XT Kit, Illumina) following the manufacturer's instructions (Illumina, CA, USA). After rigorous quality control, the prepared library was sequenced on the MiSeq platform (Illumina) using a V2 (2×250 bp) reagents kit. Detailed protocols of all the steps are described in Appendix.

The figure 3.5 captures the workflow of the whole genome sequencing procedure by next generation sequencing (NGS) technology.

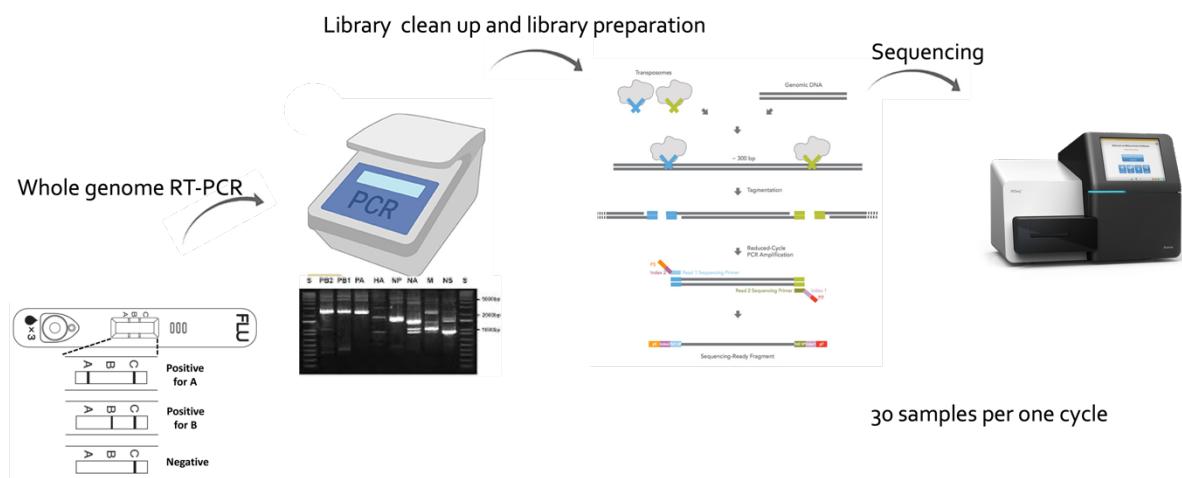


Figure 3.5: An illustration of Whole Genome Sequencing (WGS) procedure by next generation sequencing (NGS) technology

3.3 Bioinformatic Pipeline

A bioinformatic analysis of the raw sequence data is done step by step as described below (Figure 3.6).

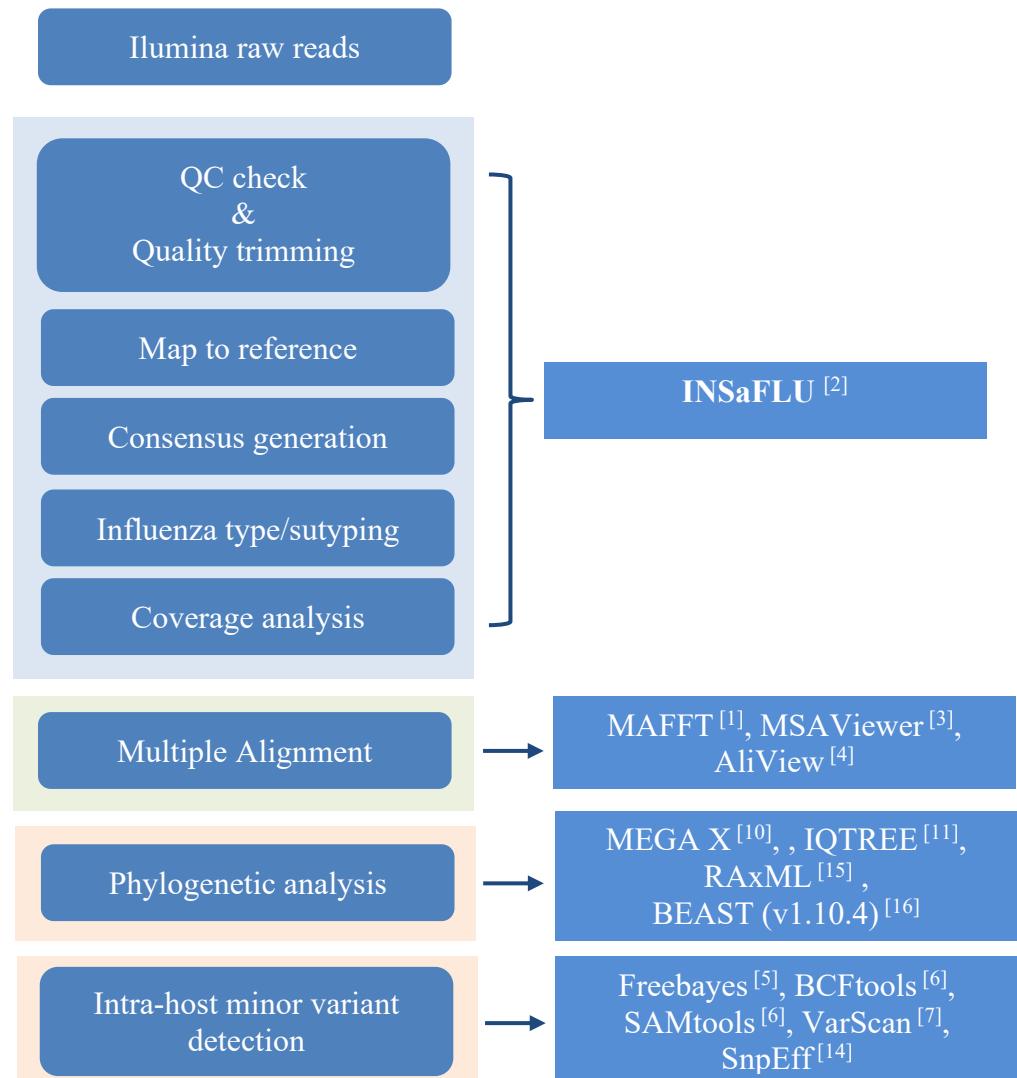


Figure 3.6: A schematic flow of the bioinformatic analysis of the sequencing data

INSAFLU bioinformatic pipeline

I uploaded the Paired-end reads (fastq.gz format) generated by the Illumina NGS platform to the INSAFLU^[2] web-bioinformatic pipeline. Once the raw reads are uploaded, I chose the reference sequences (A_H3N2_A_Perth_16_2009) out of all the available reference sequences provided on INSAFLU. The pipeline returns with quality trimmed sequences, subtype of the viruses, and then the consensus generation of the sequence. The pipeline also provides the coverage (depth and length) of the sequences. I repeated the same procedure using different reference sequences as sensitivity analysis.

Quality Trimming of Sequenced Reads

INSAFLU^[2] performed the read quality control using FastQC software^[22]. The quality was improved by Trimmomatic^[23], in which I selected the criteria: (1) discard the reads with length <30 bases, (2) trim both ends of the reads with base quality scores below 20, and (3) standardize the quality scores by converting them to Phred-33 scores. INSAFLU performed the above steps upon uploading the raw user sequences. The sequence data with an average quality score below Q30 were regarded as failed quality control and were not included in the downstream analyses. However, the QC report of each sequence, including both passed and failed quality control, was kept and is available online at https://insaflu.insa.pt/managing_files/samples/samples.

Type and subtype identification and coverage analysis

INSAFLU pipeline also performed the draft de novo assembly of qualified filtered reads using SPAdes^[24]. Type and subtype were also identified by the pipeline using the ABRicate tool^[25], and their in-house database is applied to query the draft assemblies against an in-house database (“influenza_typing”). If more than one type (HA or NA) was identified, the INSAFLU flagged the samples as “putative mixed infections. Incomplete type and subtype were also alerted.

Alignment of reads to a reference database and consensus generation.

As a next step, the quality processed reads were aligned against reference strain for A/H3N2 (A/Perth/16/2009). Subsequently, the consensus sequences were generated by following steps: rapid read mapping (Burrows-Wheeler Aligner—BWA^[26]), SNP and indel calling (samtools^[27] and freebayes^[28], and annotation was done by the SnpEff^[14]. All of these steps were automatically performed by the INSAFLU pipeline, which applied Snippy^[29] multi-software tools. I followed the default criteria setting for read mapping and SNP/INDEL annotation. In short, (i) mapping quality of ≥ 20 , (ii) at least ten (10) quality processed reads coverage per variant position, and (iii) at least 51% of quality processed reads per variant position that differs from the reference sequence.

Phylogenetic analysis

For the phylogenetic analysis, I downloaded all the available data of seasonal influenza A/(H3N2) global sequences collected between January 2011 and December 2013 from GISAID (accessed 1st December 2022).^[30] I removed the duplicate isolates and sequences with ambiguous bases before the alignment. Sequences are initially aligned with the MAFFT^[1] online version; alignments were viewed and edited with MSAViewer^[3] and AliView^[4]. Then I chose IQTREE (v2.0.7) to reconstruct maximum-likelihood trees.^[11] The software determines the best-fit model. I chose the non-parametric bootstrapping method, with 100 replicates. I also built maximum-likelihood trees using MEGA-X^[10] and RaXML^[15] to decide which software to use for the analysis in my PhD project.

To analyze the temporal signature required for time-scaled analysis, I performed a regression of genetic distances from the ML tree's root-to-tip against the collection dates of the samples. I used TempEst (v.1.5.3)^[31] for this purpose. I removed outliers that significantly

deviated from the average values as they likely contained excessive sequencing artifacts. I excluded these outliers from further analysis.

Next, I built a time-scaled phylogenetic analysis (for the HA segment and entire genome) using BEAST (v.10.1.4).^[32] Rather than using MODELTEST^[33] or any other software to identify the best-fit nucleotide substitution model, I selected a Hasegawa-Kishino-Yano (HKY) + G4 nucleotide substitution model, strict molecular clock with a Laplace distribution prior and a Coalescent: Exponential Growth tree model.^[34] I did the literature review on methods applied on many phylogenetic studies of influenza, and by choosing different substitution model to run my dataset, it finally occurs to me that the selected model was the best fit for my data. The Markov chain Monte Carlo was repeated at least twice, covering 50-100 million steps and sampling every 1,000 to 20,000 steps. 10% of the samples were discarded as burn-in. I used Tracer (v.1.7.1)^[35] to ensure that the posterior was sufficiently sampled (with an effective sample size (ESS) of >200). The tree was visualized and annotated in Figtree. (v.1.4.4).

Intra-host or within-host minor variant calling.

As a next step, I extracted the minor within-host or intra-host single nucleotide variants (iSNVs) (SNV with intra-sample frequency less 50%) for the analysis. INSaFLU pipelines identified and analyzed iSNVs using Freebayes^[5], BCFtools^[6], SAMtools^[6], VarScan^[7] and annotated by SnpEff^[14]. I regarded iSNV as true positive iSNV, if the sequences have these criteria: (i) average MapQ score on variant reads of more than 30, (ii) average phred score on variant positions >35, (iii) minimum 10 reads supporting an alternate allele within a single individual to evaluate the iSNVs frequency, (iv) requires a minimum of 100-fold depth of coverage to process a site for iSNVs analysis, and (v) variant frequency >2%. I discussed the detailed analysis of the minor variants calling in the relevant chapter (Chapter 6).

Previous studies [36, 37], estimated that around 66% of patients infected with H3N2 and 40% of those infected with H1N1/2009 were likely to have mixed-lineage infections. To identify samples with potential mixed infection, I followed the assumption in Poon et al. 2016 [36] and Carrat et al. 2008 [37] studies, which assumed the infected cases reached the peak viral titre at the time of onset (48 hours from infection), and it may be beyond 12-24 hours of peak, when the patients arrived the clinic/hospital. It is expected that average of 10-12 replications events (6-8 hours of replication cycles) have happened. The mean mutation rate of influenza A is assumed to be 1 mutation per replication per genome. Based on this, average of 10–12 variants across the genome in one sample are de novo mutations. Any number clearly above that (15 as cut-off in this study following the original authors) would be indicative of a mixed infection.

Reassortment analysis

I performed manual reassortment detection, by comparing the ML tree of HA segment with each other segment obtained by IQTREE. A topology reconciliation was sought between the eight influenza segment trees. When a topological inconsistency in sample positioning in one of the segment trees was present, indicative of belonging to another phylogenetic group, the posterior probability value of the ancestral nodes in the segment tree between the group of the sample defined by the whole-genome tree and the group in which the reassorted genome was present was checked. If this posterior probability value was ≥ 0.95 , the genome was retained as an intra-subtype reassortant. I tried to use Graph-incompatibility-based Reassortment Finder (GiRaF) software [38] or other computational software to identify the reassortment. However, I failed to learn this and did not include it in this PhD thesis.

Accession number

All the consensus sequences generated from this study were deposited in GISAID. The list of the submitted sequences with corresponding GISAID IDs is described in Appendix Table

12. The intra-host sequence data were submitted to the Sequence Read Archive under Bio Project accession number **PRJNA941384**.

3.4 Statistical Analysis

All statistical analyses, unless stated, were carried out using R software, version 4.1.2 (R Foundation for Statistical Computing). [39] A detailed of analysis for each sub-study/chapter is described in relevant chapters.

I performed all the web-laboratory procedures as well as bioinformatic analysis by myself, with the guidance and support from my advisors and supervisors.

3.5 Data outputs from web-laboratory and bioinformatic analysis of sequenced data

In this chapter, I showed the results of the multiplex RT-PCR and sequencing output data, which become the raw data for Chapter 5 and Chapter 6 of the thesis.

Multiplex RT-PCR results

A total of 2,410 NPS were collected during 2012/2013 season. Only 2,313 samples were available for the multiplex PCR procedure. Of these, 1,425 samples were negative for any respiratory viruses. 546 samples were positive for IAV, 30 were positive for IBV and 399 were positive for other respiratory viral pathogens. Co-detections were found in 100 samples (95 samples with two viruses and 5 samples with three viruses). (Figure 3.7)

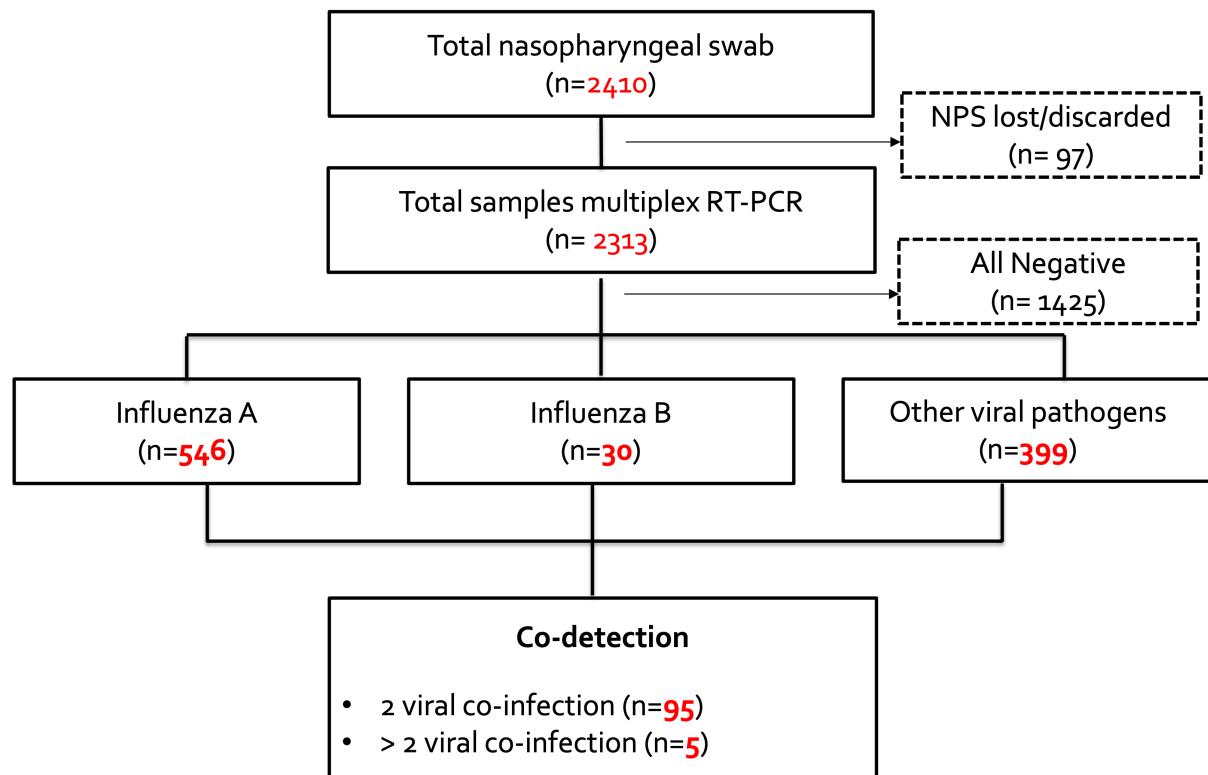


Figure 3.7: Diagram of the samples processing for multiplex RT-PCR

Comparison of influenza RT-PCR with Rapid Influenza Diagnostic test (RIDT)

Out of 2,313 samples available for RT-PCR, IAV was detected in 546 samples and IBV in 30 samples. These samples were tested with RIDT where 573 were positive for IAV and 31 were positive for IBV. Only 2 samples were positive for both IAV and IBV. We evaluated the sensitivity and specificity of RIDT (Tables 3.2 and 3.3). Here, the assumption was that RT-PCR is the gold standard diagnostic test, with perfect accuracy for influenza detection. The analysis was done on the online data tool.

<https://www2.ccrb.cuhk.edu.hk/stat/confidence%20interval/Diagnostic%20Statistic.htm>.

Table 3.2: Diagnostic Test Evaluation of influenza A – sensitivity and specificity

Influenza A	RT-PCR		Total
	Positive	Negative	
RIDT Positive	472	101	573
RIDT Negative	74	1666	1740
	546	1767	2313

Table 3.3: Diagnostic Test Evaluation of influenza B – sensitivity and specificity

Influenza B	RT-PCR		Total
	Positive	Negative	
RIDT Positive	22	9	31
RIDT Negative	8	2274	2282
	30	2283	2313

The sensitivity and specificity were [86.5% (85.5 - 87.4) IAV, 73.3% (67.9 – 78.8) IBV] and [94.3% (93.9 – 94.7) IAV, 99.6% (99.5 – 99.7) IBV] respectively (Table 3.4). The results were consistent with the reported overall sensitivity of the ESPLINE® test in their evaluation study [40] and other RIDT evaluation studies [41, 42].

Table 3.4: Evaluation results of IAV and IB RIDT in comparison with RT-PCR.

	IAV	IBV
True Positive	472	22
False Positive	101	9
True Negative	1666	2274
False Negative	74	8
% sensitivity (95% CI)	86.5% (85.5 - 87.4)	73.3% (67.9 – 78.8)
% specificity (95% CI)	94.3% (93.9 – 94.7)	99.6% (99.5 – 99.7)
Positive Predictive Value (95% CI)	82.4% (81.3 -83.4)	70.9% (65.5 – 76.5)
Negative Predictive Value (95% CI)	95.7% (95.4 – 96.1)	99.6% (99.5 – 99.7)
Likelihood ratio positive (95% CI)	15.12 (14.16 – 16.16)	186.02 (146.86 -235.62)
Likelihood ratio negative (95% CI)	0.14 (0.13 – 0.15)	0.26 (0.21 – 0.32)

Next-generation sequencing of influenza A(H3N2) directly from clinical specimens

Of the 250 samples (72 from 2011/12 and 178 from 2012/13) sequenced, 229 were identified as A(H3N2). The remaining samples can be influenza However, I did not focus on the IBV in my thesis and thus I didn't do the influenza B sequencing. Of the 229 sequences identified as a/H3N2, complete genome coverage was achieved for 171 samples, genome coverage of >90% was generated for 197 viruses. The mean depth of coverage per segment is shown in Figure 3.8.

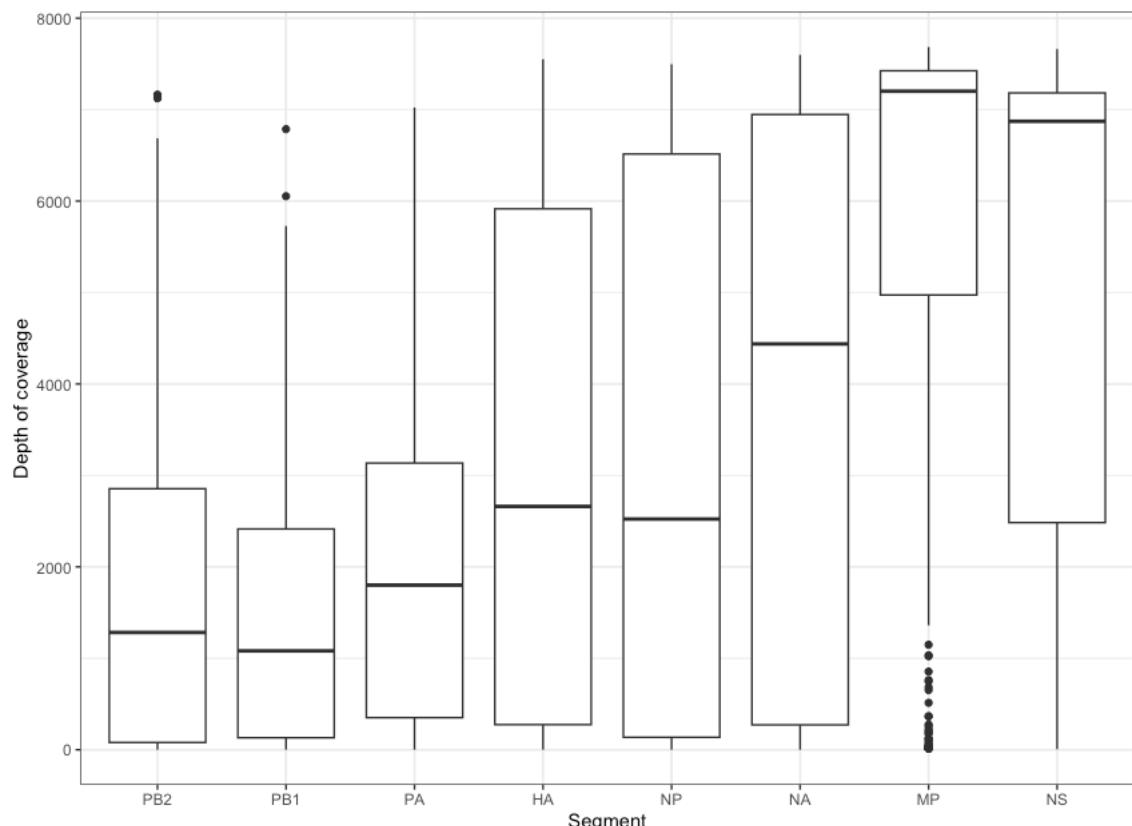
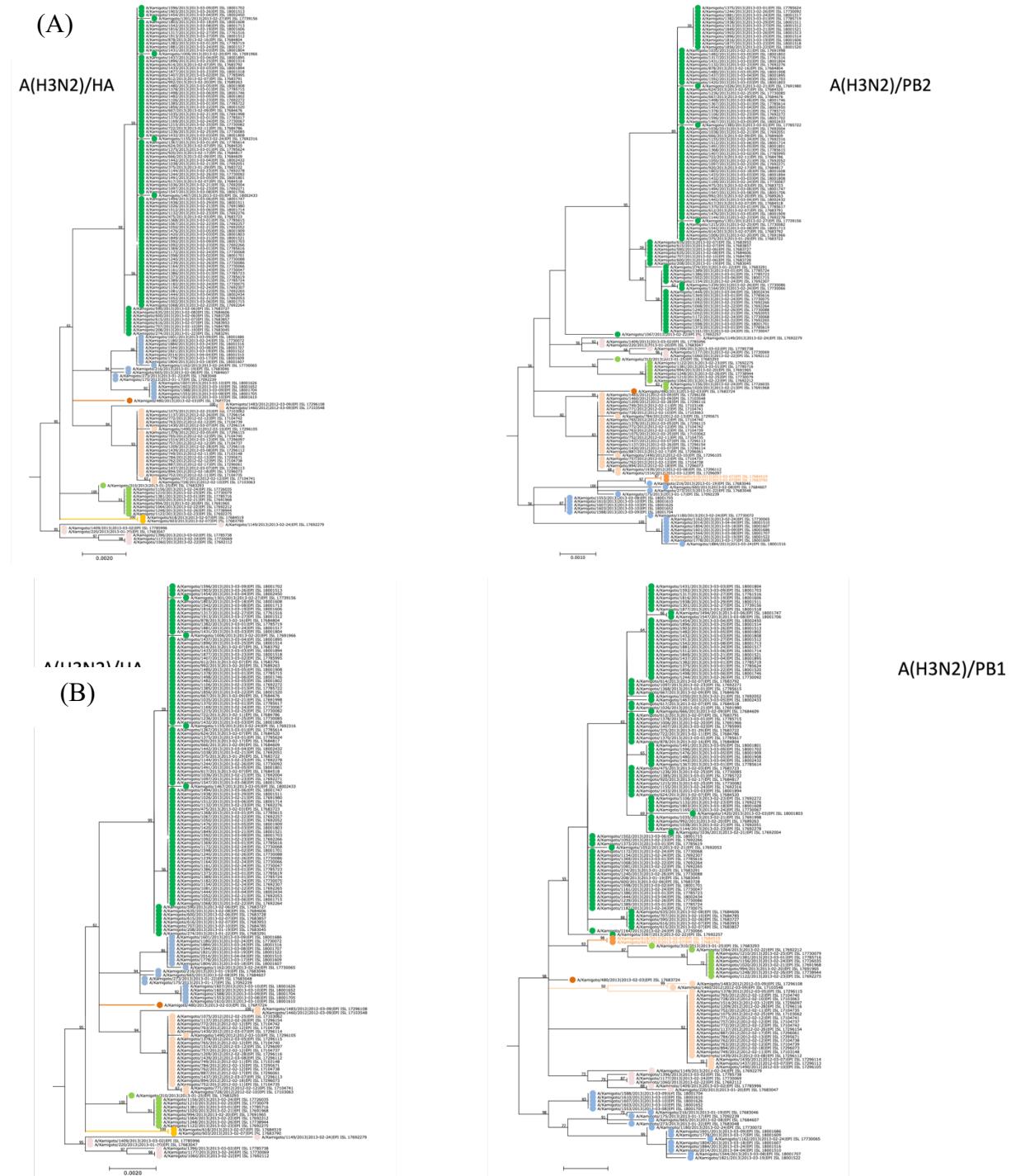


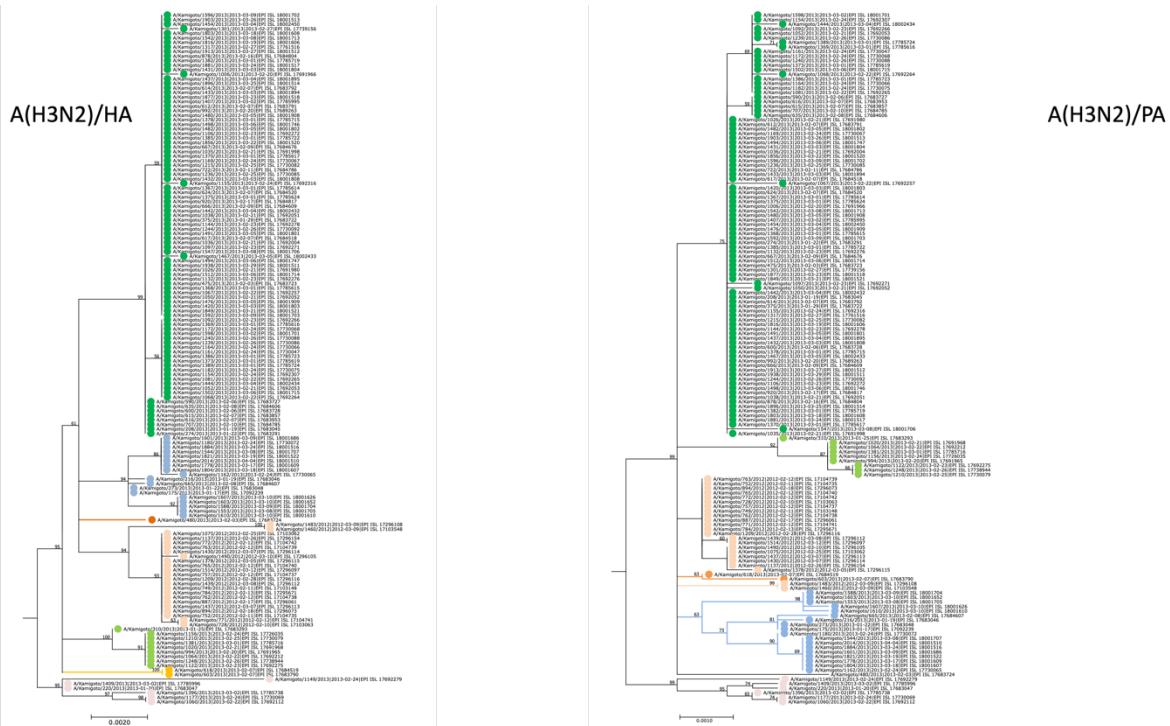
Figure 3.8: Mean depth of sequence coverage by segment

Analysis of whole-genome sequence data and identification of reassortments

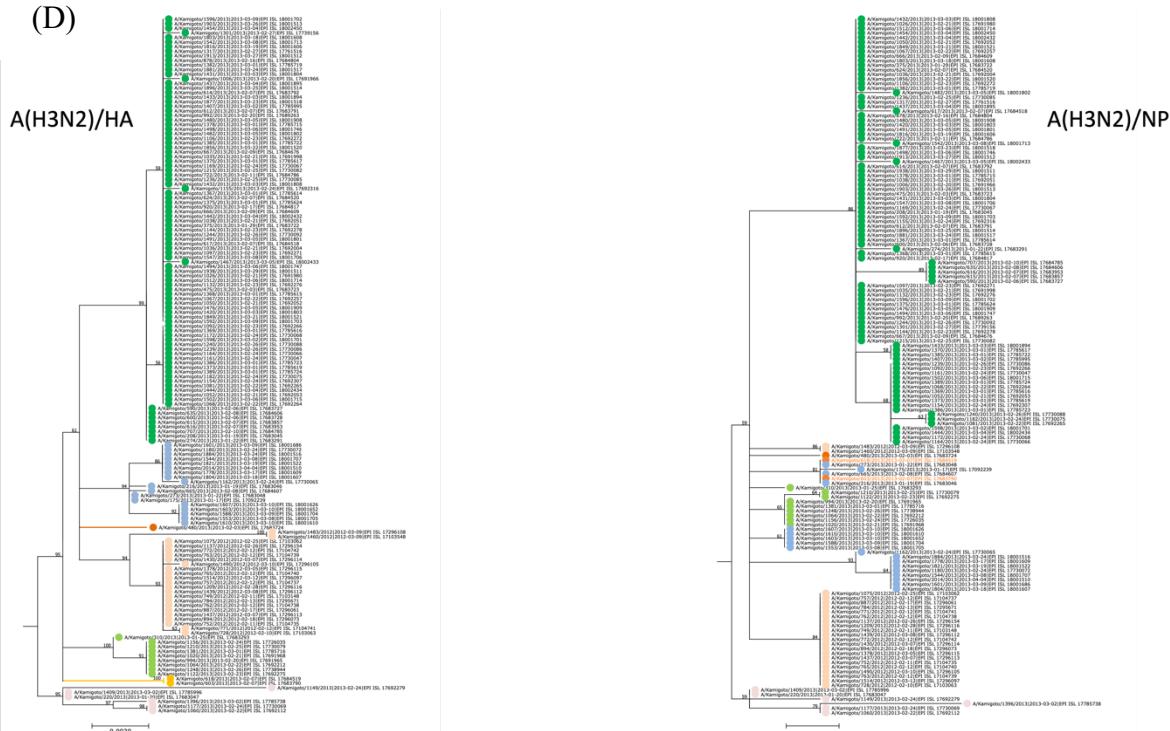
I didn't identify any intersegment reassortment (Figure 3.9). The reassortment identification is done manually by comparing HA segment with other individual segment for all the segments. However, I didn't use any computational software for confirming the results.



(C)

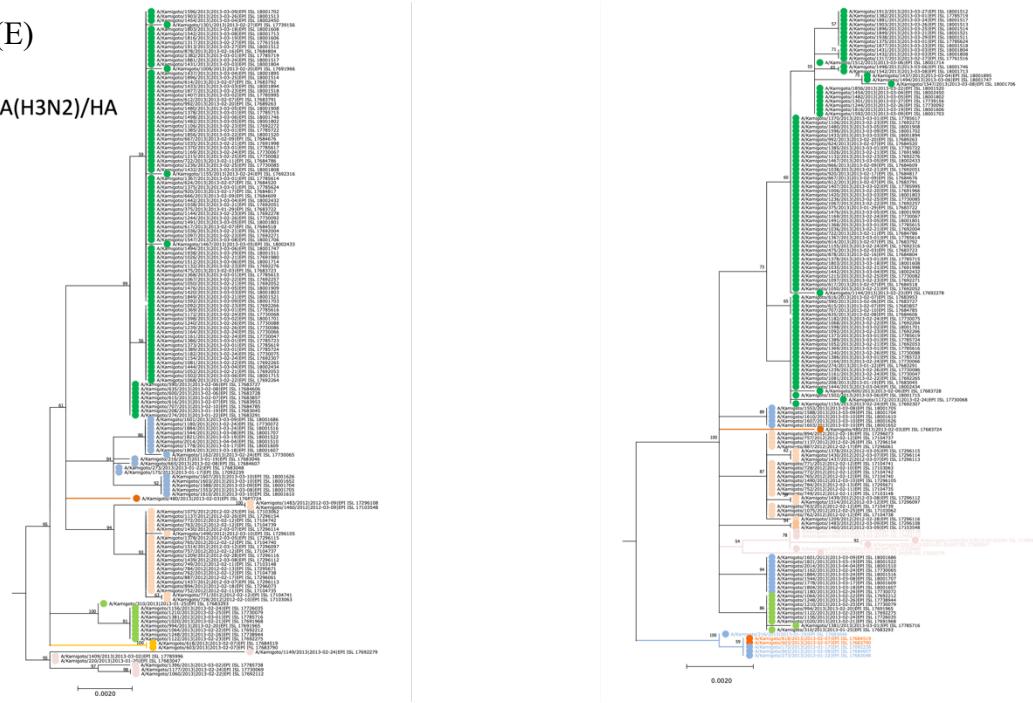


(D)

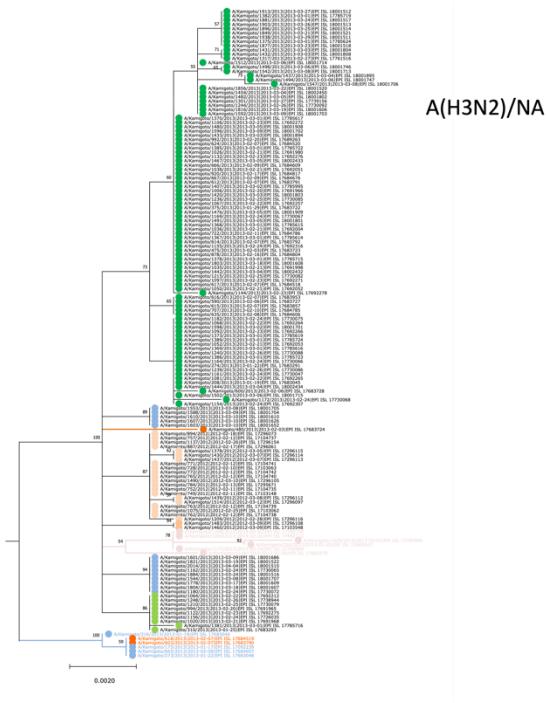


(E)

A(H3N2)/HA

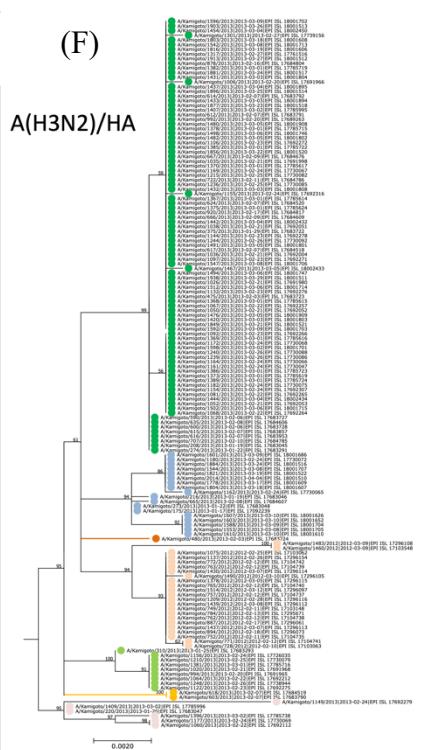


A(H3N2)/NA

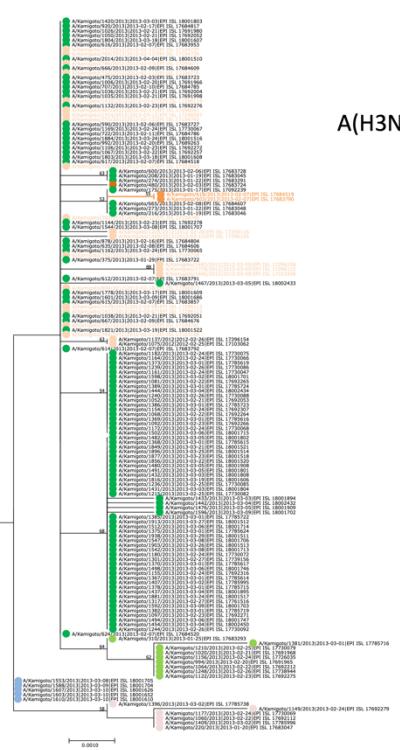


(F)

A(H3N2)/HA



A(H3N2)/MP



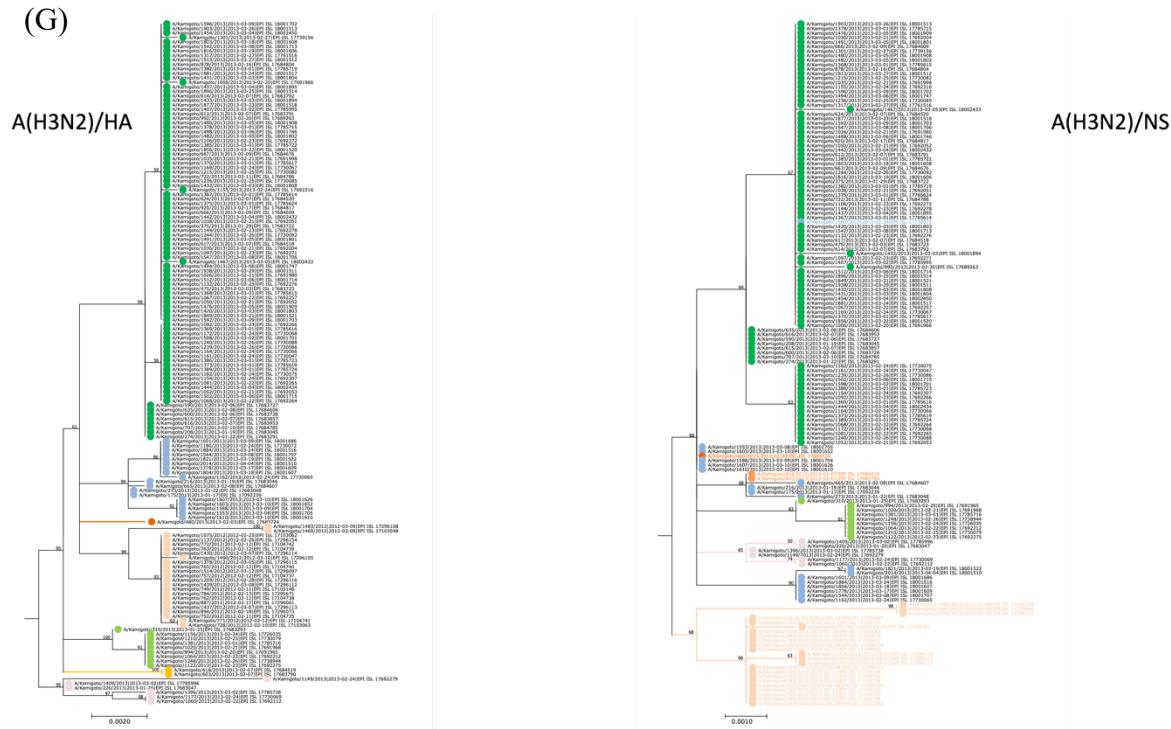


FIGURE 3.9. The maximum likelihood phylogenetic of individual segment (A-G): HA segment with PB2, PB1, PA, NP, NA, MP and NS. (Each group is defined by color)

Phylogeny of Whole genome sequences (WGS) of Kamigoto strains

I performed the maximum likelihood phylogenetic tree of WGS. To do so, I first concatenated each individual segment in order of PB2, PB1, PA, HA, NP, NA, MP and NS. I searched online database (GISAID and flu research database) for available A/H3N2 from Japan. Six viral sequences were available for all segments in Japan. I concatenated them in the same order as above. Then the concatenated WGS of these six virus sequences were included in the ML phylogeny. Additionally, I included the three vaccine strains that were mostly selected in Japan. The Kamigoto sequences grouped closely together based on the year they were collected. Moreover, Kamigoto strains were found to be part of the same clade as the vaccine strain selected during these seasons indicating that there was no vaccine mismatch during these two years period. (Figure 3.10)

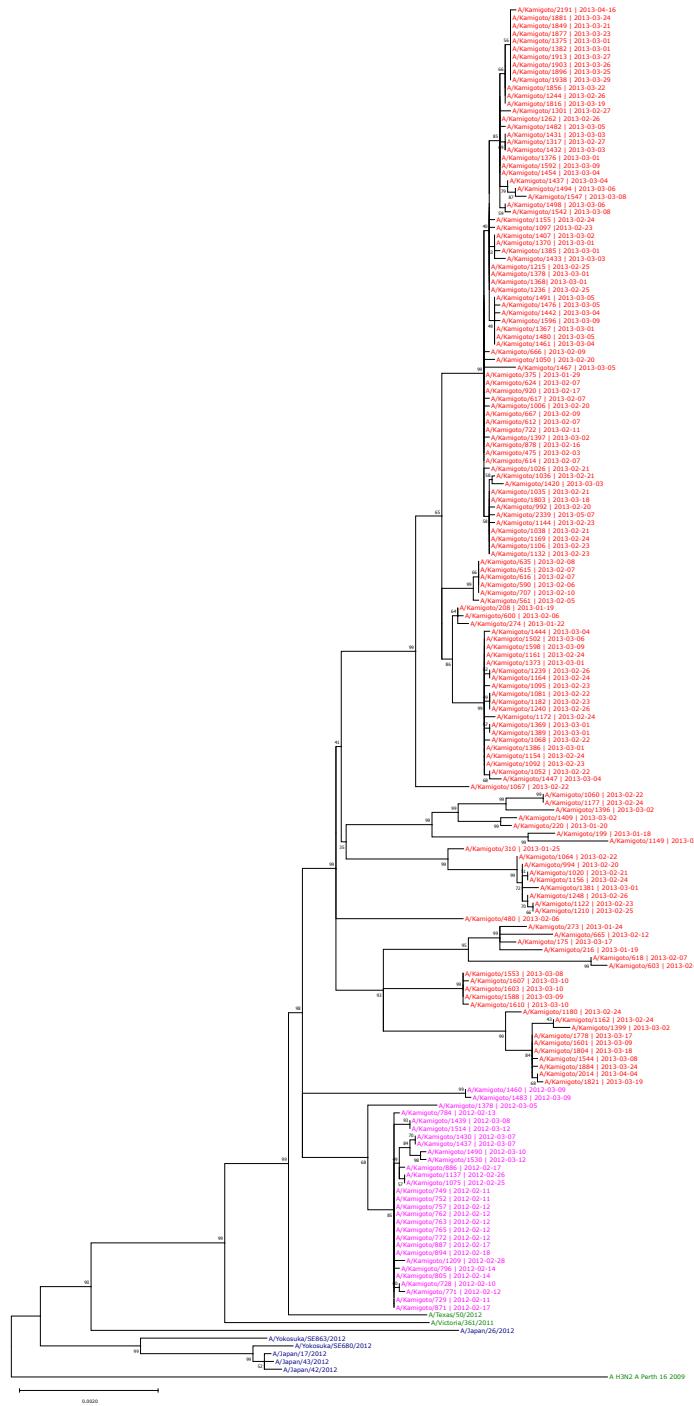


FIGURE 3.10. The maximum likelihood phylogenetic tree includes 168 WGS collected during the 2011/12 (red) and 2012/13 (purple) influenza seasons alongside the WGS in Japan, that were available in the GISAID (blue), and the vaccine strains (green). For each sequence the date of the sample collection is mentioned (yyyy-mm-dd). WGS for 2012/2013 in Japan were not available during the study period.

Table 3.5: Variant counts (>2% and <50% frequency for each segment,) (50-90% frequency for whole genome length) and evidence of mixed infections.

SAMPLE	iSNVs (>2% to < 50%) frequency									iSNV 50-90%	Potential mixed infection?
	PB2	PB1	PA	HA	NP	NA	NS	MP	TOTAL		
175	0	0	0	0	0	0	0	2	2	0	
199	0	0	0	0	0	6	0	0	6	2	
208	0	0	0	0	0	0	0	0	0	0	
216	0	0	0	1	1	0	0	0	2	0	
220	2	2	1	0	0	1	0	1	7	1	
273	0	0	1	2	1	1	1	1	7	0	
274	1	0	1	1	1	0	0	0	4	1	
310	2	1	0	1	0	1	0	1	6	0	
375	3	0	1	1	3	1	1	1	11	0	
475	0	0	0	0	0	0	0	0	0	0	
561	1	0	4	0	1	0	0	0	6	4	
590	2	0	0	0	0	0	0	0	2	0	
600	3	1	1	3	5	2	0	2	17	1	X
603	1	1	1	0	0	0	0	0	3	0	
612	2	2	1	2	1	2	1	1	12	0	
614	4	2	4	1	2	1	0	1	15	2	X
615	3	1	0	3	1	0	0	0	8	1	
616	4	3	5	0	0	0	0	0	12	0	
617	2	0	1	0	0	1	0	0	4	1	
618	0	0	0	4	0	1	0	1	6	1	
635	0	0	0	0	0	0	1	1	2	0	
665	0	0	1	0	0	0	1	0	2	0	
666	1	2	1	1	0	1	0	0	6	0	
667	0	0	0	0	0	0	0	0	0	0	
707	0	0	1	1	1	0	0	0	3	1	
722	2	0	3	3	1	1	1	2	13	0	
878	4	1	1	1	2	0	0	0	9	0	
920	1	0	0	1	0	0	0	0	2	0	
992	0	0	1	0	0	0	0	0	1	0	
994	2	1	2	1	0	0	0	0	6	0	
1006	0	0	0	0	1	0	0	0	1	0	
1020	2	0	2	0	0	0	0	0	4	2	
1026	1	0	3	1	1	0	0	0	6	0	

1035	0	0	0	0	0	0	0	0	0	0	
1036	4	4	0	0	2	0	0	0	10	0	
1038	0	0	0	0	0	0	0	0	0	0	
1050	0	1	0	0	1	0	0	1	3	1	
1052	3	0	1	2	3	2	1	1	13	1	
1060	0	0	0	0	0	0	1	0	1	0	
1064	0	1	1	0	0	0	0	0	2	0	
1067	0	0	0	0	0	0	2	2	4	12	X
1068	0	3	2	1	0	1	1	1	9	0	
1081	2	0	0	0	0	0	0	0	2	0	
1092	2	1	2	2	4	1	0	1	13	1	
1095	1	3	0	0	1	1	1	1	8	1	
1097	2	2	0	2	2	2	1	1	12	0	
1106	0	0	0	1	2	0	1	1	5	2	
1122	2	2	0	0	0	0	0	0	4	0	
1132	1	0	0	0	0	0	0	1	2	1	
1144	0	0	0	0	0	0	0	0	0	3	
1149	0	1	0	0	0	0	0	0	1	0	
1154	1	0	0	0	1	0	1	0	3	1	
1155	0	2	1	0	1	0	0	0	4	1	
1156	0	1	1	0	0	1	0	0	3	0	
1161	1	0	0	1	0	2	1	0	5	1	
1162	1	1	0	0	0	0	0	0	2	0	
1164	0	0	1	1	0	1	0	0	3	1	
1169	2	1	1	0	0	0	0	0	4	1	
1172	2	0	0	0	0	1	0	0	3	0	
1177	0	1	1	0	0	0	0	0	2	0	
1180	0	0	1	0	0	0	0	2	3	17	X
1182	3	1	3	5	1	1	0	1	15	0	
1210	3	1	3	5	1	1	0	1	15	1	X
1215	0	0	0	0	1	1	0	2	4	0	
1236	1	0	1	1	0	1	0	0	4	1	
1239	0	0	1	1	0	1	0	0	3	1	
1240	0	0	0	0	0	0	0	1	1	0	
1244	1	2	0	1	0	0	0	0	4	0	
1248	0	0	0	1	0	0	1	1	3	0	
1262	0	1	2	2	1	1	1	1	9	1	
1317	0	0	0	1	0	0	0	0	1	3	
1356	0	0	1	0	0	0	0	0	1	0	

1367	0	0	0	0	0	0	1	0	1	0	
1368	0	0	1	1	0	0	0	0	2	0	
1369	0	0	0	0	1	0	1	0	2	0	
1370	1	1	0	0	0	0	0	0	2	1	
1373	0	0	1	0	1	1	0	0	3	1	
1375	0	3	3	1	1	1	0	0	9	1	
1376	2	3	1	0	1	0	0	0	7	0	
1378	1	0	1	0	0	0	0	0	2	1	
1381	1	1	1	0	1	0	0	0	4	4	
1382	1	2	4	0	1	1	0	0	9	1	
1385	1	0	0	0	1	0	0	0	2	1	
1386	0	1	2	0	1	1	1	0	6	0	
1389	1	1	1	0	0	0	0	0	3	0	
1396	0	1	0	0	1	0	0	0	2	0	
1397	4	1	5	0	1	1	0	0	12	3	
1399	0	0	0	0	0	0	0	2	2	3	
1407	0	0	0	0	0	0	1	0	1	2	
1409	2	0	0	1	0	0	0	0	3	0	
1431	0	0	0	0	0	1	0	0	1	2	
1432	1	0	1	0	0	0	0	1	3	0	
1433	0	0	0	0	0	0	2	1	3	3	
1442	0	1	1	0	0	0	1	1	4	0	
1444	0	0	0	1	0	0	0	0	1	0	
1454	0	0	1	0	0	0	0	0	1	0	
1461	0	0	0	1	0	2	0	0	3	0	
1467	0	0	0	0	0	1	0	0	1	0	
1482	2	1	0	0	0	0	0	0	3	0	
1494	0	0	2	0	0	0	0	0	2	0	
1498	0	0	0	0	0	0	0	1	1	0	
1502	1	0	0	0	0	0	0	0	1	0	
1512	0	0	0	0	0	2	0	0	2	0	
1542	1	0	0	2	1	1	0	1	6	0	
1544	0	0	2	3	3	1	1	2	12	2	
1547	2	0	2	0	0	0	0	0	4	1	
1553	0	0	1	0	1	0	0	0	2	0	
1592	0	0	0	2	0	0	0	0	2	0	
1596	0	0	1	0	0	0	0	0	1	4	
1598	0	2	1	0	0	0	0	0	3	0	
1601	2	0	0	0	1	0	0	0	3	0	

1603	0	0	1	1	0	1	0	0	3	0	
1610	1	0	1	0	1	0	0	0	3	0	
1778	0	1	1	0	0	0	0	0	2	0	
1803	0	0	0	0	0	0	0	0	0	0	
1804	1	0	1	1	3	1	1	1	9	1	
1816	1	0	0	0	0	0	0	0	1	0	
1821	1	1	1	1	0	1	2	1	8	0	
1849	0	1	0	0	2	1	0	1	5	0	
1856	1	0	0	3	1	1	1	1	8	0	
1876	0	0	0	2	3	1	0	1	7	0	
1877	0	1	0	0	0	0	0	1	2	0	
1881	0	1	0	0	2	1	0	1	5	0	
1884	0	1	0	0	0	1	0	1	3	1	
1896	0	0	0	1	0	0	0	0	1	2	
1903	1	3	1	0	0	0	0	0	5	0	
1913	2	0	3	6	0	0	0	2	13	0	
1938	2	1	2	0	0	0	0	1	6	0	
2014	0	0	0	0	0	0	1	0	1	3	
2146	1	0	3	0	0	0	0	0	4	2	
2191	1	1	0	0	0	0	0	0	2	4	
2339	0	0	1	0	0	1	0	0	2	1	

5/132= 3.8%

Note: Samples with a sum of the number of iSNVs at frequency 1-50% (minor iSNVs) and 50-90% counts above 15 suggests a 'putative mixed infection'.

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Chapter 4: Transmission dynamics of seasonal influenza in a remote island population

4.1 Research Paper cover sheet

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SECTION A – Student Details

Student ID Number	1901561	Title	Dr
First Name(s)	Su Myat		
Surname/Family Name	Han		
Thesis Title	Unravelling transmission dynamics of influenza and its interaction with other respiratory viral pathogens in the population of Kamigoto island, Japan		
Primary Supervisor	Professor Koya Ariyoshi		

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?	Scientific reports		
When was the work published?	03 April 2023		
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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Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	

Stage of publication	Choose an item.
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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 candidate conceived the study, designed the study model, performed the analysis and wrote the original draft of the manuscript
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SECTION E

Student Signature	Su Myat Han
Date	30 September 2023

Supervisor Signature	Koya Ariyoshi
Date	30 September 2023

4.2 Summary of the Chapter

This chapter was published as a research article in *Scientific reports* in volume 13, 03 April 2023.^[1]

In this study, I used the influenza surveillance data collected over multiple years in Kamigoto, an island in Japan. The surveillance data not only includes influenza-like illness (ILI) case information such as (date of onset, signs, and symptoms) but also all results of the rapid influenza diagnostic test (RIDT) results. In addition, the vaccination status, the residential information at the post-code level, and the history of travel outside the island before the infection were collected. It is very fortunate to have such fine-scale longitudinal data which enables me to analyse how influenza spreads in the local setting in a fine resolution. Such availability of data minimizes the requirement of complex mathematical models or different assumptions to estimate the transmission dynamics. By applying the recently developed spatial transmission model, “O2geosocial package”, an R package. I examined the detailed temporospatial transmission dynamics of influenza in the island setting.

I developed the study design, chose the mathematical model, and performed the analysis. I also wrote the paper and made the figures. Throughout the process, I received input/suggestions/edits from both my supervisors and advisors, particularly model developer Alexis Robert. The published version of the paper is attached in the 4.3 manuscript section, the supplementary tables and figures are in section 4.4.

4.3 Manuscript

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Transmission dynamics of seasonal influenza in a remote island population

Su Myat Han^{1,2}✉, Alexis Robert^{2,3}, Shingo Masuda^{1,4}, Takahiro Yasaka⁴, Satoshi Kanda⁴, Kazuhiri Komori⁴, Nobuo Saito^{5,6}, Motoi Suzuki^{1,7}, Akira Endo^{1,2,3}, Marc Baguelin^{2,8} & Koya Ariyoshi^{1,6}

Seasonal influenza outbreaks remain an important public health concern, causing large numbers of hospitalizations and deaths among high-risk groups. Understanding the dynamics of individual transmission is crucial to design effective control measures and ultimately reduce the burden caused by influenza outbreaks. In this study, we analyzed surveillance data from Kamigoto Island, Japan, a semi-isolated island population, to identify the drivers of influenza transmission during outbreaks. We used rapid influenza diagnostic test (RDT)-confirmed surveillance data from Kamigoto island, Japan and estimated age-specific influenza relative illness ratios (RIRs) over eight epidemic seasons (2010/11 to 2017/18). We reconstructed the probabilistic transmission trees (i.e., a network of who-infected-whom) using Bayesian inference with Markov-chain Monte Carlo method and then performed a negative binomial regression on the inferred transmission trees to identify the factors associated with onwards transmission risk. Pre-school and school-aged children were most at risk of getting infected with influenza, with RIRs values consistently above one. The maximal RIR values were 5.99 (95% CI 5.23, 6.78) in the 7–12 aged-group and 5.68 (95%CI 4.59, 6.99) in the 4–6 aged-group in 2011/12. The transmission tree reconstruction suggested that the number of imported cases were consistently higher in the most populated and busy districts (Tainoura-go and Arikawa-go) ranged from 10–20 to 30–36 imported cases per season. The number of secondary cases generated by each case were also higher in these districts, which had the highest individual reproduction number (R_{eff} : 1.2–1.7) across the seasons. Across all inferred transmission trees, the regression analysis showed that cases reported in districts with lower local vaccination coverage (incidence rate ratio IRR = 1.45 (95% CI 1.02, 2.05)) or higher number of inhabitants (IRR = 2.00 (95% CI 1.89, 2.12)) caused more secondary transmissions. Being younger than 18 years old (IRR = 1.38 (95%CI 1.21, 1.57) among 4–6 years old and 1.45 (95% CI 1.33, 1.59) 7–12 years old) and infection with influenza type A (type B IRR = 0.83 (95% CI 0.77, 0.90)) were also associated with higher numbers of onwards transmissions. However, conditional on being infected, we did not find any association between individual vaccination status and onwards transmissibility. Our study showed the importance of focusing public health efforts on achieving high vaccine coverage throughout the island, especially in more populated districts. The strong association between local vaccine coverage (including neighboring regions), and the risk of transmission indicate the importance of achieving homogeneously high vaccine coverage. The individual vaccine status may not prevent onwards transmission, though it may reduce the severity of infection.

Seasonal influenza remains a major public health threat globally with a substantial economic and health care burden each year¹. It is estimated that about 3–5 million people suffer severe illness due to seasonal influenza, and influenza-associated infections are estimated to cause between 290,000 and 650,000 deaths every year (WHO)².

¹School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan. ²Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK. ³Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, Keppel Street, London, UK. ⁴Department of Internal Medicine, Kamigoto Hospital, Kamigoto, Japan. ⁵Department of Microbiology, Faculty of Medicine, Oita University, Yufu, Japan. ⁶Department of Clinical Medicine, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan. ⁷Infectious Disease Surveillance Center, National Institute of Infectious Diseases, Tokyo, Japan. ⁸MRC Centre for Global Infectious Disease Analysis and the Abdul Latif Jameel Institute for Disease, London, UK. ✉email: pearl.june@gmail.com

It is therefore a key to understand the drivers of influenza transmission and identify the interventions able to reduce the burden of influenza.

Empirical and modeling studies have revealed a number of key characteristics of the spatial transmission of seasonal influenza over multiple seasons^{3–13}. The dynamics of human mobility patterns played a key role resulting in hierarchical transmission of influenza with short commuting responsible for wave-like transmission on a small geographical scale, while air travels was responsible for long-range seedings behaviors^{5,8,12}. Seasonality, dominating influenza strain in each epidemic, humidity and temperature are also reported to affect the spatial dynamics of influenza^{10,14–16}. These studies were conducted at a global, regional, or country level, with very limited representation to the transmission dynamics at smaller geographical levels, such as islands or cities. Analysis conducted at a smaller geographical granularity in areas with limited incoming transportation links may capture unique patterns of disease transmission that would not be visible in aggregated data at a larger scale.

We studied patterns of influenza transmission using the unique fine scale linelist dataset collected in Kamigoto island, Japan. Kamigoto island is located on the western coast of Nagasaki prefecture in Japan, semi-isolated from mainland Japan due to limited transportation links. The setting is therefore ideal for understanding the driving force behind local transmission without being severely affected by interferences from other regions or long-distance mobility. We first calculated the relative illness ratios and attack rates between age groups to identify groups at greatest risk of infection. Secondly, we explored what factors were associated with the risk of onwards transmission. To do so, we inferred the network of who-infected-whom (i.e., probabilistic transmission trees) using a Bayesian approach, which resulted in a set of probabilistic transmission trees that we used to estimate the likely number of secondary cases caused by each case in our dataset. We then performed a negative binomial regression analysis on each inferred transmission network to identify factors associated with increased risk of onwards transmission.

Methods

Study setting. This study is a retrospective observational study over eight influenza seasons (2010/11 to 2017/18 seasons) in Kamigoto island. Kamigoto island is located on the western coast of Nagasaki prefecture, Japan. Kamigoto island has 39 districts, with approximately 22,000 residents in total. Population sizes of the districts range from 40 to over 3000 inhabitants. The island is semi-isolated due to its limited transportation links to mainland Japan. There is only one hospital within the island, which most of influenza-like illness (ILI) cases attended for the diagnosis of influenza during the study period. Aside from the hospital, there are six clinics on the island. Influenza-like cases and rapid diagnostic test (RDT)-confirmed influenza cases within the island were monitored by the ILI registry system as influenza surveillance. In Japan, influenza vaccination is recommended annually between late October to December. Routine vaccination is recommended to people aged 65 and above, and for high-risk population aged 60 and above. For children, influenza vaccination is not under compulsory vaccination according to the national immunization schedule of Japan.

Data source. The study dataset is based on surveillance data and contains information on all patients who visited Kamigoto Hospital with RDT-confirmed influenza between October 2010 and April 2018 (8497 patients in total). In Japan, ILI and influenza had been under systematic surveillance following the new infectious disease control law effective since April 1999¹⁷. An ILI case is defined as the sudden onset of fever over 38 °C, respiratory symptoms, and other systemic symptoms (fatigue, headache, or myalgia)¹⁸. All individuals with ILI symptoms visiting the hospital during influenza season were tested with a commercial RDT to diagnose influenza A- and B-positive cases as a routine practice. RDTs are widely used in Japan and can serve as a proxy of the total symptomatic influenza case in the population¹⁸. Sensitivity of RDTs in Japan is estimated to be relatively high: 72.9–96.4% across all the studies conducted in Japan^{19,20}. Previous studies suggested that the reporting ratio of ILI and influenza cases were higher in Japan compared to other countries due to the wide use of RDTs²¹. In our dataset, 107 cases were not RDT positive but clinically diagnosed influenza, and only one case was coinfecting (A + B). Cases with the history of travelling into/outside the island within 7 days prior to the onset were identified as import cases in the surveillance system. A total of 959 cases (11.2% of all the RDT-confirmed influenza cases) were recorded as epidemiologically identified imported cases.

The surveillance dataset contains the age, sex, date of onset, date and result of RDT test of each case. In addition, the local health authorities and government collected data on influenza vaccination statuses, distribution of the age group of residents, influenza vaccination coverage by district and by age group in each season via the vaccination record system for the entire population on the island. Individuals were classified as ‘vaccinated’ if they were 14 days past vaccine administration. Postcode of residence was collected for influenza positive cases²². In the dataset, 134 cases (1.6% of total cases) had no post-code information recorded and thus were excluded in the reconstruction of transmission analysis. Demographic characteristics of the cases are presented in Fig. 1.

Relative illness ratio (RIR). To identify the burden of age groups most infected by influenza, first we calculated the relative illness ratio (RIR). RIR is defined as the ratio of the percentage of influenza cases in age group i (seven age groups in this study: below 3 years old; 4–6; 7–12; 13–18; 19–64; 65–74; above 75 years old), to the percentage of the total population belonging to that i th age-group. The formula as follows.

$$RIR_i = \frac{C_i / \sum_{j=1}^n C_j}{N_i / \sum_{j=1}^n N_j}$$

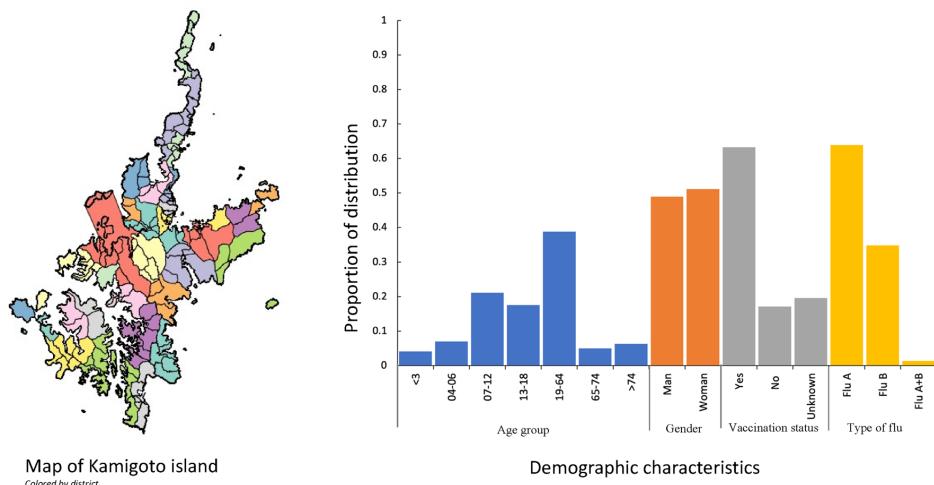


Figure 1. Map of Kamigoto island (each color represents a district), and demographic characteristics of the surveillance dataset of influenza, Kamigoto Island, Japan 2010/11–2017/18 influenza season.

C_i ; number of influenza cases in age group i (n age groups), N_i ; population size of age group i , C_j ; total number of influenza cases, N_j ; total population size.

RIR values above 1 indicate excess risk of infection. Confidence interval (CIs) were calculated with the Poisson exact method^{23–25}. More details about age-standardized relative illness ratio (RIR) were described in previous studies^{23–25}.

Probabilistic reconstruction of transmission chains. In order to highlight determinants frequently associated with onward transmission, we had to reconstruct who-infected-whom during influenza outbreaks reported on Kamigoto Island. Transmission history can be reconstructed through contact-tracing investigations, where infected cases are asked who they had been in contact with over their infectious period. However, such contact-tracing investigations were not carried out as part of flu surveillance on Kamigoto island. Therefore, we needed an inference framework to estimate who-infected-whom using features available in the case data.

Transmission tree reconstruction methods often require genetic sequences, and group cases according to how closely they are genetically related. However, we did not have access to genetic sequences in this analysis, only to epidemiological information (age groups, onset dates, location). We used the R package “o2geosocial” (v1.0.2)²⁶, developed to infer who-infected-whom when genetic sequences are unavailable or uninformative. The package uses the age, location, type of influenza and onset date of each case, the distributions of influenza incubation period and generation time, and estimates of social contact patterns between age groups. It applies Bayesian inference using a Markov-chain Monte Carlo method to jointly estimate the probabilistic transmission trees, and the importation status of each case in each region for each influenza season. The method implemented in the package generates transmission tree samples from the posterior distribution, with a likelihood function relying on various components.

Influenza type component. Influenza cases were either diagnosed clinically or by RDTs. RDTs can identify the type of influenza for a given nasopharyngeal swab sample as A, B, or both. We categorized cases in the dataset into Influenza A, B and ‘not attributed’ (clinically diagnosed and A + B coinfecting cases) classes. In our model, we assumed that there can be a single type of influenza for each transmission tree. For each influenza (A or B) case, only cases from trees containing the same influenza type could be listed as potential infector, while cases coinfecting with both types and clinically diagnosed (less than 1% of all cases) could belong to any tree. This reduced the pool of potential infectors for genotyped cases, and helped the model identify plausible transmission links.

Age mixing component. We used a social contact survey study conducted in Japan²⁷ to estimate the probability of social contact between age groups. This contact survey was conducted in 2014 and included 1476 households covering all 47 prefectures in Japan. Contacts were grouped into 5-years age groups to derive the social contact matrix. We calculated the weighted average between weekday and weekend contact rates with 5:2 weights. The same matrix was used for all the seasons investigated and the impact of long school holidays on contact patterns was not considered.

Conditional reporting ratio. Conditional report ratio refers to the likelihood of missing generation between two cases. It differs from the overall report ratio in that it describes the reporting ratio between reported cases (i.e., it does not consider entirely unreported transmission chains). Influenza surveillance data in Japan is assumed to be high given the cultures of patients-initiated diagnosis during the influenza season²¹. However, in this study, conditional report ratio was estimated using a beta distribution prior (mean 0.9, Standard Deviation: 0.08) as one of the parameters of the model.

Time component. For each case, the probabilistic distribution of infection date of each case was inferred from the reported date of onset and distribution of the incubation period. The probability of a case being infected by another case is estimated from generation time of influenza and the number of generations between the two cases. The distributions (shifted Weibull distribution) of incubation period (Mean: 1.63 days, SD: 0.26 days) and generation time (Mean: 3.2 days, SD: 0.4 days) of influenza were taken from previous studies^{28,29}. Given the distributions of the generation time and incubation period, we assumed that only cases reported less than 8 days prior to the report date of a case could be potential infectors for computational efficiency (Temporal pre-clustering, δ).

Spatial component. The estimates of the probability of transmission between regions were calculated using Stouffer's rank model^{30,31}. In the Stouffer's rank method, rather than the absolute distance between the districts, the connectivity between the districts was estimated as the summed population of all the districts closer to district of infected case than the district of infector case. Stouffer's distance is calculated as $p_{kl} = m_l^c * \left(\frac{m_k}{\sum_{i \in \Omega_{kl}} m_i} \right)^a$, where m is the population size of the regions, and the regions are defined as

$$\Omega_{k,l} = \{ i : 0 \leq d(i, l) \leq d(k, l) \}$$

$d(i, l)$, $d(k, l)$; distance between regions (i, l) and (k, l) .

Then the probability of a case from region l infected by a case from region k is

$$s(kl) = \frac{P_{kl}}{\sum_h P_{hl}} = \frac{\left(\frac{m_k}{\sum_{i \in \Omega_{kl}} m_i} \right)^a}{\sum_h \left(\frac{m_k}{\sum_{i \in \Omega_{kl}} m_i} \right)^a}$$

The parameter a was estimated by the model. We chose to implement a Stouffer's rank model rather than use a gravity model (which would depend on the absolute number of inhabitants per region and distance) because of the variance in the number of inhabitants per district on Kamigoto Island (from 40 to 3000 inhabitants). This variance would lead to populated areas causing an abnormally high number of transmissions in a gravity model, and underestimate within-region transmission in low populated areas. We assumed that only cases reported in a 100 km radius of a given case could be listed as potential infectors of this case for computational efficiency.

Therefore, the overall log-likelihood that the case i was infected by case j , belonging to the transmission tree τ_j is estimated as²⁷

$$L_{ji}(t_i, t_j, \theta) = \log \left(p(\kappa_{ij}|\Pi) * w^{(kji)}(t_i - t_j) * \alpha^{(kji)}(\alpha_i, \alpha_j) * G(g_i, g_{\tau_j}) * s^{(kji)}(r_i r_j | a) * f(t_i - T_i) \right)$$

where, κ_{ij} is the number of generations between cases i and j , equal to 1 if j infected i , equal to 2 if there is an unreported case between j and i . $G(g_i, g_{\tau_j})$ is the likelihood associated with the influenza type (equal to 0 if $g_i = g_{\tau_j}$, 1 otherwise, and where g_i is the influenza type reported for i , while g_{τ_j} is the influenza type reported in the transmission tree τ_j containing j), $\alpha^{(kji)}(\alpha_i, \alpha_j)$ is the age component (with α_i and α_j the age groups of cases i and j), $s^{(kji)}(r_i r_j | a)$ is the spatial component (with r_i and r_j the regions of residence of i and j , and a the parameter of the Stouffer's rank spatial kernel), $p(\kappa_{ij}|\Pi)$ is the likelihood of the conditional report ratio (with Π the conditional report ratio of the tree), $w^{(kji)}(t_i - t_j) * f(t_i - T_i)$ is the time component (with t_i and t_j the estimated infection dates of i and j , T_i the reported onset date of i , w the distribution of the generation time, and f the distribution of the incubation period).

Cases identified by the surveillance data as importations and cases with no plausible infectors (i.e., no other case reported within the temporal pre-clustering threshold δ (8 days), and with the spatial pre-clustering threshold γ (100 km radius)) were set as importations in the model. In addition, we used the importation threshold (λ) as defined in the package o2geosocial to infer the importation status of cases that were not previously identified as importations. In o2geosocial, for each case and iteration, connections with a likelihood below the importation threshold are defined as non-plausible and removed.

The prior distributions used are listed in Table 1. We ran a Monte Carlo Markov Chain (MCMC) with 40,000 iterations to sample from the probabilistic distribution of likely transmission trees. The first 5000 samples were discarded as burn-in and 1 in 50 samples were kept thinning the chain, leaving 700 sampled trees describing the posterior distribution (Supplementary S-Fig. 1). To assess the convergence of the MCMC chain, we run the chain with different initial values and observe their convergence to the same mean and variance for each parameter. The final convergence agreement is shown in the S-Fig. 1. The posterior distribution of the parameters was consistent throughout the chain. The reconstructed cluster size distribution in the inferred trees is shown in supplementary S-Fig. 2. The maps describing the spatial distribution of transmission and importation risks were plotted at the post-code level using the shapefile of the Kamigoto Island obtained from ESRI Japan's website²⁸.

Parameters	Symbols	Values	Ref/comments
Incubation period	$f(t)$	Shifted Weibull distribution with: Mean: 1.63 days SD: 0.26 days	(28)
Generation time	$w(t)$	Shifted Weibull distribution with: Mean: 3.2 days SD: 0.4 days	(29)
Conditional report ratio	Π	Prior: beta distribution, mean = 0.9, s.d. = 0.08	Estimated
Spatial parameter	a	Prior: uniform distributions between 0 and 5	Estimated
Spatial pre-clustering	γ	100 km	Fixed
Temporal pre-clustering	δ	8 days (based on incubation period and generation times)	Fixed
Importation threshold (absolute) $5 \times \log 0.05 = -15$	λ	Default in o2geosocial package	Fixed

Table 1. Parameters used in the Bayesian analysis.

Regression analysis to identify factors associated with onwards transmission. The inferred probabilistic transmission trees were then used to identify factors consistently associated with increased risks of onwards transmission. To do so, we implemented a negative binomial regression analysis on each sampled transmission tree kept from the MCMC and pooled the results together. The outcome variable of the analysis was the number of onwards transmission per case. The sociodemographic variables used as explanatory variables were: (1) age group, (2) vaccination status, (3) vaccine coverage in the district of the reported case, (4) type of flu (5) number of inhabitants in the district of the reported case, (6) mean household size, (7) average vaccination coverage in neighboring districts, (8) epidemic year, and (9) within-year seasonality (sin and co-sin).

We grouped the age of cases into categories: < 3, 4–6, 7–12, 13–18, 19–64, 65–74 and ≥ 75 years-old. Individual vaccination status was categorized as vaccinated, unvaccinated, and unknown. We controlled for the impact of seasonality (the peak of the influenza in each influenza season) on transmission by adding two covariates (sine–cosine) in the regression analysis. The vaccination coverage in nearby district was defined as the population- and district-wise average coverage in the neighbors of each region.

The regression was run independently on each transmission network sampled from the MCMC (i.e., 700 samples, obtained after removing the burn-in phase and thinning the chain). The coefficients were then pooled together following “Rubin’s rules” to identify factors consistently associated with increased transmission risks across all samples³². We examined collinearity among the variables before running the regression models. We run different models to evaluate the robustness of our results: in model II, we categorized the population per district and vaccine coverage variables, and in model III, we also removed the seasonality variables.

All analyses were performed with R software, version 4.1.2 (R Foundation for Statistical Computing)³³.

Ethics approval. This study is a secondary analysis of data collected as part of routine surveillance of influenza in Japan. All methods were performed in accordance with the relevant guidelines and regulations. The research was approved by the institutional review boards of Kamigoto Hospital, Nagasaki University Research Ethics Committee (reference number 200619236), and the London School of Hygiene and Tropical Medicine Research Ethics Committee (reference number 26706). Both Nagasaki University and London School of Hygiene and Tropical Medicine granted waivers for obtaining informed consent due to the nature of this retrospective study and the preserved anonymity of patients.

Role of the funding source. SMH was supported by WISE Program (Doctoral Program for World-leading Innovative & Smart Education) of Ministry of Education, Culture, Sports, Science and Technology. AR was supported by the National Institute for Health Research (NIHR200908). The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Epidemiological analysis. In Kamigoto Island, a total of 8497 RDT-confirmed influenza cases were reported from 2010/11 to 2017/18. Figure 2 shows the distribution of influenza cases by RDT-confirmed influenza type. A-H3N2 subtype dominated in majority of the seasons, while influenza B subtype dominated in 2017/18. (Fig. 2, supplementary S-Table 1).

To assess which age groups were more likely to be infected, we calculated the relative illness ratio (RIR) of each age group in each epidemic season (Fig. 3). Consistently across all epidemics, RIRs were higher in the pre-school and school children age-group (below 19 years old). The RIR was lower in other age groups in all epidemic seasons. The attack rate was highest among school-aged children (4–6, 7–12 and 13–18) years old across all the epidemic seasons (Supplementary S-Table 2).

Reconstruction of probabilistic transmission trees. We used the R package o2geosocial to infer who-infected-whom among cases reported between 2010 to 2018 and estimate the number of secondary transmis-

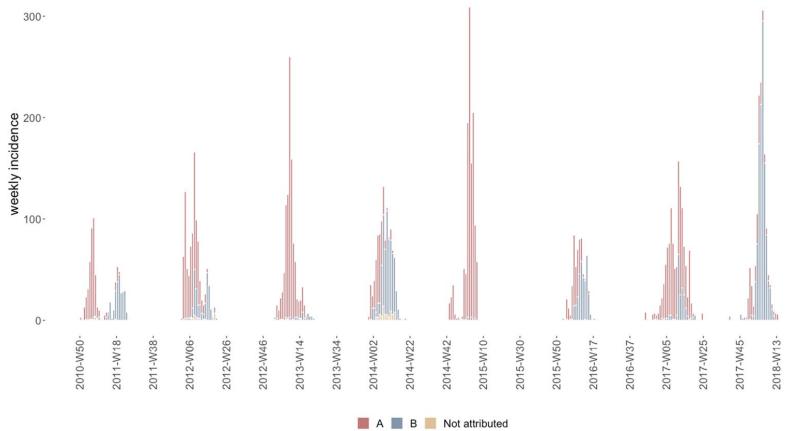


Figure 2. Weekly incidence of RDT-confirmed influenza cases in Kamigoto Island, Japan 2010/11–2017/18 influenza seasons.

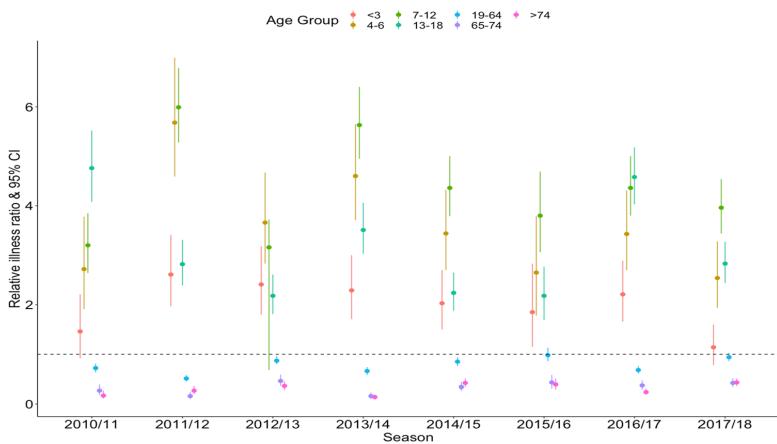


Figure 3. Relative illness ratio of influenza.

sions per case. The conditional report ratio ranged between 86 and 91% (Supplementary S-Fig. 1). The inference method therefore considered that most of the reported transmission chains captured by the surveillance data were complete, with a low risk of missed generation between reported cases. The spatial parameter ranged between 1.6 and 1.7 (Supplementary S-Fig. 1), which corresponds to a decrease in the probability of connection between regions as the number of inhabitants living in the area between these two regions increases. Figure 4 shows the inferred distribution of imported cases in each district for each season. There were 1050 cases classified as importations in the inferred transmission trees over the study period. MCMC inference therefore identified an additional 91 imported cases which were not classified as imports in the epidemiological data. These 91 cases were cases with no plausible infector and highlight the good performance of the surveillance system. The regions associated with most importations were consistent across epidemic seasons. Three districts (Tainourago, Arikawa-go, and Aokata-go) were estimated to have recorded most imported cases (orange and red) across the seasons. Tainourago and Arikawa-go are the main port areas of the island and are therefore the main connection from and to areas outside the Kamigoto island. Aogata-go is a more urban area of the town and the district and contains Kamigoto hospital, the only hospital within the island. Arikawa-go and Aogata-go districts are the tourist attractions within the island. The district on the southern part of the island (Naraao-go), another port area, was also suggested to have large number of imports in alternate years examined. We also found a

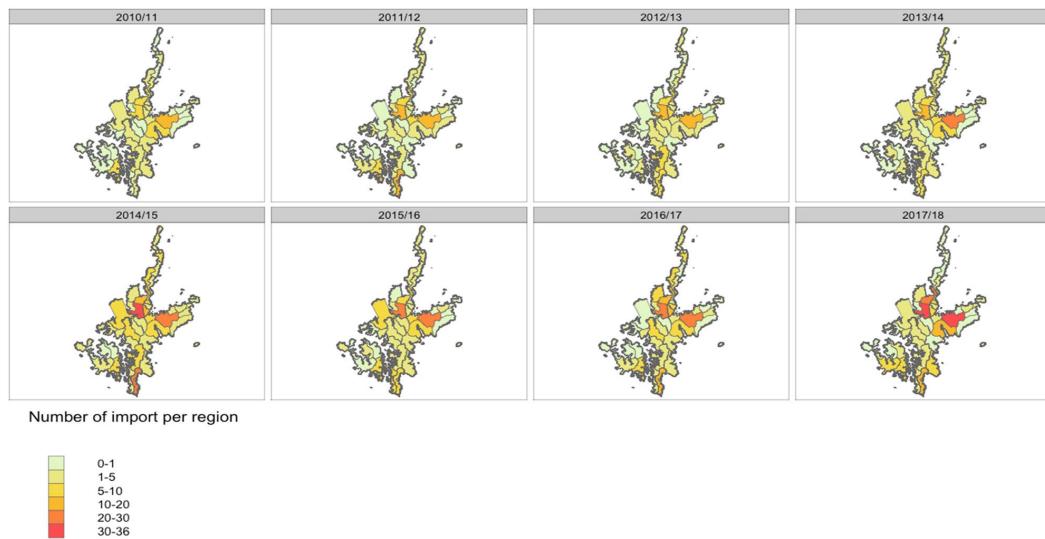


Figure 4. Median number of imported cases stratified by district and by season (2010/11–2017/18).

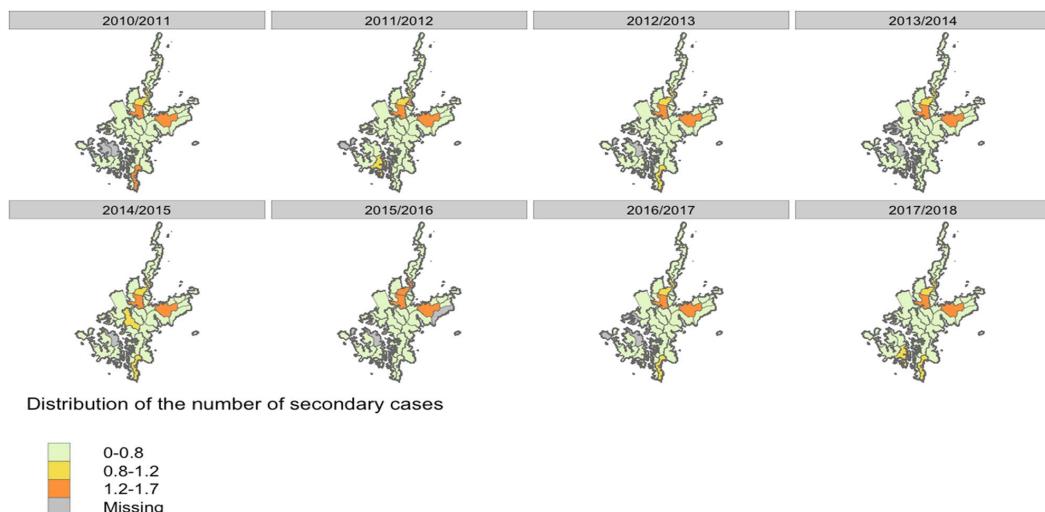


Figure 5. Median number of secondary cases per each influenza case, stratified by district and by season (2010/11–2017/18).

gradual increase in the overall number of imported cases over the years studied (73 import cases in 2010/11 to 201 import cases in 2017/18).

We then used the set of inferred transmission trees to compute the average number of secondary cases per primary case or individual reproduction number (R_{eff}) in each district. The geographical distribution of individual reproduction number (R_{eff}) was very similar across the epidemic seasons (Fig. 5). The districts at higher risks of importations also consistently had the highest individual reproduction number ($R_{\text{eff}} \geq 1.2$) (Fig. 5, Supplementary S-Fig. 4). The R_{eff} was below 0.8 in the majority of the remaining districts, with localized outbreaks causing increases in the number of secondary cases per case in certain years (e.g., in the south of the island in 2014/15 and 2017/18) (Fig. 5, supplementary S-Fig. 3). We categorized the average number of secondary cases for each case, as: (1) no onward transmission, (2) moderate transmitters (1–3 cases), or (3) high transmitters (more than 3 cases). Preschool (< 3 years old), adult (19–64) and older age group (65–74, > 74 years old) had

Variable	Secondary cases	IRR	95% CI	p-value
Intercept	0.01		(0.01, 0.03)	<0.001**
Age group, years				
<3		0.95	(0.78, 1.14)	0.574
4–6		1.38	(1.21, 1.57)	<0.001**
7–12		1.45	(1.33, 1.59)	<0.001**
13–18		1.51	(1.37, 1.66)	<0.001**
19–64		1	Reference	
65–74		0.72	(0.58, 0.89)	0.002*
≥75		0.76	(0.63, 0.91)	0.003*
RDT results				
Flu A		1	Reference	
Flu B		0.83	(0.77, 0.90)	<0.001**
Not attributed		0.68	(0.48, 0.98)	0.037*
Vaccination history				
No		1	Reference	
Yes		1.06	(0.96, 1.17)	0.278
Unknown		1.10	(0.95, 1.27)	0.213
Mean household size		1.04	(0.66, 1.62)	0.873
Population per district		2.00	(1.89, 2.12)	<0.001**
Proportion unvaccinated in the district		1.45	(1.02, 2.05)	0.037*
Average proportion unvaccinated in neighboring districts		2.41	(1.11, 5.21)	0.026*
Influenza season				
2010/11		1	Reference	
2011/12		0.87	(0.76, 1.00)	0.044
2012/13		0.96	(0.84, 1.10)	0.580
2013/14		0.95	(0.84, 1.09)	0.476
2014/15		0.90	(0.79, 1.03)	0.141
2015/16		1.28	(1.06, 1.54)	0.010*
2016/17		0.91	(0.79, 1.06)	0.232
2017/18		1.31	(1.10, 1.57)	0.003*
Seasonality				
Sin		0.99	(0.95, 1.04)	0.769
Cosin		1.01	(0.96, 1.05)	0.823

Table 2. Association factors to the number of secondary cases generated, Kamigoto island, Japan, 2010/11–2017/18. Note: * <0.05 ; ** <0.001 .

lower onward transmission while the school age group (4–6, 7–12 and 13–18) were more likely to have higher number of secondary cases generated (supplementary S-Fig. 5 and S-Fig. 6). The probability of transmission between and within district are displayed in supplementary S-Fig. 7.

Determinants of onwards transmission. Next, we identified the factors consistently associated with increases in the risk of onwards transmission across the inferred transmission trees. In each transmission tree from the posterior distribution (i.e., 700 samples), we computed the number of secondary transmissions per case, and ran a negative binomial regression analysis to explore characteristics associated with the risk of onwards transmission. The coefficients were then pooled across all regressions.

We found that age, number of inhabitants per district, district- level vaccination coverage, type of influenza and epidemic season had significant associations with the number of secondary cases per case (Table 2). Pre-school and school-aged children (aged 4–18) were significantly associated with higher secondary cases (incidence rate ratio (IRR) = 1.38 (95% confidence interval (CI) 1.21, 1.57), 1.45 (95% CI 1.33, 1.59), and 1.51 (95% CI 1.37, 1.66) compared to the adult (aged 19–64) group. On the contrary, adults over 65 years were associated with significantly fewer secondary cases (IRR = 0.72 (95% CI 0.58, 0.89) in aged 65–74 and 0.76 (95% CI 0.63, 0.91) in aged 75 years and over).

Cases living in districts that achieved lower vaccine coverage were more likely to cause further transmission (IRR = 1.45 (95% CI 1.02, 2.05)). There was a significant positive association between the number of inhabitants per district and the number of onwards transmissions (IRR = 2.00 (95% CI 1.89, 2.12)). The average proportion of unvaccinated individuals in neighboring regions was also associated with an increased risk of secondary transmissions 2.41 (95% CI 1.11, 5.21). Type B influenza were less likely to generate more secondary transmission compared to type A influenza (IRR = 0.83 (95% CI 0.77, 0.90)). Epidemic seasons 2015/16 and 2017/18 were

associated with higher transmission compared to 2010/11 (IRR = 1.28 (95% CI 1.06, 1.54), 1.31 (95% CI 1.01, 0.57) respectively). There was no significant association between individual vaccination status, mean household size, seasonality and onwards transmission. The results were consistent with different models. (Supplementary S-Table 3).

Discussion

We analysed the dynamics of influenza transmission in a remote island setting in Japan (Kamigoto Island), using fine scale influenza surveillance data collected between 2010 and 2018. Kamigoto island provides a unique opportunity to explore the dynamics of influenza transmission in an heterogeneous population, with limited mobility. We analysed the age-specific influenza burden, the importation status of the cases, and the risk of secondary transmission for each case by reconstructing transmission trees using a Bayesian approach. We also explored factors associated with onwards influenza transmission.

The result from our study adds to the evidence that children play an important role in influenza outbreaks^{34–42}. Across all epidemic seasons, pre-school, and school-aged children (i.e., 4–18-year-old) were infected at higher rate than the other age groups (Fig. 3). Previous studies have reported that age distribution patterns vary between the influenza subtypes/lineages, with school-aged children most likely to be affected by A(H3N2) and B^{15,36}. In Japan A(H3N2) was the dominant subtypes in four of the eight seasons, A/H1N1pmd09 in three seasons (2010/11, 2013/14 and 2015/2016) whereas B was predominant 2017/18 (supplementary S-Table 1). We also found that school-aged children were associated with the highest number of secondary cases generated. This is in line with studies reporting that social contact rates within the same age group is higher among school-aged children^{27,34}. On the other hand, we found that adults over 65 years-old were associated with the lowest influenza attack rate, and lower risks of onwards transmission. Similar results were previously reported in a study conducted in Italy¹⁵.

Our study highlighted that vaccination had different impacts on influenza dynamics. Firstly, high vaccine coverage in a district was consistently associated with lower levels of transmission, highlighting the importance of vaccination campaigns to reduce the risks of outbreaks through direct and indirect protection. Moreover, high vaccine coverage in regions neighboring a given district were also associated with reduced transmission risks. This may show the importance of reaching homogeneously high vaccine coverage, rather than focusing on a limited number of districts, to reduce opportunities for onward transmission. However, the spatial heterogeneity of the median number of secondary cases per region shows that active transmission clusters was only observed around a limited number of districts (Fig. 5). More analysis, potentially using mechanistic transmission models, is needed to compare the impact of different vaccination strategies.

In this study, the vaccine status of the individual cases was not associated with changes in the risk of secondary cases, suggesting that while vaccination is protective against infection, it might not necessarily prevent onwards transmission if breakthrough infection happens. A study conducted among children in Matsumoto city, Japan also reported an association between vaccination and reduction in susceptibility, with vaccination having a more limited association with onwards transmission⁴³. Recently published studies also reported the low degree of indirect protection by childhood vaccination supporting the results of the current study⁴⁴.

The RIR and attack rate was highest among school-aged children despite very high childhood vaccination coverage in the island (Supplementary S-Table 4). RIR and attack rate was lowest among the elderly age group (> 65 years old), and the vaccination coverage among these age group were above 70% in almost all epidemic seasons (Supplementary S-Table 2 and S-Table 4). The highest attack rates among children implies that their higher number of contacts was not fully offset by the high immunization rates. The majority of the reported cases were vaccinated, which indicates that although it does provide protection, the efficacy of the vaccine is not perfect. Previous studies on vaccine effectiveness reported the negative impact of repeated vaccination in children without prior history of natural infection^{45–48}. The type of influenza vaccine may also play a role, since Japan uses the inactivated influenza vaccine while other countries (for example: UK)^{42,49} use live attenuated influenza vaccine (LAIV). Similar results were previously reported when comparing the incidence among age groups with vaccination status in the United States: estimated incidence for children below 18 years old was 8.7% while it was 5.1% for adults after adjustment for median vaccine coverage and effectiveness⁵⁰.

To summarise, our study reveals different effects of vaccination on influenza transmission in Kamigoto Island: Firstly, although the proportion of vaccinated cases in our dataset implies that the protection provided by vaccines may not be perfect, cases reported in highly vaccinated regions were associated with lower risk of secondary transmission. This suggests that the protection provided by high vaccine coverage in a region did minimize opportunities for onward transmission (by reducing the pool of susceptible individuals available to be infected). Vaccination history of cases (i.e. conditioned that they were infected) were not associated with lower risk of onward transmission, showing that although the vaccine may provide protection against infection, we cannot conclude that it provided significant protection against onward transmission from those who experienced a ‘breakthrough’ infection.

The inferred transmission trees suggested that the distribution of influenza transmission within the island was similar across the epidemic seasons with the same districts having the highest number of importation and secondary transmissions per case (Arikawa-go, Tainoura-go, Aogata-go and Narao-go). With the presence of the ports connecting the islands to mainland Japan, major tourists' attraction sides of the island, and the highest number of inhabitants, these districts provide the best opportunities for the influenza transmission in the community. Moreover, people residing within the island but working outside (e.g., Nagasaki city) need to take a ferry from these ports to commute daily to their workplaces. This connectivity to the outside of the island likely contributes to the importation of influenza into the island.

The determinants of onward transmission identified by the regression analysis were consistent throughout all samples generated in the transmission tree inference. The Bayesian inference model, implemented using o2geosocial, was able to identify a robust history of transmission from routinely collected surveillance data (location, age, timing of disease onset). The different parameters estimated in the MCMC converged to consistent means and variances. The sampled transmission tree could not be compared to sequence data or contact tracing investigations to assess their accuracy, however, the results and estimates from the inference are in line with prior results, for instance on the high number of infectious contacts among children²⁷, or the low risk of unreported cases in Japan³⁹, and were robust to sensitivity analysis. We believe this indicates that our findings are reliable. This analysis is therefore an example of how even limited surveillance data can be used to reconstruct complex dynamics of transmission, highlight factors associated with transmission, and inform how to limit the risks of flu outbreak.

There are several limitations to our study. First, we assumed the same reporting rates across all the seasons we analyzed. Second, influenza transmission is suggested to be influenced by some meteorological variables such as temperature, absolute humidity and precipitation^{16,51}. We did not consider these factors in our analysis. Third, we did not account for the effect of nonpharmaceutical interventions, such as mask wearing and hand hygiene. The period of school closure can also have impact on the transmission dynamics; however, this was not included this in our study. Lastly, district with higher proportion of children may influence the onwards transmissibility and higher infection rates. However, we do not have access to the distribution of age group by district.

Conclusion

Our study used geospatial method to better describe spatiotemporal patterns in a fine-scale epidemiological setting. We show that age, population density, local vaccination coverage, and dominant strain of influenza play a significant role in shaping recurrent influenza spatial patterns across the seasons studied. The local vaccine coverage was found to be strongly associated with the risk of onwards transmission, highlighting the importance to focus public health efforts on achieving high vaccine coverage throughout the island or prioritizing vaccination in areas with high transmission rates. The individual vaccine status may not prevent onwards transmission, though it reduces the susceptibility to infection. Thus, the other social precaution measures such as social distancing, handwashing, and wearing a mask must be practiced once someone is infected. Similar analysis could potentially be reproduced in similar settings (e.g. Oceania and pacific island countries), to study the transmission of influenza or other infectious disease such as COVID-19.

Data availability

All data generated or analysed during this study, is publicly available on Github repository (<https://github.com/Su06690/Temporal-Spatial-Flu-spread-Island-community>).

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Author contributions

S.M.H.: study design, literature search, data analysis, data interpretation, writing original draft; A.R.: data analysis, data interpretation, writing review and editing; S.M.: data collection, writing review and editing; T.Y., S.K., K.K.: data collection; N.S., M.S.: conceptualization, data collection; A.E.: data analysis, writing review and editing; M.B.: conceptualization, study design, data analysis, data interpretation, writing review and editing; K.A.: conceptualization, data collection, supervision, writing review and editing.

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Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to S.M.H.

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4.4. Supplementary materials

Supplementary

Transmission dynamics of seasonal influenza in remote island populations: epidemiological and modelling Study

Su Myat Han^{1,2*}, Alexis Robert^{2,3}, Shingo Masuda^{1,4}, Takahiro Yasaka⁴, Satoshi Kanda⁴, Kazuhiri Komori⁴, Nobuo Saito^{5,6}, Motoi Suzuki^{1,7}, Akira Endo^{1,2,3}, Marc Baguelin^{2,8}, Koya Ariyoshi^{1,6}

1. School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan
2. Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom
3. Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, Keppel Street, London, UK
4. Department of Internal Medicine, Kamigoto Hospital, Kamigoto, Japan
5. Department of Microbiology, Faculty of Medicine, Oita University, Yufu, Japan
6. Department of Clinical Medicine, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan
7. Infectious Disease Surveillance Center, National Institute of Infectious Diseases, Tokyo, Japan
8. MRC Centre for Global Infectious Disease Analysis; and the Abdul Latif Jameel Institute for Disease

S Table 1: Circulating strains of influenza by season (<https://www.niid.go.jp/niid/images/idsc/iasr/39/465e.pdf>)

	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17	2017/18
Circulating strains								
A/H1N1pmd09	52%	0.2%	2%	43%	1%	49%	4%	23%
A/H3N2	32%	71%	76%	21%	85%	7%	78%	32%
B	15%	28%	21%	36%	14%	44%	18%	45%
Vaccine strains	A/California/7/2009 [A(H1N1) pdm09]	A/California/7/2009 [A(H1N1) pdm09]	A/California/7/2009 [A(H1N1) pdm09]	A/California/7/2009 [A(H1N1) pdm09]	A/California/7/2009 [A(H1N1) pdm09]	A/Switzerland/9715293/2013 [A(H3N2)]	A/California/7/2009 [A(H1N1) pdm09]	A/Michigan/45/2015-like A/Singapore/GP1908/2015 [A(H1N1) pdm09]
	A/Victoria/210/2009 [A(H3N2)]	A/Victoria/210/2009 [A(H3N2)]	A/Victoria/361/2011 [A(H3N2)]	A/Texas/50/2012 [A(H3N2)]	A/New York/39/2012 [A(H3N2)]	B/Phuket/3073/2013 [B(Yamgata)]	A/Switzerland/9715293/2013 [A(H3N2)]	A/Singapore/GP1908/2015 [A(H1N1) pdm09]
	B/Brisbane/60/2008 [B(Victoria)]	B/Brisbane/60/2008 [B(Victoria)]	B/ Wisconsin /01/2010 [B(Yamgata)]	B/ Massachusetts /02/2012 [B(Yamgata)]	B/ Massachusetts /02/2012 [B(Yamgata)]	B/Phuket/3073/2013 [B(Yamgata)]	B/Texas/2/2013 [B(Victoria)]	A/Hong Kong/4801/2014 [A(H3N2)]
						B/Texas/2/2013 [B(Victoria)]	B/Texas/2/2013 [B(Victoria)]	B/Phuket/3073/2013 [B(Yamgata)]
Circulating strains								
A/H1N1pmd09	Vaccine match	Vaccine match (50%)	Vaccine match (97%)	Vaccine match	Vaccine match	Vaccine match	Vaccine mismatch	Vaccine match
A/H3N2	Vaccine match	Vaccine match	Vaccine match	Vaccine match	Vaccine mismatch	50-60% match	Vaccine mismatch	Vaccine match (50-60%)
B	Vaccine match	Vaccine match	Vaccine match	Vaccine match	Vaccine match	Vaccine match	Vaccine match	Vaccine match

S-Table 2: Incidence attack rate per 1,000 individuals at risk, stratified by age group in Kamigoto island, Japan over (2010/11- 2017/18) influenza season

Season	<3	4-6	7-12	13-18	19-64	65-74	≥75	Total
2010/11	42.6	79.4	93.3	138.7	20.9	7.8	5.0	29.2
	(27.0, 63.9)	(56.5, 108.6)	(77.5, 111.3)	(120.0, 159.5)	(18.3, 23.6)	(5.2, 11.4)	(3.1, 7.7)	(27.0, 31.4)
2011/12	115.1	250.5	264.0	124.5	22.5	6.8	12.0	44.1
	(88.0, 147.8)	(206.9, 300.7)	(235.9, 294.5)	(106.4, 144.6)	(19.9, 25.4)	(4.3, 10.4)	(8.9, 15.7)	(41.4, 46.9)
2012/13	113.1	171.5	148.3	102.2	41.0	21.8	16.7	46.9
	(85.5, 146.9)	(135.3, 214.3)	(126.9, 172.4)	(85.6, 121.2)	(37.4, 44.9)	(16.9, 27.5)	(13.1, 21.1)	(44.1, 49.8)
2013/14	115.3	231.5	283.7	176.9	33.2	7.9	6.9	50.4
	(86.9, 150.1)	(188.3, 281.5)	(252.8, 317.4)	(154.1, 202.0)	(29.9, 36.7)	(5.1, 11.7)	(4.6, 9.8)	(47.4, 53.4)
2014/15	115.3	195.1	247.2	127.0	48.2	19.5	23.6	56.7
	(85.3, 152.4)	(154.4, 243.1)	(217.4, 280.1)	(107.5, 148.9)	(44.1, 52.5)	(14.9, 25.0)	(19.2, 28.6)	(53.6, 60.0)
2015/16	57.9	82.7	118.9	68.1	30.8	13.4	12.1	31.2
	(36.3, 87.7)	(56.2, 117.3)	(97.1, 144.0)	(53.6, 85.4)	(27.4, 34.4)	(9.8, 18.0)	(9.1, 15.9)	(28.9, 33.8)
2016/17	133.7	207.3	263.8	276.5	41.0	22.2	14.6	60.4
	(101.0, 173.6)	(164.2, 258.4)	(232.3, 298.3)	(246.6, 309.1)	(37.2, 45.1)	(17.4, 28.0)	(11.3, 18.7)	(57.1, 63.9)
2017/18	81.9	183.4	285.4	204.2	68.0	30.2	31.0	72.1
	(56.4, 115.0)	(140.6, 235.2)	(250.6, 323.7)	(177.7, 233.7)	(62.9, 73.4)	(24.5, 36.7)	(26.0, 6, 36.6)	(68.5, 76.0)

S-Table 3: Sensitivity analysis (Model comparison of negative regression analysis)

Variable	IRR (95% CI)		p-value	
	Model 2	p-value	Model 3	p-value
Age group, years				
<3	0.96 (0.79, 1.16)	0.564	0.96 (0.79, 1.16)	0.556
4-6	1.39 (1.22, 1.59)	<0.001*	1.39 (1.22, 1.59)	<0.001*
7-12	1.47 (1.34, 1.61)	<0.001*	1.47 (1.34, 1.61)	<0.001*
13-18	1.50 (1.36, 1.65)	<0.001*	1.50 (1.36, 1.65)	<0.001*
19-64	1 (Reference)		1 (Reference)	
65-74	0.72 (0.59- 0.89)	<0.001*	0.73 (0.59- 0.89)	<0.001*
=75	0.77 (0.64, 0.92)	<0.001*	0.77 (0.64, 0.92)	<0.001*
RIDT results				
Flu A	1 (Reference)		1 (Reference)	
Flu B	0.84 (0.77, 0.90)	<0.001*	0.84 (0.78, 0.91)	<0.001*
Not attributed	0.70 (0.48, 0.98)	0.014	0.70 (0.49, 1.00)	0.014
Vaccination history				
No	1 (Reference)		1 (Reference)	
Yes	1.08 (0.97, 1.19)	0.088	1.08 (0.97, 1.19)	0.087
Unknown	1.13 (0.98, 1.31)	0.042	1.13 (0.98, 1.31)	0.042
Mean household size	1.18 (0.71, 1.86)	0.411	1.20 (0.74, 1.94)	0.376
Population per district				
<500	1 (Reference)		1 (Reference)	
500-2000	2.31 (2.04, 2.63)	<0.001*	2.31 (2.04, 2.63)	<0.001*
>2000	4.41 (3.81, 5.14)	<0.001*	4.42 (3.81, 5.14)	<0.001*
Vaccination coverage				
<50	1.10 (0.85, 1.43)	0.363	1.10 (0.84, 1.42)	0.375
50-60	1 (Reference)		1 (Reference)	
60-65	0.97 (0.89, 1.06)	0.423	0.97 (0.89, 1.06)	0.416
>65	0.76 (0.66, 0.88)	<0.001*	0.76 (0.66, 0.88)	<0.001*
Proportion unvaccinated in neighborhood district	1.54 (0.74, 3.20)	0.174	1.54 (0.74, 3.20)	0.173
Influenza season				
2010/11	1 (Reference)		1 (Reference)	
2011/12	0.83 (0.73, 0.96)	0.007	0.83 (0.72, 0.95)	0.006
2012/13	0.93 (0.81, 1.07)	0.296	0.93 (0.81, 1.06)	0.263
2013/14	0.87 (0.77, 0.99)	0.039	0.88 (0.72, 1.00)	0.042
2014/15	0.82 (0.72, 0.94)	0.003	0.83 (0.72, 0.95)	0.005
2015/16	1.13 (0.94, 1.35)	0.159	1.16 (0.96, 1.40)	0.104
2016/17	0.81 (0.70, 0.94)	0.004	0.82 (0.71, 0.95)	0.006
2017/18	1.09 (0.92, 1.29)	0.273	1.11 (0.94, 1.33)	0.184
Seasonality				
Sin	1.00 (0.95, 1.05)	0.600	NA	NA
Cosin	1.01 (0.96, 1.06)	0.619	NA	NA

Results of regression analysis after we changed the population per district and vaccination coverage to categorical variables (Model 2 and Model 3), after removal of control for seasonality (Model 3)

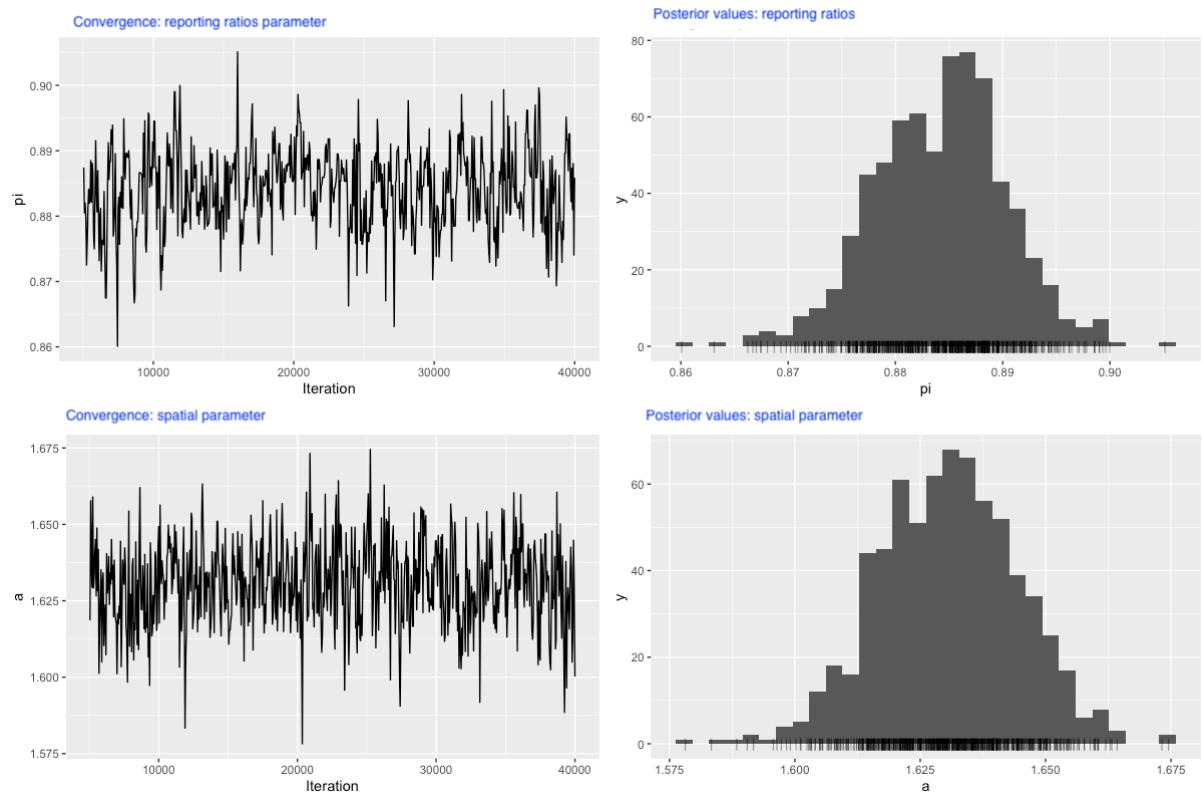
S-Table 4: Seasonal influenza vaccine coverage by age group (year) for influenza vaccine in the period 2010/11- 2017/18, Kamigoto island, Japan

(A)

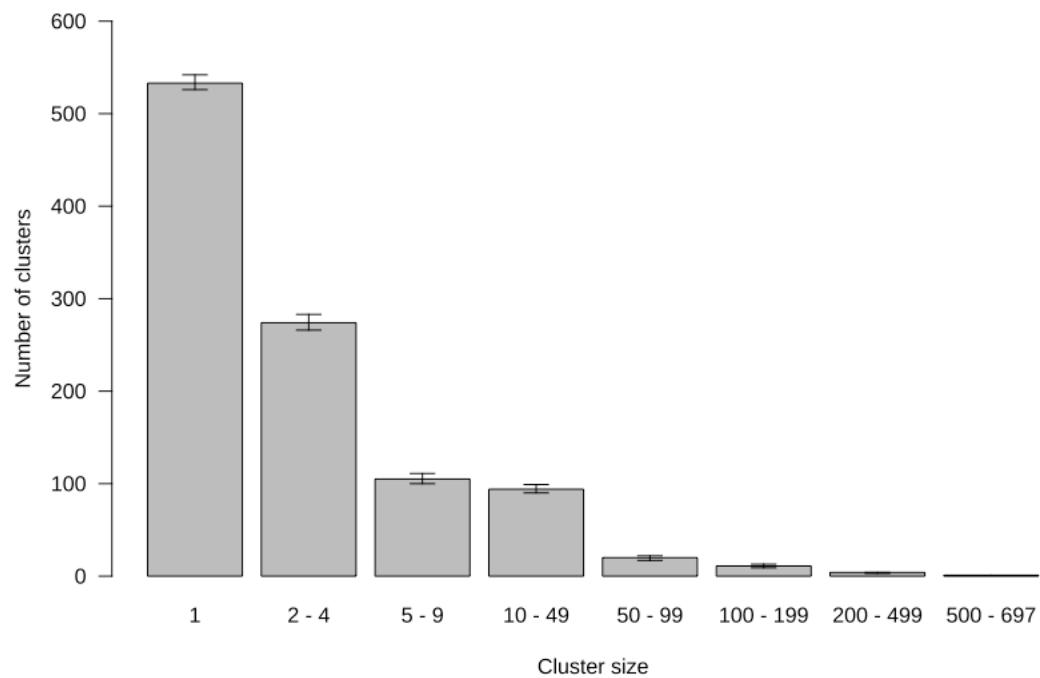
Season	<5	5-14	15-64	>65	Total
2010/11	79.4	77.1	41.1	72.9	56.0
2011/12	83.7	88.2	43.1	72.9	58.0
2012/13	81.6	86.7	41.7	70.4	56.3
2013/14	84.1	88.2	42.2	68.9	56.4

(B)

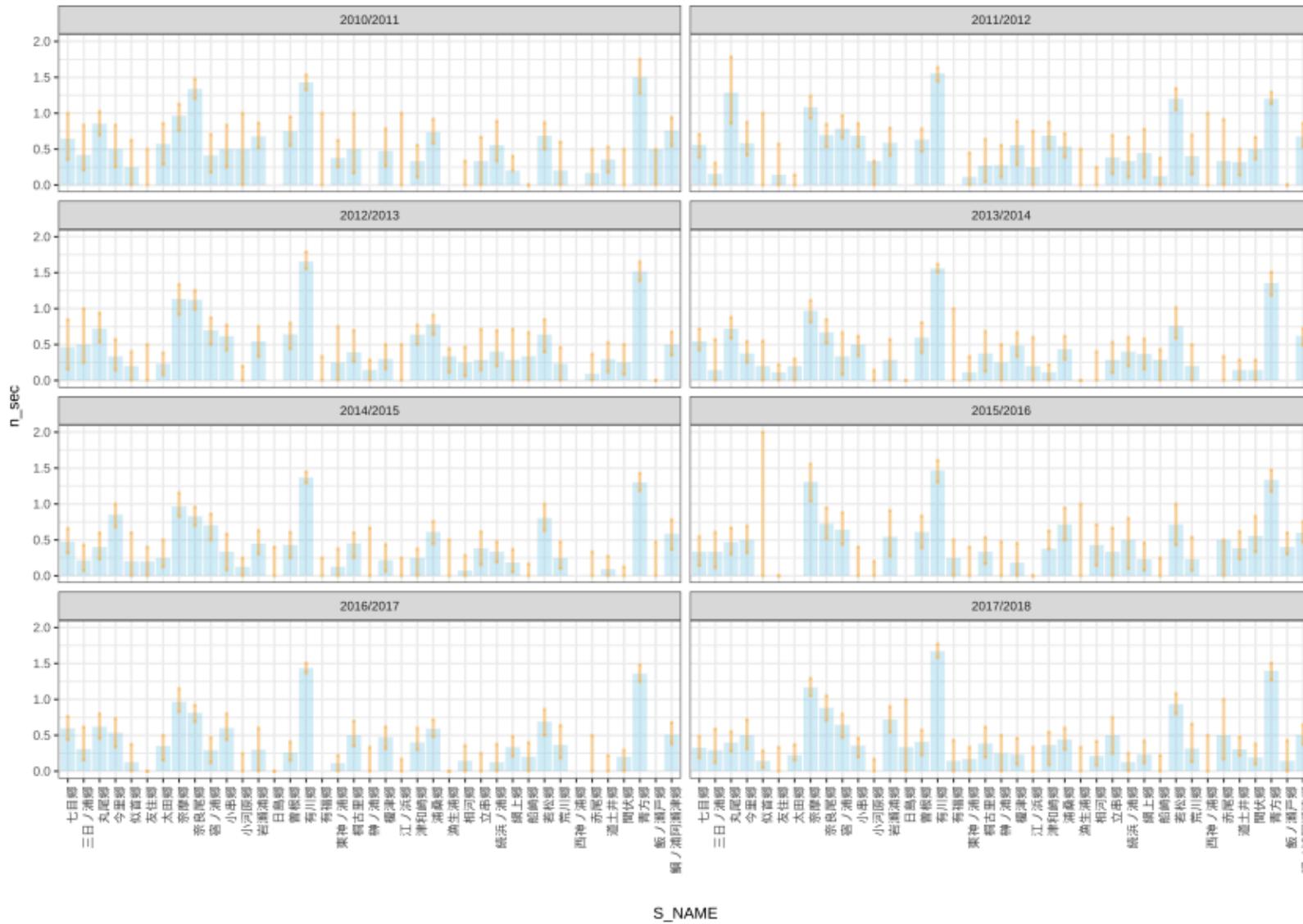
SEASON	<3	4-6	7-12	13-18	19-64	65-74	>=75	TOTAL
2014/15	77.6	87.7	83.3	74.1	44.7	58.9	78.1	58.6
2015/16	86.6	90.1	92.6	84.2	47.5	62.4	78.9	62.1
2016/17	69.9	84.5	81.3	75.8	46.7	63.3	78.0	60.0
2017/18	78.7	91.1	85.7	83.2	49.8	62.4	77.6	61.1



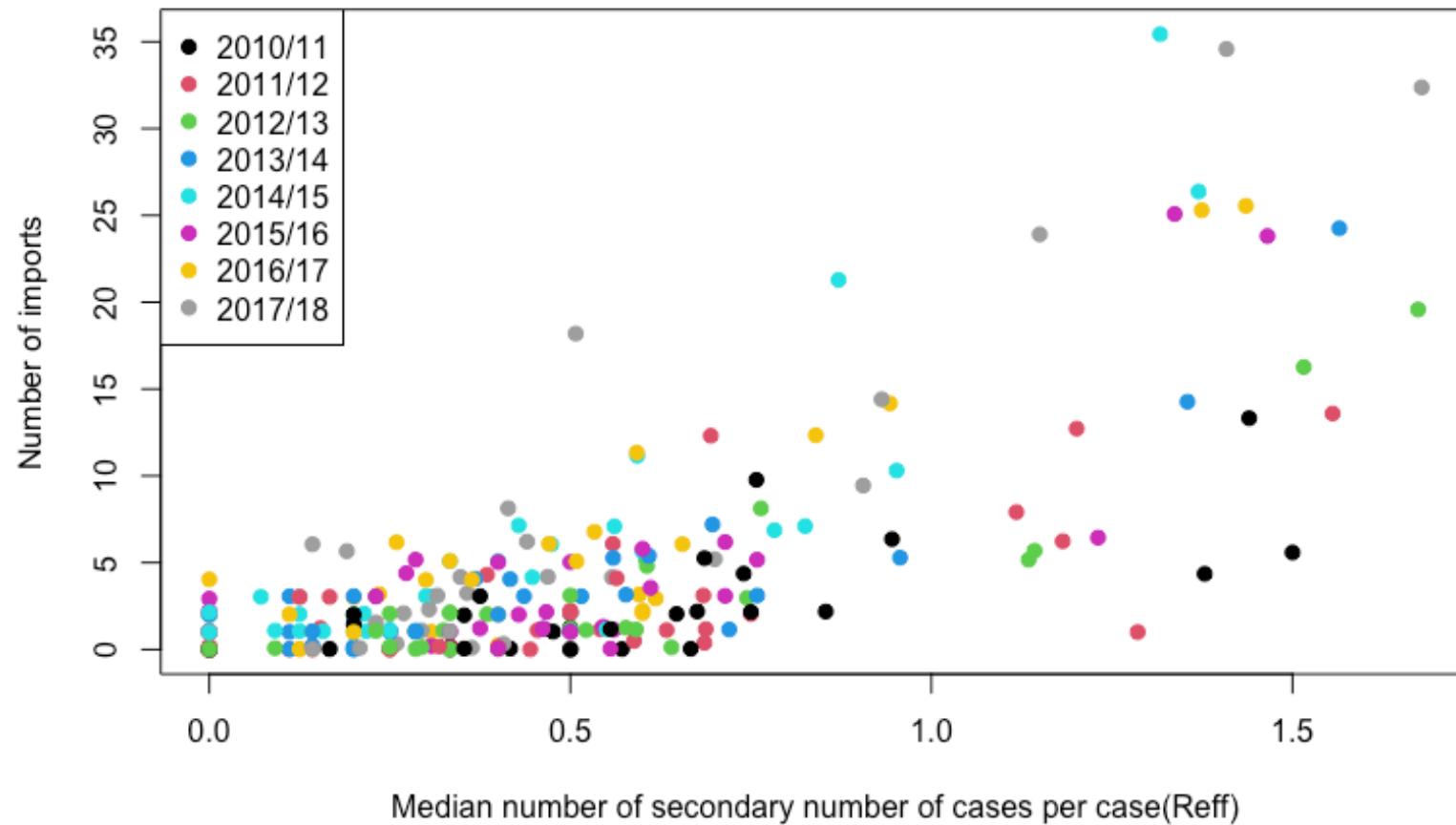
S-Figure 1: Convergence of posteriors and results of posterior estimates



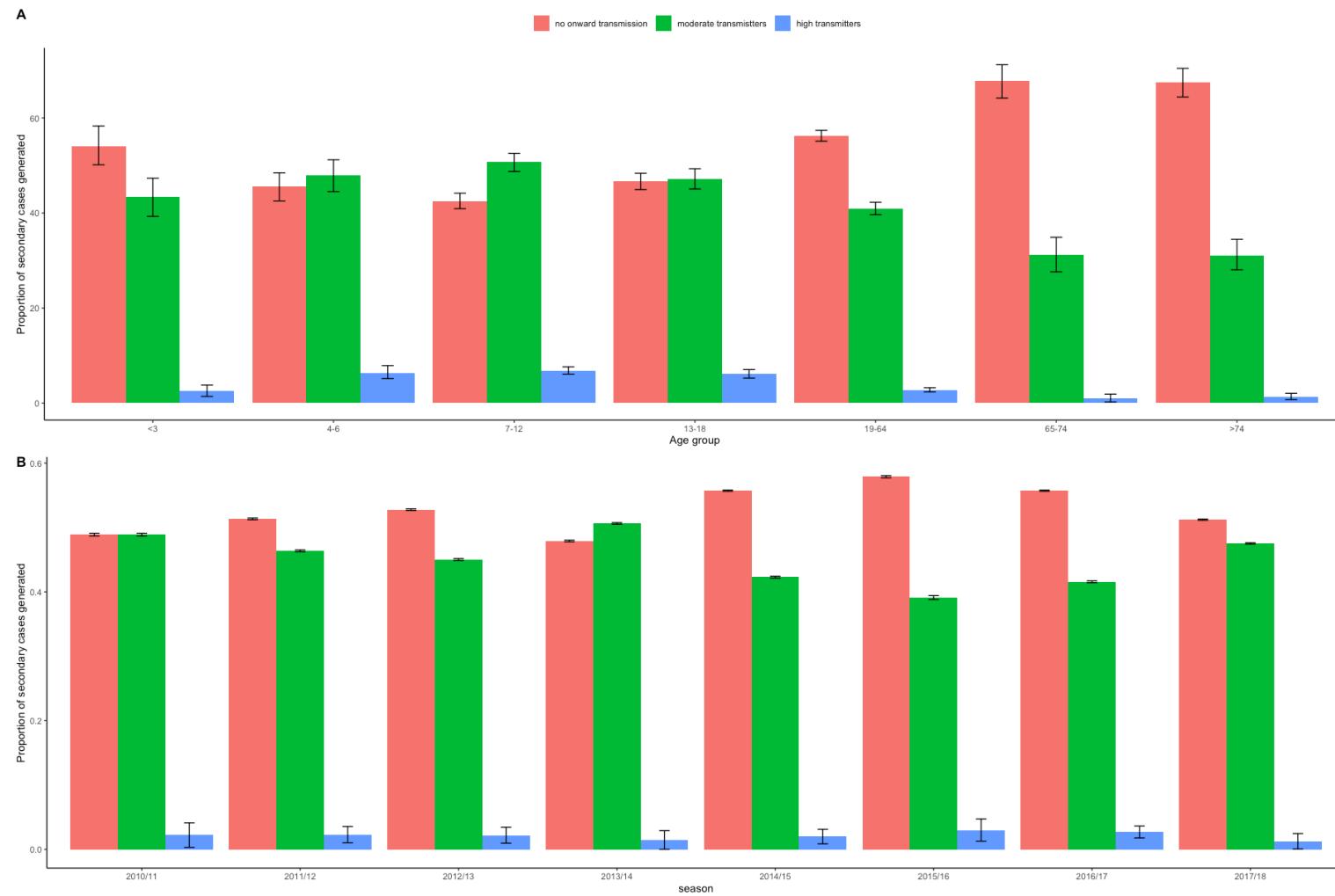
S-Figure 2: Cluster size distribution generated by o2geosocial using the Stouffer rank method



S-Figure 3: Median number of secondary cases per case by district and by season (2010/11- 2017/18)

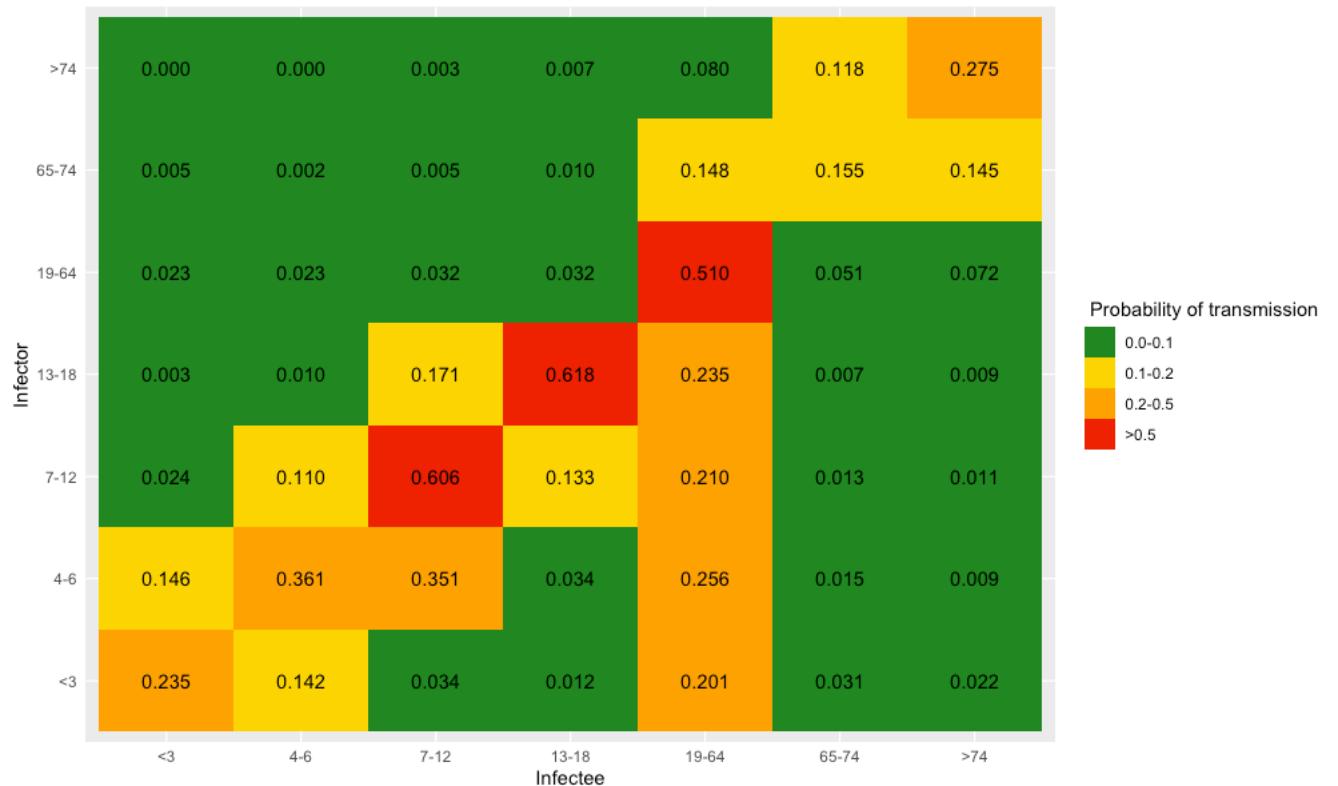


S-Figure 4: The relationship between the median number of imported cases and the median number of secondary cases generated by case in each region, colored by seasons



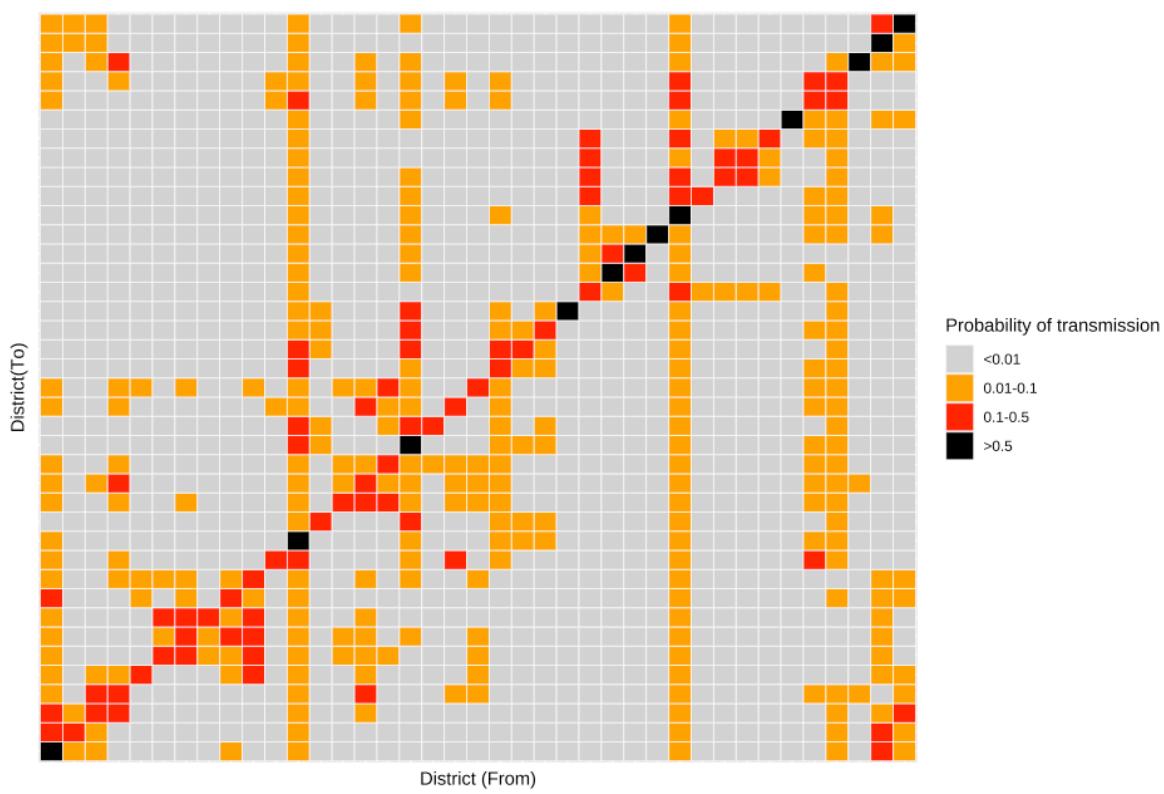
S-Figure 5: Distribution of Reff by age-group and by season

Note: No onward transmission = zero transmission, moderate transmitter = 1-3 secondary cases, High transmitter= more than three secondary cases)



S-Figure 6: Heatmap of the probability of transmission between and within different age groups.

The color of each tile in the heatmap corresponds to proportion of an individual from the age group in each row infecting to another individual from the group in column. The values are extracted from the transmission tree (700 MCMC trees) constructed using o2geosocial package.



S-Figure 7: Heatmap of the probability of transmission between and within districts

Reference:

1. Han SM, Robert A, Masuda S, Yasaka T, Kanda S, Komori K, et al. **Transmission dynamics of seasonal influenza in a remote island population.** *Sci Rep* 2023; 13(1):5393.
2. **QIAmp Viral RNA Mini Handbook.**
3. Zhou B, Donnelly ME, Scholes DT, St George K, Hatta M, Kawaoka Y, et al. **Single-reaction genomic amplification accelerates sequencing and vaccine production for classical and Swine origin human influenza a viruses.** *J Virol* 2009; 83(19):10309-10313.

4.5. Limitation of the study

In estimating the relative illness ratio in each epidemic season, although the results are similar across seasons, the estimated values are different among seasons. The variation in the estimated values might be attributed to due to;

1. Biological Differences: For instance, different influenza virus strains circulating in each season might exhibit varying transmissibility, which could affect the relative illness ratios across age groups. Additionally, differences in prior immunity or vaccine effectiveness against specific strains could also contribute to this seasonal variability.
2. Random Effects: Random fluctuations in the data, such as differences in sample sizes, or reporting practices could influence the estimated values.

Conducting additional statistical tests (e.g., including random intercepts for each season in a mixed-effects model to account for season-specific variability) may allow us to assess whether the observed variation is statistically significant beyond what would be expected by chance.

Another limitation of this study is the reliance on estimated values for the regression analyses, which may introduce biases stemming from uncertainties in the estimation process. These biases could arise from the underlying assumptions used in generating the estimates and the quality of the input data. Although we employed robust statistical methods and performed sensitivity analyses (S-Table 3) to mitigate these effects, the possibility of residual bias remains. This could potentially impact the precision of our findings, warranting cautious interpretation. Future research incorporating direct measurements or more comprehensive data sources could help to validate and refine the associations observed in this study.

1 **Chapter 5: Phylogenetic study of local patterns of**
2 **influenza A (H3N2) virus transmission in a semi-**
3 **isolated population in a remote island in Japan**
4 **between 2011-2013**

5
6

7 5.1 Research Paper cover sheet



London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1901561	Title	Dr
First Name(s)	Su Myat		
Surname/Family Name	Han		
Thesis Title	Unravelling transmission dynamics of influenza and its interaction with other respiratory viral pathogens in the population of Kamigoto island, Japan		
Primary Supervisor	Professor Koya Ariyoshi		

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?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Virus Evolution
Please list the paper's authors in the intended authorship order:	Su Myat Han, Yuki Furuse, Shingo Masuda, Peterson Mathenge, Takahiro Yasaka, Satoshi Kanda, Kazuhiri Komori, Nobuo Saito, Motoi Suzuki, Teiichiro Shiino, Chris Smith, Alexis Robert, Marc Baguelin, Koya Ariyoshi

Stage of publication	Submitted
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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 candidate conceived the study, designed the study model, performed the analysis and wrote the original draft of the manuscript
---	--

SECTION E

Student Signature	Su Myat Han
Date	18 December 2023

Supervisor Signature	Koya Ariyoshi
Date	18 December 2023

11 **5.2 Summary of the chapter**

12 This chapter was submitted as a research article in *Virus evolution* as of December 2023.

13 In chapter 4, I used surveillance data of RIDT confirmed influenza cases to understand the
14 transmission dynamics of influenza in the Kamigoto island, Japan. RIDT provides the results of
15 either influenza A and/or B positive. However, influenza A has several subtypes and strains, and
16 IBV has two lineages. Transmission studies using the RIDT or ILI surveillance data can explain
17 the overall patterns of transmission within the island, however, the data cannot provide the answer
18 to the direction of transmission or “who-infect-whom”. Geomics sequence data plays a key role
19 in revealing the relatedness of the cases in the transmission chains. Moreover, the genomic data
20 can explain the relatedness of influenza strains in the island to the mainland Japan or other parts
21 of the world. To understand this, I performed the whole genome sequencing of the RT-PCR
22 confirmed IAV positive samples collected over two years period of time in Kamigoto island. From
23 this, I did the phylogenetic analysis to place the Kamigoto strains at global context and explore the
24 spatio-temporal pattern of influenza transmission within the island.

25 I did the development of the study design, selection of the mathematical model, and execution
26 of the analysis. I took charge of writing the paper and creating the figures. Throughout the process,
27 I received input/suggestions/edits from both my supervisors, advisors and research collaborator.
28 The submitted version of the paper is attached in the 5.3 manuscript section, the supplementary
29 tables and figures are in section 5.4.

30 **5.3 Manuscript**

31 **Phylogenetic study of local patterns influenza A(H3N2) virus**
32 **transmission in a semi-isolated population in a remote island in**
33 **Japan between 2011-2013**

34 Su Myat Han^{1,2,3}, Teiichiro Shiino^{4,5}, Shingo Masuda^{1,6}, Yuki Furuse⁷, Takahiro Yasaka⁶, Satoshi
35 Kanda⁶, Kazuhiri Komori⁶, Nobuo Saito^{1,8}, Yoshiano Kubo⁹, Chris Smith^{1,10}, Akira Endo^{1,2,11,12},
36 Alexis Robert^{1,2,11*}, Marc Baguelin^{2,11,13*}, Koya Ariyoshi^{1,9*}

- 37
- 38 1. School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan
39 2. Department of Infectious Disease Epidemiology, Faculty of Epidemiology and
40 Population Health, London School of Hygiene and Tropical Medicine, London, United
41 Kingdom
42 3. National Center for Infectious Disease, Singapore
43 4. Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo,
44 Japan
45 5. AIDS Research Center, National Institute of Infectious Diseases, Tokyo, Japan
46 6. Department of Internal Medicine, Kamigoto Hospital, Kamigoto, Japan
47 7. Department of Medical Virology, Nagasaki University Graduate School of Biomedical
48 Sciences, Nagasaki, Japan
49 8. Department of Microbiology, Faculty of Medicine, Oita University, Yufu, Japan
50 9. Department of Clinical Medicine, Institute of Tropical Medicine, Nagasaki University,
51 Nagasaki, Japan
52 10. Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London
53 School of Hygiene & Tropical Medicine, London, UK
54 11. Centre for the Mathematical Modelling of Infectious Diseases, London School of
55 Hygiene & Tropical Medicine, Keppel Street, London, UK
56 12. Saw Swee Hock School of Public Health, National University of Singapore
57 13. MRC Centre for Global Infectious Disease Analysis; and the Abdul Latif Jameel Institute
58 for Disease

59

60 * These authors are joint last authors

61

62 **Abstract**

63 **Background:** Influenza A outbreak risk is impacted by the potential for importation and local
64 transmission. Reconstructing transmission history with phylogenetic analysis of genetic sequences
65 can help assess outbreak risk but relies on regular collection of genetic sequences. Few influenza
66 genetic sequences are collected in Japan, which makes phylogenetic analysis challenging,
67 especially in rural, remote settings. We generated influenza A genetic sequences from
68 nasopharyngeal swabs (NPS) samples collected using rapid Influenza diagnostic tests, and used
69 them to analyse the transmission dynamics of influenza in a remote island in Japan.

70 **Methods** We generated 229 whole-genome sequences of influenza A/H3N2 collected during
71 2011/12 and 2012/13 influenza seasons in Kamigoto Island, Japan, of which 178 sequences passed
72 the quality check. We built time-resolved phylogenetic trees from HA sequences to classify the
73 circulating clades by comparing the Kamigoto sequences to global sequences. Spatio-temporal
74 transmission patterns were then analyzed for the largest local clusters.

75 **Results:** Using a time-resolved phylogenetic tree, we showed that the sequences clustered in six
76 independent transmission groups (1 in 2011/12, 5 in 2012/13). Sequences were closely related to
77 strains from mainland Japan. All 2011/12 strains were identified as clade 3C.2 (n=29), while
78 2012/13 strains fell into two clades: clade 3C.2 (n=129), and 3C.3a (n=20). Clusters reported in
79 2012/13 circulated simultaneously in the same regions. The spatio-temporal analysis of the largest
80 cluster revealed that while the first sequences were reported in the busiest district of Kamigoto,
81 the later sequences were scattered across the island.

82 **Conclusion:** Kamigoto island was exposed to repeated importations of Influenza A(H3N2),
83 mostly from mainland Japan, sometimes leading to local transmission and ultimately outbreaks.
84 As independent groups of sequences overlapped in time and space, cases may be wrongly allocated
85 to the same transmission group in absence of genomic surveillance, thereby underestimating the
86 risk of importations. Our analysis highlights how NPS could be used to better understand influenza
87 transmission patterns in little-studied settings and improve influenza surveillance in Japan.

88 **Keywords:** Influenza, A/H3N2, transmission dynamics, molecular epidemiology

89

90 **Introduction**

91 Seasonal influenza remains a major public health threat, causing substantial morbidity and
92 mortality annually. It is estimated that influenza affects 3-5 million people globally, resulting in
93 approximately 290,000-650,000 deaths each year.¹ The transmission patterns of seasonal influenza
94 viruses have been extensively studied using surveillance data,²⁻⁶ which helped inform influenza
95 seasonal outbreak dynamics, the type of strain circulating at each season, and vaccine selection
96 based on genomic surveillance. It has also provided guidance on the optimal timing for
97 vaccination.^{3,7,8}

98 In Japan, the estimated annual prevalence of seasonal influenza exceeds 10% of the
99 population.⁹ Japan is home to many small islands, some of which have limited connections to
100 mainland Japan¹⁰, such as Kamigoto Island (Nagasaki Prefecture). In a previous study,² we used
101 influenza surveillance data containing cases confirmed via rapid influenza diagnostic test (RIDT)
102 in Kamigoto Island between 2010 and 2018 to identify determinants of transmission and local
103 dynamics of influenza transmission. The study revealed patterns of transmission largely influenced
104 by age, vaccine coverage, and district population density. However, surveillance data, based on
105 onset dates, age groups, and residence of the cases, would not be able to distinguish between
106 transmission chains co-circulating at the same time and areas, rendering accurate importation risk
107 assessment challenging.

108 Phylogenetic analysis is instrumental in reconstructing the evolutionary relationship
109 between genomic sequences of infected individuals sampled at different dates,¹¹⁻¹³ and can help
110 distinguish independent importations, and ultimately identify the epidemiological relationship
111 between cases. Cases with close genomic sequences are more likely to be epidemiologically

112 connected, while different strains indicate separate importations. The time-resolved phylogeny can
113 also be used to infer who-infected-whom among the sampled cases, thereby exploring the
114 pathogen's transmission dynamics when the sampling density is high.^{11,12,14-16}

115 Since diverse Influenza A strains and subtypes can cocirculate, reliance solely on
116 influenza-like illness (ILI) and RIDT data often falls short of identifying distinct influenza strains.
117 In Japan, a subset of the samples collected through RIDT are processed for subtype identification,
118 but the size and representativeness of this subset is not sufficient to identify independent clusters
119 and their origin or reconstruct transmission history. Genomic sequence data can bridge this
120 knowledge gap, resulting in a deeper understanding of influenza's antigenic variability in a given
121 setting, and their connections to other parts of the world.

122 In this study, we generated whole-genome sequences on reverse transcription-polymerase
123 chain reaction (RT-PCR) using NPS samples from Kamigoto hospital routinely collected during
124 the 2011/12 and 2012/13 influenza seasons. We made the sequences publicly accessible to improve
125 the pool of available Japan influenza genetic sequences. We used these sequences and the date of
126 collection of the cases to conduct phylogenetic analysis and understand the relationship between
127 Kamigoto strains, mainland Japan strains, and the rest of the world. We assessed whether all cases
128 were grouped in the same cluster or if they were related to independent importations and analyzed
129 the role of importation and local transmission in the island. Finally, we describe the temporal and
130 spatial distribution of the phylogenetic clusters. This analysis shows how NPS samples could be
131 used for genomic surveillance in Japan, improving our understanding of influenza importation risk
132 and spatial spread, and gives insights into influenza spread in rural settings.

133 **Methods**

134 **Study design and setting**

135 The samples used in this study were collected from patients recorded with ILI visiting to the
136 Kamigoto hospital in Kamigoto island, Japan, during the 2011/12 and 2012/13 influenza seasons.
137 Kamigoto Island is located in Nagasaki Prefecture, on the western coast of Japan, with a population
138 of 22,599 inhabitants in 2011.¹⁷ Kamigoto Hospital is the only hospital in the island with all levels
139 of care (primary, secondary, and tertiary care) and is part of the sentinel sites for influenza
140 surveillance in Japan.

141 **Sample collection and whole-genome sequencing**

142 The residual NPS from the RIDTs were temporarily stored at -20°C in the laboratory
143 department of the hospital after being used for the RIDTs. The samples were transported to the
144 Institute of Tropical Medicine at Nagasaki University within a week. The samples were stored in
145 a deep freezer (-80°C) until further processed. Additional sociodemographic and clinical
146 information on the patients was collected from the hospital database.

147 **RNA extraction and influenza virus detection**

148 Viral nucleic acid was extracted directly from the NPS samples using a QIAamp viral RNA
149 mini kit (QIAGEN Inc., Valencia, CA) following the manufacturer's instructions. RNA was eluted
150 to a final volume of 60 µL, aliquoted, and stored at -20°C for immediate use in reverse
151 transcriptase-polymerase chain reaction (RT-PCR) or -80°C for long term storage. Multiplex RT-
152 PCR assays were applied to screen influenza viruses (A and B) and other eleven other respiratory
153 viruses. One Step RT-PCR Kit (QIAGEN Inc., Valencia, CA, USA) was used for RNA viruses,
154 and GoTaq Flexi DNA Polymerase (Promega, San Luis Obispo, CA, USA) and PCR Nucleotide

155 Mix (Promega, San Luis Obispo, CA, USA) were used for DNA viruses. The details of the
156 multiplex PCR assay protocols were described elsewhere.¹⁸

157 **Multi-segment RT-PCR, library preparation and next-generation sequencing**

158 For all RT-PCR-confirmed influenza A positive samples, all 8 segments of RT-PCR-
159 confirmed influenza samples were amplified following the protocols from Zhou, B., et al. (2009)¹⁹
160 for influenza A. Each PCR product was purified again using Ampure XP beads (Beckman Coulter)
161 according to the manufacturer's instructions. The purity was then assessed with Agilent
162 Technology 2100 Bioanalyzer using a High Sensitivity DNA chip and Qubit dsDNA HS Assay
163 Kit (Life Technology). 1 ng of the DNA was used for library preparation (Nextera XT Kit,
164 Illumina) following the manufacturer's instructions (Illumina, CA, USA). The prepared library
165 was sequenced on the MiSeq platform (Illumina) using a V2 2 × 250 bp reagents kit at Nagasaki
166 University.

167 **Next-generation sequencing (NGS) data processing and genome assembly.**

168 A total of 254 samples were available for whole genome sequencing (supplementary figure
169 S-1). The sequencing output was uploaded to the INSaFLU,²⁰ a web-based bioinformatic platform
170 for influenza sequencing analysis. By providing raw sequence data, INSaFLU performs (i) quality
171 check (using FastQC),²¹ and (ii) removal of adapter sequences and low-quality reads (using
172 Trimmomatic)²². Trimmed and filtered sequences of less than 100 bp were discarded in
173 downstream analysis. The sequence reads were mapped to reference sequence
174 *A/H3N2_A_Perth_16_2009*. Consensus for sequences with at least 10-fold coverage was then
175 generated. The INSAFLU also performed the genome annotation (using Prokka)²³.

176 **Phylogenetic analysis**

177 To contextualize the Kamigoto samples within the landscape of viruses circulating in Japan
178 and globally during the 2011/12 and 2012/2013 influenza seasons, we downloaded A/H3N2
179 influenza sequences from GISAID (<https://www.gisaid.org>) sampled between 1st January 2011,
180 and 31st December 2013 for each individual segment (PB2, PB1, PA, HA, NP, NA, MP and NS)
181 (as of 1st January 2023). For each individual segment, sequence alignment was performed with
182 MAFFT version 7²³, and the alignments were visualized and manually edited in AliView.²⁴

183 Phylogenetic trees of each segment data were estimated using the maximum likelihood
184 (ML) procedure in IQTREE v2.0.7,²⁵ under the best-fitting model of nucleotide substitution
185 TVM+F+I+R5, as determined by the ModelFinder option implemented in software. Branch
186 supports were estimated by standard non-parametric bootstrap analysis with 100 replicates. Clades
187 were labelled following WHO nomenclature. TempEst v1.5.3²⁶ was used to assess the presence of
188 a molecular clock signal in the analyzed data, and linear regression of root-to-tip genetic distances
189 against sampling dates was reconstructed (supplementary figure S-5). Outlier sequences that
190 significantly deviated from the mean likely contain sequencing artifacts and were excluded from
191 further analysis. We performed time-scaled phylogenies of final HA segment and root-to-tip linear
192 regressions using TreeTime²⁷ based on the maximum likelihood (ML) trees generated by IQTREE.
193 The spatial distribution of the sequences included in this analysis was: Africa (n=39), Asia (n=180,
194 including 90 sequences from Japan), Europe (n= 57), North America (n=365), Oceania (n=111),
195 and South America (n=82).

196 We also downloaded all publicly available full-length sequences from Japan for all eight
197 influenza segments from the GISAID³² (n=88, as of April 2020). All eight influenza A(H3N2)
198 coding sequences in the sequences downloaded from Japan and Kamigoto were concatenated into
199 an alignment of 13,136 nucleotides in the order of the segment number (PB2-PB1-PA-HA-NP-

200 NA-M-NS). The concatenated sequences were aligned using MAFFT version 7²³ and the
201 alignments were visualized and manually edited in AliView.²⁴ Maximum likelihood phylogenetic
202 trees were reconstructed for the whole genome sequences of Japan and Kamigoto strains, as
203 mentioned above.

204 **Data availability / Accession number(s).**

205 All consensus sequences we generated have been submitted to the GISAID database. The
206 details of isolate IDs and assigned accession numbers are listed in the supplementary data
207 (Supplementary Table-1).

208 **Results**

209 **Whole genome sequencing of A/H3N2 samples**

210 Figure 1 displays the epidemiological curve aggregated by reported RIDT positive cases
211 and sequenced cases. From 538 flu samples collected across Kamigoto, we generated 254 whole
212 genome sequences (WGS). Of the 254 samples successfully sequenced, 229 were characterized
213 as A(H3N2) (29 samples from the 2011/12 season and 200 from the 2012/13 season), while the
214 remaining samples, characterized as influenza B, were not included in this study. Out of the 229
215 A(H3N2) WGS samples, 178 samples achieved 100% of sizes covered by at least 1-fold (see
216 Supplementary Figure-S1 for a description of the sample selection process). The overview of the
217 depth and length sequence coverage for each segment for all samples is provided in
218 Supplementary Figure S-2.

219 The maximum likelihood phylogeny of WGS of A/H3N2 from Kamigoto island
220 (Supplementary Figure S-3) showed that Kamigoto sequences grouped closely together based on
221 the year they were collected. No sequence from the 2011/12 season grouped with the 2012/13
222 sequences.

223 **Phylogenetic analysis of sequences**

224 We assessed how the HA segments of the sampled cases in Kamigoto compared to publicly
225 available sequences from GISAID sampled globally between January 2011 and December 2013
226 by inferring a phylogenetic tree using the hemagglutinin (HA) sequences (Figure 2, Supplementary
227 Figure S-4, S-5). As in the WGS phylogenetic tree, Kamigoto sequences grouped together based
228 on the year they were collected. Within the seasons, smaller and closely related sub-groups were
229 identified: The maximum likelihood phylogenetic analysis of the HA segment for Kamigoto
230 strains revealed the prevalent circulation of clade 3C.2 on the island, with a few Kamigoto
231 sequences (20) from 2012/13 classified under 3C.3a (Supplementary Figure S-6).

232 Most Kamigoto sequences were clustered clustered in six independent transmission groups
233 (Figure 2), with sequences in Group 5 further classified as 5A (28 sequences) and 5B (81
234 sequences), as these sequences are closer than other groups, but their date of coalescence is too far
235 from their onset date of the cases, suggesting different introductions (supplementary Figure S-4).
236 The phylogeny identified that the Kamigoto sequences were closely related to strains from
237 mainland Japan, and local sequences in each group were observed to be closely clustered with
238 strains from mainland Japan. The biggest group (Group 5) consists of 109 local sequences and 21
239 non-local sequences from mainland Japan (n=13), North America (n=6), Europe (n=1), and Asia
240 (n=1). The second biggest group (Group 1) was from the 2011/12 season, which consisted of 27
241 local sequences and 33 non-local sequences from mainland Japan (n=10), North America (n=12),
242 Europe (n=3), Oceania (n=3), and Asia (n=5). The others groups (group 2, 3 and 4) consists of 6,
243 10 and 11 kamigoto sequences respectively, closely related to strains from mainland Japan. The
244 clustering of a large number of sequences on the phylogeny suggested that the majority of the
245 cases sequenced in this study are likely to be part of different local transmission chains. A few

246 Kamigoto sequences (n=7) were isolated, without clustering with any other Kamigoto sequences.
247 This suggested the presence of independent introductions that either did not cause onward
248 transmission within the island or, alternatively, were not sampled in this study.

249 We also constructed phylogenetic trees of the other individual segments of Kamigoto
250 strains (PB2, PB1, PA, NP, NA, MP, and NS), with publicly available strains from Japan and
251 global sequences from GISAID as of the December 1, 2022, submission date (Supplementary
252 Figures S-7 to S-14). We separately performed the phylogenetic analysis for each segment to avoid
253 the reassortment bias between the segments.

254 **Epidemiological description of the transmission clusters**

255 Kamigoto sequences collected in 2012/13 clustered in five groups, which co-circulated
256 during the same period, mainly between February and April 2013 (Figure 3). This suggested that
257 different importation events initiated the transmission and further drove local transmission. We
258 then explored the geographic distribution of the Kamigoto strains within these groups (Figure 4).
259 Group 3, Group 4 and Group 5a had overlapping locations of the sequenced cases, while Group 2
260 was geographically isolated. The biggest local Kamigoto sequence group 5B was found to be
261 distributed across the island (Figure 4).

262 We further analyzed the biggest transmission group of Kamigoto sequences (Group 5A
263 and 5B) to explore the spatio-temporal distribution patterns (Figure 5, Supplementary Figure S-
264 15). The spatio-temporal assessment of the clusters showed the virus spreading from populous
265 districts to less populous ones and between busier or more populous districts, such as Aogata-go
266 (an urban area of the island) and Tainoura-go and Arikawa-go (port areas connecting to mainland
267 Japan). The earliest sequenced case of Group 5A was reported on 18th January 2013. The number
268 of cases increased in subsequent weeks in the same districts and further spread out to other districts

269 in February and March. The earliest sequenced case of Group 5B was reported in 24th January
270 2013 and the highest number of cases from this cluster was reported in February 2013. The
271 outbreaks slowly declined from March onwards in both groups. The last sequenced case was
272 reported on the 8th March 2013 in Group 5A and 5th May 2013 in Group. RT-PCR confirmed
273 Influenza positive surveillance data (Figure 1) also showed February to April as peak of the season.
274 A similar temporospatial distribution was also observed in local sequences cluster in group 1
275 (Supplementary Figure S-16).

276 **Discussion**

277 In this study, we conducted a retrospective genomic characterization of seasonal influenza
278 A/H3N2 viruses collected from Kamigoto island, Japan, during 2011/12 and 2012/13 influenza
279 seasons. We extracted RNA from NPS samples and successfully sequenced and generated whole
280 genome sequences of 229 A/H3N2 samples: 29 from the 2011/12 season and 200 from the 2012/13
281 season. This contribution is particularly valuable, as there are limited whole genome sequences
282 (WGS) available from Japan for that time period: 88 sequences between 1968 and 2020, but less
283 than 10 in 2011/12 and zero in 2012/13 influenza season (as of March 2022). Given the increasing
284 importance of genomic surveillance in monitoring and controlling influenza outbreaks, this study
285 provides crucial data that enhances our understanding of the virus's evolution and spread within
286 Japan during these seasons.

287 Using the time-resolved phylogeny, we identified multiple independent importations of
288 A(H3N2) viruses into the Kamigoto island community during the study period, some of these
289 importations led to long-lasting local transmission. Kamigoto is a semi-isolated island with only
290 two ports linking it to mainland Japan. The Kamigoto strains were closely related to strains from
291 mainland Japan. This contrasts with findings from studies conducted in Kilifi County, Kenya²⁴
292 and Basel city in Switzerland²⁵. In those studies, strains from Kenya and Basel displayed close
293 genetic relations to global strains, reflecting the high connectivity of these urban centers with other
294 parts of the world. Such differences highlight the significance of understanding influenza dynamics
295 at the local or rural level since transmission patterns can vary based on geographical factors.
296 Interestingly, our study revealed a few potential international importation events where the
297 Kamigoto strains closely resembled those from outside Japan in the phylogenetic analysis. This
298 underscores the importance of regularly testing visitors and returning residents, especially during

299 influenza. Low density of sequence numbers publicly available from the southern part of Japan
300 during the same period may also be another reason explaining the close relatedness of the
301 Kamigoto strains to outside Japan.

302 We found Kamigoto strains clustered in six different groups of sequences in the
303 phylogenetic tree. Notably, Kamigoto sequence clusters in 2012/13 were co-circulating during the
304 same period (between February and April 2013), indicating that different importation events fueled
305 the transmission of influenza in each group. In absence of genomic surveillance, cases circulating
306 simultaneously may be inaccurately classified into the same cluster using only epidemiological
307 data, which would underestimate the importation risks, and potentially overestimates the risk of
308 local outbreak following importations. Integrating sequence data with epidemiological information
309 provided a more accurate geographical distribution of cases in each group. We identified five
310 sequences that did not closely relate to any other sequences in our study that may represent
311 independent introductions that did not lead to further transmission. It's possible that subsequent
312 transmission for these outliers either didn't occur or cases arising from them weren't available for
313 sequencing to be included in this study. In this study, we were able to sequence only 254 samples
314 out of 538 RT-PCR confirmed influenza cases reported (Figure 1).

315 The largest cluster of local sequences (Group 5B) contained 81 sequences, all from
316 Kamigoto, suggesting that they all belonged to the same local transmission chain. The second
317 largest group (Group 5A) included 28 Kamigoto sequences and was found to be clustered with
318 sequences from mainland Japan (n=9) and other parts of the world. Kamigoto sequences in Group
319 5A and 5B identified on the phylogeny suggested repeated importations of similar strains,
320 potentially circulating simultaneously outside Kamigoto, primarily from mainland Japan. This
321 could be due to concurrent transmission in mainland Japan and Kamigoto, with repeated

322 introductions of the same strain. The finding of the spatial distribution of the sequences in Group
323 5B align with our earlier epidemiological study,² which identified districts with connections
324 outside the island and high population density as the main drivers of influenza transmission
325 patterns at the local community level.

326 Although the study used samples that were collected more than 9 years ago, a good viral
327 yield was retrieved by direct RNA extraction from the samples. This is a benefit of sequencing
328 directly from the samples (rather than passaging or isolation) and storage with optimal temperature
329 for long duration. Only few sequences were available from the Kyuushuu regions (where
330 Kamigoto is located) prior to this project. The sequences collected, shared, and analysed in this
331 paper therefore greatly improve our understanding and knowledge of influenza phylogeny in Japan.
332 In Japan, RIDT was widely used during the influenza season, and the residual samples from NPS
333 can be utilized for genomic surveillance to describe the genetic diversity of circulating Influenza
334 A strains. This nationwide data provides a valuable resource for understanding viral evolution and
335 informing public health strategies.

336 The sequenced samples were dependent on the sample viral load and cDNA concentration
337 to pass the sequencing quality and thus it limits the representativeness of the data in reconstruction
338 of the influenza transmission. However, the sequenced samples were roughly proportional to the
339 reported RIDT-confirmed influenza cases. The number of sequences generated in this study were
340 relatively low compared to the reported number of influenza cases in that period (1,009 and 1,053
341 RIDT cases were reported in 2011/12 and 2012/13, Supplementary Figure 1). An increased
342 sequencing frequency may capture more introduction events and clusters. Finally, the study was
343 part of the surveillance system, and thus data were collected during the influenzas season (October-

344 June) rather than the whole year. This limits our study's assessment of year-round influenza
345 transmission patterns within the islands.

346 **Conclusion**

347 This analysis helps to better understand the transmission patterns of seasonal influenza
348 because it was conducted in rural setting such as Kamigoto island with a semi-isolated population
349 in Japan. Influenza A(H3N2) virus epidemics in Kamigoto island were marked by multiple
350 introductions and fueled by local transmission. A closer examination of local transmission through
351 genomic data indicates concurrent independent introduction events and local proliferation. These
352 might be misinterpreted as part of the same cluster without sequencing data. However, the results
353 of this study are based on a two-years analysis of influenza sequences from the island, thus
354 repeated analyzes for different influenza seasons and geographic locations will help us better
355 understand detailed transmission patterns.

356 **Authors contributions**

357 **Su Myat Han;** Conceptualization, Data curation, Formal Analysis, Writing – original draft,
358 Visualization, Writing – review & editing

359 **Teiichiro Shiino;** Data curation, Software, Validation, Visualization, Writing – review & editing

360 **Shingo Masuda, Takahiro Yasaka, Satoshi Kanda, Kazuhiri Komori, Nobuo Saito1;**
361 Resources, Investigation

362 **Yuki Furuse;** Methodology, Writing – review & editing

363 **Yoshiano Kubo;** Validation, Visualization

364 **Chris Smith;** Funding acquisition, Writing – review & editing

365 **Akira Endo;** Conceptualization, Writing – review & editing

366 **Alexis Robert**; Formal Analysis, Methodology, Supervision, Validation, Writing – review &
367 editing

368 **Marc Baguelin and Koya Ariyoshi**; Project administration, Funding acquisition, Supervision,
369 Resources, Writing – review & editing

370 **Ethics**

371 The research was approved by the institutional review boards of Kamigoto Hospital,
372 Nagasaki University Research Ethics Committee (reference number 200619236), and the London
373 School of Hygiene and Tropical Medicine Research Ethics Committee (reference number 26706).
374 Both Nagasaki University and London School of Hygiene and Tropical Medicine granted waivers
375 for obtaining informed consent due to the nature of this retrospective study and the preserved
376 anonymity of patients.

377 **Supplementary data**

378 Supplementary data are available at online.

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389 **Conflict of interest**

390 NA

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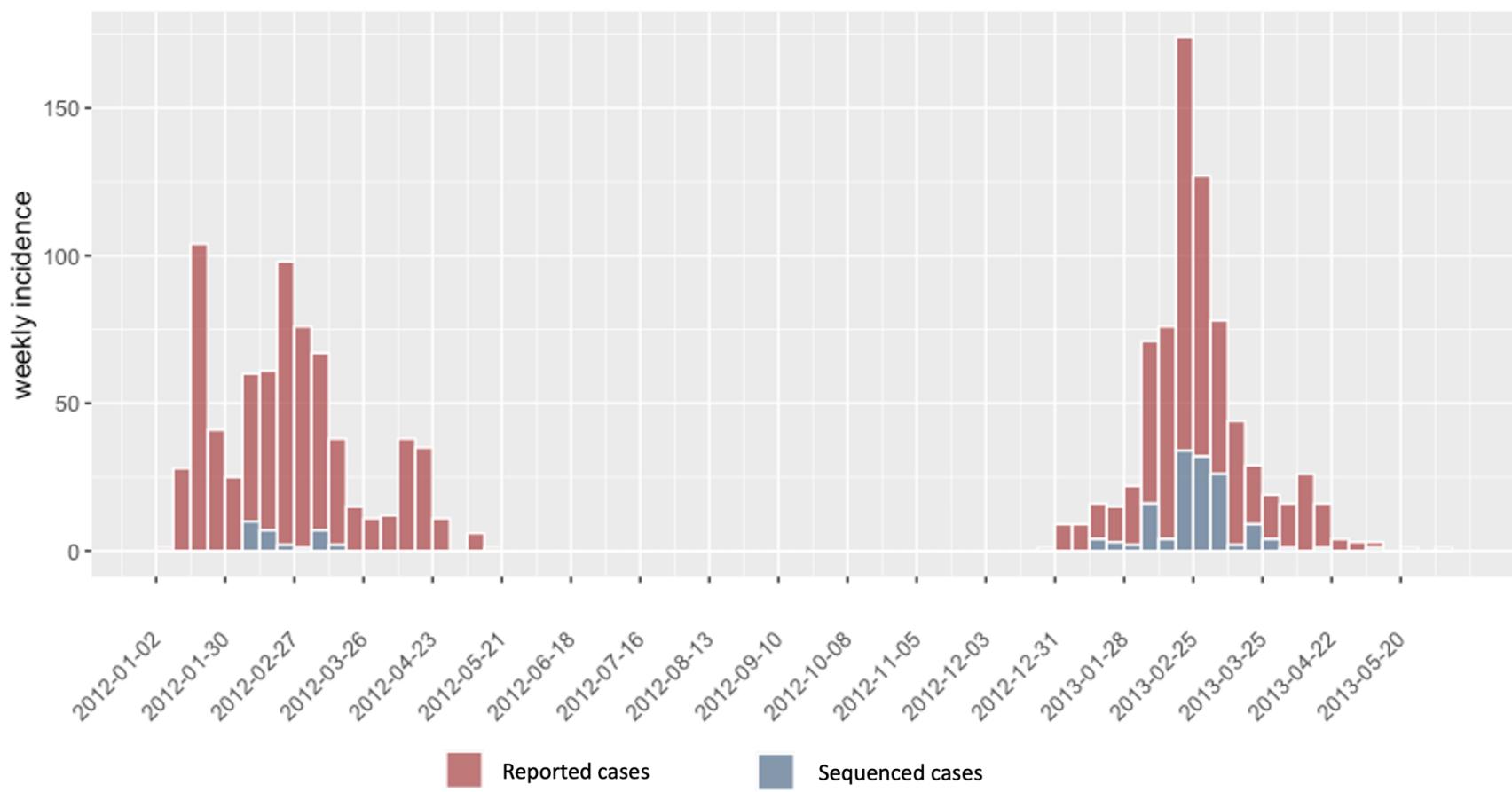
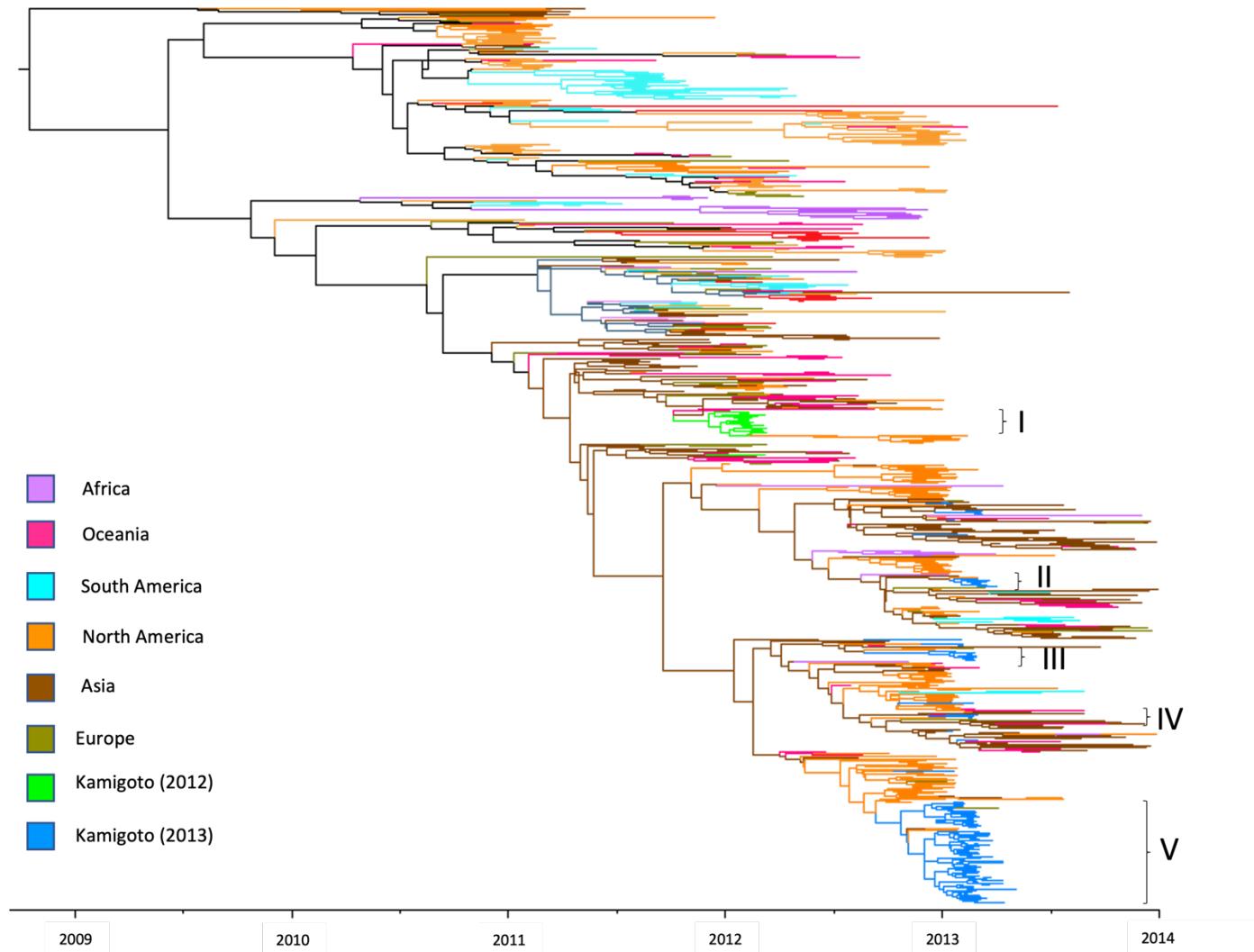
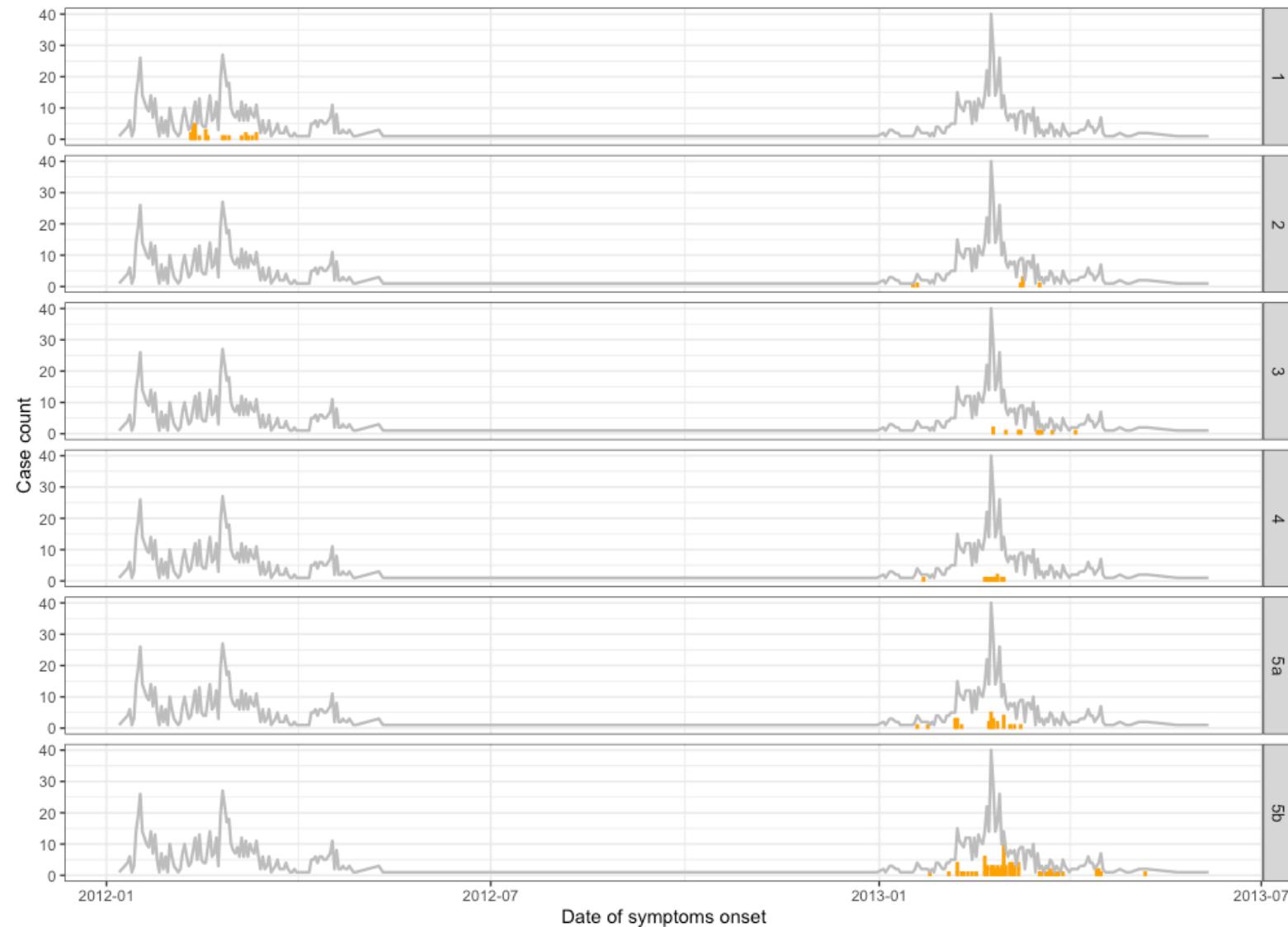


Figure 1: Epidemic curve of the daily number of rapid influenza diagnostic test positive cases reported by the Hospital influenza surveillance system (red), and whole genome sequenced (WGS) cases (blue) during the 2011/12 and 2012/2013 epidemic seasons.

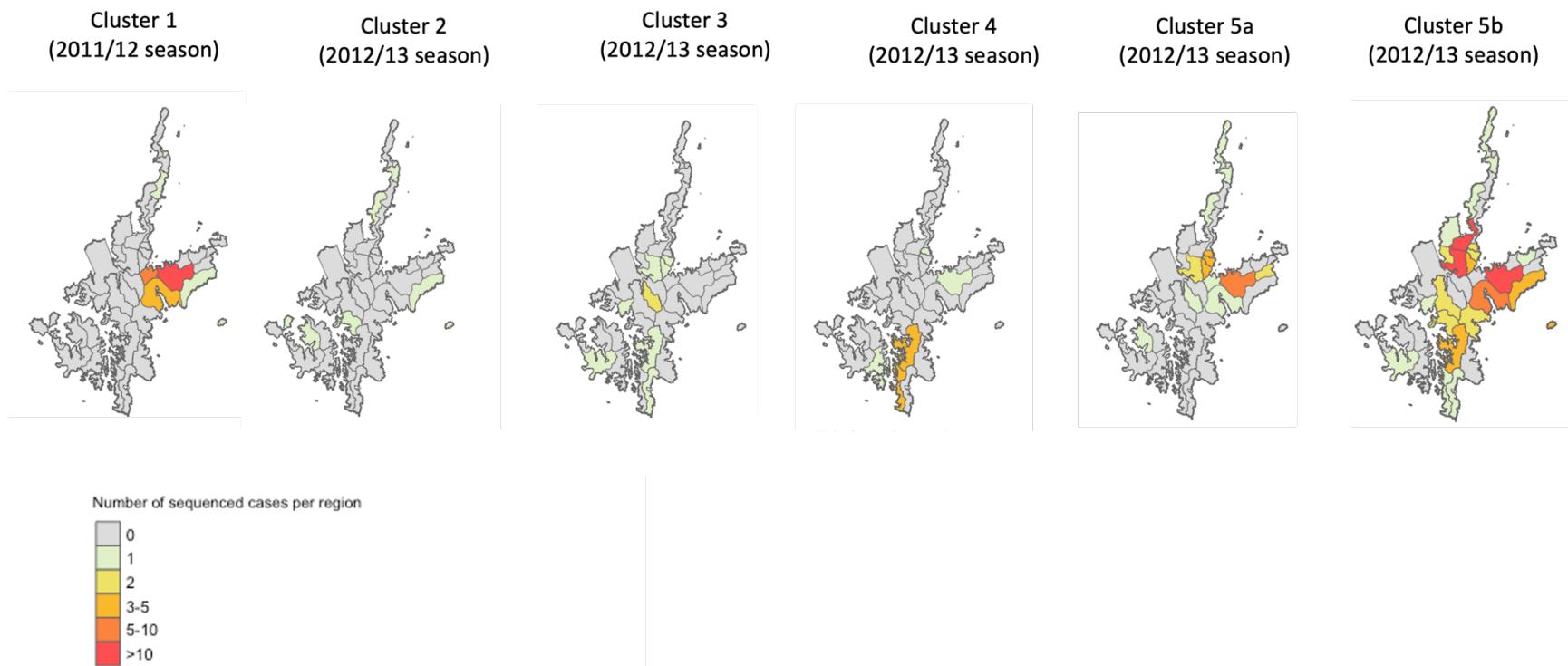


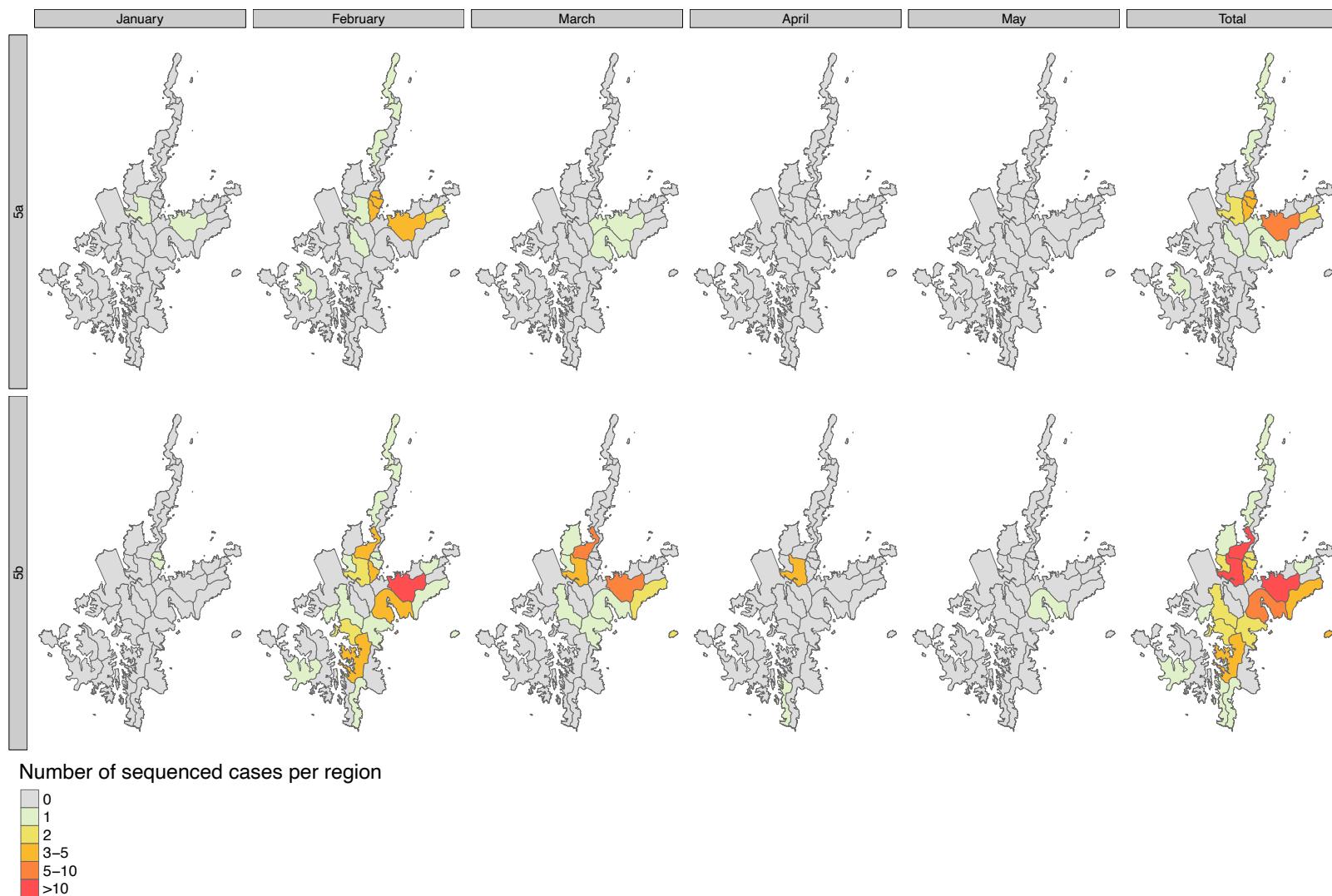
1
2 Figure 2: Time-scaled Maximum-likelihood phylogenetic trees of HA coding sequences for A(H3N2) viruses circulating in Kamigoto
3 and comparing sequences from strains isolated in Japan and other parts of the world from GISAID collected between 2011 and 2013.
4 (as of 1st December 2022 as submission date). All full-length HA coding gene sequences were downloaded from GISAID, with
5 duplicate sequences removed. Colored by geographical region.



6

7 Figure 3: Clusters distribution from time-resolved Phylogenetic tree of HA segments of A(H3N2) viruses from Kamigoto island, Japan





13
14

Figure 5: Spatio-temporal distribution of the group 5A and 5B

5.4 SUPPLEMENTARY

Phylogenetic study of local patterns influenza A(H3N2) virus transmission in a semi-isolated population in a remote island in Japan between 2011-2013

Su Myat Han^{1,2,3}, Teiichiro Shiino^{4,5}, Shingo Masuda^{1,6}, Yuki Furuse⁷, Takahiro Yasaka⁶, Satoshi Kanda⁶, Kazuhiri Komori⁶, Nobuo Saito^{1,8}, Yoshiano Kubo⁹, Chris Smith^{1,10}, Akira Endo^{1,2,11,12}, Alexis Robert^{1,2,11*}, Marc Baguelin^{2,11,13*}, Koya Ariyoshi^{1,9*}

1. School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan
2. Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom
3. National Center for Infectious Disease, Singapore
4. Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan
5. AIDS Research Center, National Institute of Infectious Diseases, Tokyo, Japan
6. Department of Internal Medicine, Kamigoto Hospital, Kamigoto, Japan
7. Department of Medical Virology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
8. Department of Microbiology, Faculty of Medicine, Oita University, Yufu, Japan
9. Department of Clinical Medicine, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan
10. Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK
11. Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, Keppel Street, London, UK
12. Saw Swee Hock School of Public Health, National University of Singapore
13. MRC Centre for Global Infectious Disease Analysis; and the Abdul Latif Jameel Institute for Disease

* These authors are joint last authors

Table S-1: GISAID accession number of sequences produced in this stud.

Isolate Name	Isolate Id	PB2	PB1	PA	HA	NP	NA seg	MP	NS
A/Kamigoto/1447/2013	EPI ISL 18002728	NA	EPI2635352	EPI2635353	EPI2635354	EPI2635355	EPI2635356	EPI2635357	EPI2635358
A/Kamigoto/1454/2013	EPI ISL 18002450	EPI2635343	EPI2635344	EPI2635345	EPI2635346	EPI2635347	EPI2635348	EPI2635349	EPI2635350
A/Kamigoto/1461/2013	EPI ISL 18002449	EPI2635335	EPI2635336	NA	EPI2635338	EPI2635339	EPI2635340	EPI2635341	EPI2635342
A/Kamigoto/1444/2013	EPI ISL 18002434	EPI2635327	EPI2635328	EPI2635329	EPI2635330	EPI2635331	EPI2635332	EPI2635333	EPI2635334
A/Kamigoto/1467/2013	EPI ISL 18002433	EPI2635319	EPI2635320	EPI2635321	EPI2635322	EPI2635323	EPI2635324	EPI2635325	EPI2635326
A/Kamigoto/1442/2013	EPI ISL 18002432	EPI2635311	EPI2635312	EPI2635313	EPI2635314	EPI2635315	EPI2635316	EPI2635317	EPI2635318
A/Kamigoto/1476/2013	EPI ISL 18001909	EPI2635303	EPI2635304	EPI2635305	EPI2635306	EPI2635307	EPI2635308	EPI2635309	EPI2635310
A/Kamigoto/1480/2013	EPI ISL 18001908	EPI2635295	EPI2635296	EPI2635297	EPI2635298	EPI2635299	EPI2635300	EPI2635301	EPI2635302
A/Kamigoto/1437/2013	EPI ISL 18001895	EPI2635239	EPI2635240	EPI2635241	EPI2635242	EPI2635253	EPI2635265	EPI2635278	EPI2635283
A/Kamigoto/1433/2013	EPI ISL 18001894	EPI2635231	EPI2635232	EPI2635233	EPI2635234	EPI2635235	EPI2635236	EPI2635237	EPI2635238
A/Kamigoto/1432/2013	EPI ISL 18001808	EPI2635135	EPI2635136	EPI2635146	EPI2635161	EPI2635174	EPI2635186	EPI2635197	EPI2635211
A/Kamigoto/1431/2013	EPI ISL 18001804	EPI2635127	EPI2635128	EPI2635129	EPI2635130	EPI2635131	EPI2635132	EPI2635133	EPI2635134
A/Kamigoto/1420/2013	EPI ISL 18001803	EPI2635119	EPI2635120	EPI2635121	EPI2635122	EPI2635123	EPI2635124	EPI2635125	EPI2635126
A/Kamigoto/1482/2013	EPI ISL 18001802	EPI2635111	EPI2635112	EPI2635113	EPI2635114	EPI2635115	EPI2635116	EPI2635117	EPI2635118
A/Kamigoto/1491/2013	EPI ISL 18001801	EPI2635076	EPI2635094	EPI2635105	EPI2635106	EPI2635107	EPI2635108	EPI2635109	EPI2635110
A/Kamigoto/1494/2013	EPI ISL 18001747	EPI2634970	EPI2634971	EPI2634972	EPI2634973	EPI2634974	EPI2634975	EPI2634976	EPI2634977
A/Kamigoto/1498/2013	EPI ISL 18001746	EPI2634962	EPI2634963	EPI2634964	EPI2634965	EPI2634966	EPI2634967	EPI2634968	EPI2634969
A/Kamigoto/1502/2013	EPI ISL 18001715	EPI2634954	EPI2634955	EPI2634956	EPI2634957	EPI2634958	EPI2634959	EPI2634960	EPI2634961
A/Kamigoto/1512/2013	EPI ISL 18001714	EPI2634946	EPI2634947	EPI2634948	EPI2634949	EPI2634950	EPI2634951	EPI2634952	EPI2634953
A/Kamigoto/1542/2013	EPI ISL 18001713	EPI2634937	EPI2634938	EPI2634939	EPI2634940	EPI2634941	EPI2634942	EPI2634943	EPI2634944
A/Kamigoto/1544/2013	EPI ISL 18001707	EPI2634922	EPI2634923	EPI2634924	EPI2634925	EPI2634926	EPI2634927	EPI2634928	EPI2634929
A/Kamigoto/1547/2013	EPI ISL 18001706	EPI2634865	EPI2634887	EPI2634908	EPI2634917	EPI2634918	EPI2634919	EPI2634920	EPI2634921
A/Kamigoto/1553/2013	EPI ISL 18001705	EPI2634844	EPI2634845	EPI2634846	EPI2634847	EPI2634848	EPI2634849	EPI2634850	EPI2634851
A/Kamigoto/1588/2013	EPI ISL 18001704	EPI2634835	EPI2634837	EPI2634838	EPI2634839	EPI2634840	EPI2634841	EPI2634842	EPI2634843
A/Kamigoto/1592/2013	EPI ISL 18001703	EPI2634778	EPI2634798	EPI2634819	EPI2634830	EPI2634831	EPI2634832	EPI2634833	EPI2634834
A/Kamigoto/1596/2013	EPI ISL 18001702	EPI2634504	EPI2634523	EPI2634543	EPI2634563	EPI2634578	EPI2634600	EPI2634618	EPI2634641

A/Kamigoto/1598/2013	EPI ISL 18001701	EPI2634425	EPI2634426	EPI2634427	EPI2634428	EPI2634429	EPI2634430	EPI2634431	EPI2634432
A/Kamigoto/1601/2013	EPI ISL 18001686	EPI2634336	EPI2634350	EPI2634362	EPI2634374	EPI2634387	EPI2634401	EPI2634412	EPI2634415
A/Kamigoto/2146/2013	EPI ISL 18000339	NA	NA	NA	EPI2632321	EPI2632322	EPI2632323	EPI2632324	EPI2632325
A/Kamigoto/2164/2013	EPI ISL 18000338	NA	EPI2632314	EPI2632315	EPI2632316	EPI2632317	EPI2632318	EPI2632319	EPI2632320
A/Kamigoto/2166/2013	EPI ISL 18000336	NA	NA	NA	EPI2632301	EPI2632302	EPI2632304	EPI2632306	EPI2632308
A/Kamigoto/1419/2013	EPI ISL 17786021	NA	NA	NA	EPI2589364	EPI2589365	EPI2589366	EPI2589367	EPI2589368
A/Kamigoto/1409/2013	EPI ISL 17785996	EPI2589356	EPI2589357	EPI2589358	EPI2589359	EPI2589360	EPI2589361	EPI2589362	EPI2589363
A/Kamigoto/1407/2013	EPI ISL 17785995	EPI2589348	EPI2589349	EPI2589350	EPI2589351	EPI2589352	EPI2589353	EPI2589354	EPI2589355
A/Kamigoto/1399/2013	EPI ISL 17785743	EPI2589340	NA	NA	EPI2589343	EPI2589344	EPI2589345	EPI2589346	EPI2589347
A/Kamigoto/1397/2013	EPI ISL 17785739	EPI2589324	EPI2589325	NA	EPI2589327	EPI2589328	EPI2589329	EPI2589330	EPI2589331
A/Kamigoto/1396/2013	EPI ISL 17785738	EPI2589316	EPI2589317	EPI2589318	EPI2589319	EPI2589320	EPI2589321	EPI2589322	EPI2589323
A/Kamigoto/1389/2013	EPI ISL 17785724	EPI2589308	EPI2589309	EPI2589310	EPI2589311	EPI2589312	EPI2589313	EPI2589314	EPI2589315
A/Kamigoto/1386/2013	EPI ISL 17785723	EPI2589228	EPI2589229	EPI2589230	EPI2589231	EPI2589232	EPI2589233	EPI2589234	EPI2589235
A/Kamigoto/1385/2013	EPI ISL 17785722	EPI2589220	EPI2589221	EPI2589222	EPI2589223	EPI2589224	EPI2589225	EPI2589226	EPI2589227
A/Kamigoto/1382/2013	EPI ISL 17785719	EPI2589212	EPI2589213	EPI2589214	EPI2589215	EPI2589216	EPI2589217	EPI2589218	EPI2589219
A/Kamigoto/1381/2013	EPI ISL 17785716	EPI2589204	EPI2589205	EPI2589206	EPI2589207	EPI2589208	EPI2589209	EPI2589210	EPI2589211
A/Kamigoto/1378/2013	EPI ISL 17785715	EPI2589196	EPI2589197	EPI2589198	EPI2589199	EPI2589200	EPI2589201	EPI2589202	EPI2589203
A/Kamigoto/1376/2013	EPI ISL 17785627	EPI2588519	NA	EPI2588521	EPI2588522	EPI2588523	EPI2588524	NA	EPI2588525
A/Kamigoto/1375/2013	EPI ISL 17785624	EPI2588511	EPI2588512	EPI2588513	EPI2588514	EPI2588515	EPI2588516	EPI2588517	EPI2588518
A/Kamigoto/1373/2013	EPI ISL 17785619	EPI2588503	EPI2588504	EPI2588505	EPI2588506	EPI2588507	EPI2588508	EPI2588509	EPI2588510
A/Kamigoto/1370/2013	EPI ISL 17785617	EPI2588495	EPI2588496	EPI2588497	EPI2588498	EPI2588499	EPI2588500	EPI2588501	EPI2588502
A/Kamigoto/1369/2013	EPI ISL 17785616	EPI2588487	EPI2588488	EPI2588489	EPI2588490	EPI2588491	EPI2588492	EPI2588493	EPI2588494
A/Kamigoto/1368/2013	EPI ISL 17785615	EPI2588479	EPI2588480	EPI2588481	EPI2588482	EPI2588483	EPI2588484	EPI2588485	EPI2588486
A/Kamigoto/1367/2013	EPI ISL 17785614	EPI2588471	EPI2588472	EPI2588473	EPI2588474	EPI2588475	EPI2588476	EPI2588477	EPI2588478
A/Kamigoto/1360/2013	EPI ISL 17785613	NA	NA	EPI2588465	EPI2588466	EPI2588467	EPI2588468	EPI2588469	EPI2588470
A/Kamigoto/1356/2013	EPI ISL 17761517	NA	NA	NA	EPI2582636	EPI2582637	EPI2582634	EPI2582639	EPI2582640
A/Kamigoto/1317/2013	EPI ISL 17761516	EPI2582626	EPI2582627	EPI2582628	EPI2582629	EPI2582630	EPI2582631	EPI2582632	EPI2582633
A/Kamigoto/1301/2013	EPI ISL 17739156	EPI2580996	EPI2580997	EPI2580998	EPI2580999	EPI2581000	EPI2581001	EPI2581002	EPI2581003

A/Kamigoto/1262/2013	EPI ISL 17738971	EPI2580988	EPI2580989	NA	EPI2580991	EPI2580992	EPI2580993	EPI2580994	EPI2580995
A/Kamigoto/1248/2013	EPI ISL 17738944	EPI2580980	EPI2580981	EPI2580982	EPI2580983	EPI2580984	EPI2580985	EPI2580986	EPI2580987
A/Kamigoto/1247/2013	EPI ISL 17730095	NA	NA	NA	EPI2579590	EPI2579591	EPI2579592	EPI2579593	EPI2579594
A/Kamigoto/1244/2013	EPI ISL 17730092	EPI2579582	EPI2579583	EPI2579584	EPI2579585	EPI2579586	EPI2579587	EPI2579588	EPI2579589
A/Kamigoto/1240/2013	EPI ISL 17730088	EPI2579574	EPI2579575	EPI2579576	EPI2579577	EPI2579578	EPI2579579	EPI2579580	EPI2579581
A/Kamigoto/1239/2013	EPI ISL 17730086	EPI2579566	EPI2579567	EPI2579568	EPI2579569	EPI2579570	EPI2579571	EPI2579572	EPI2579573
A/Kamigoto/1236/2013	EPI ISL 17730085	EPI2579558	EPI2579559	EPI2579560	EPI2579561	EPI2579562	EPI2579563	EPI2579564	EPI2579565
A/Kamigoto/1215/2013	EPI ISL 17730082	EPI2579542	EPI2579543	EPI2579544	EPI2579545	EPI2579546	EPI2579547	EPI2579548	EPI2579549
A/Kamigoto/1210/2013	EPI ISL 17730079	EPI2579534	EPI2579535	EPI2579536	EPI2579537	EPI2579538	EPI2579539	EPI2579540	EPI2579541
A/Kamigoto/1182/2013	EPI ISL 17730075	EPI2579526	EPI2579527	EPI2579528	EPI2579529	EPI2579530	EPI2579531	EPI2579532	EPI2579533
A/Kamigoto/1180/2013	EPI ISL 17730072	EPI2579517	EPI2579518	EPI2579519	EPI2579520	EPI2579521	EPI2579523	EPI2579524	EPI2579525
A/Kamigoto/1177/2013	EPI ISL 17730069	EPI2579508	EPI2579509	EPI2579511	EPI2579512	EPI2579513	EPI2579514	EPI2579515	EPI2579516
A/Kamigoto/1172/2013	EPI ISL 17730068	EPI2579500	EPI2579501	EPI2579502	EPI2579503	EPI2579504	EPI2579505	EPI2579506	EPI2579507
A/Kamigoto/1169/2013	EPI ISL 17730067	EPI2579492	EPI2579493	EPI2579494	EPI2579495	EPI2579496	EPI2579497	EPI2579498	EPI2579499
A/Kamigoto/1164/2013	EPI ISL 17730066	EPI2579484	EPI2579485	EPI2579486	EPI2579487	EPI2579488	EPI2579489	EPI2579490	EPI2579491
A/Kamigoto/1162/2013	EPI ISL 17730065	EPI2579476	EPI2579477	EPI2579478	EPI2579479	EPI2579480	EPI2579481	EPI2579482	EPI2579483
A/Kamigoto/1161/2013	EPI ISL 17730047	EPI2579468	EPI2579469	EPI2579470	EPI2579471	EPI2579472	EPI2579473	EPI2579474	EPI2579475
A/Kamigoto/1159/2013	EPI ISL 17730041	EPI2579461	NA	EPI2579462	EPI2579463	EPI2579464	EPI2579465	EPI2579466	EPI2579467
A/Kamigoto/1156/2013	EPI ISL 17726035	EPI2579164	EPI2579165	EPI2579166	EPI2579167	EPI2579168	EPI2579169	EPI2579170	EPI2579171
A/Kamigoto/1060/2013	EPI ISL 17692112	EPI2563156	EPI2563157	EPI2563158	EPI2563159	EPI2563160	EPI2563161	EPI2563162	EPI2563163
A/Kamigoto/1052/2013	EPI ISL 17692053	EPI2563148	EPI2563149	EPI2563150	EPI2563151	EPI2563152	EPI2563153	EPI2563154	EPI2563155
A/Kamigoto/1050/2013	EPI ISL 17692052	EPI2563140	EPI2563141	EPI2563142	EPI2563143	EPI2563144	EPI2563145	EPI2563146	EPI2563147
A/Kamigoto/1038/2013	EPI ISL 17692051	EPI2563132	EPI2563133	EPI2563134	EPI2563135	EPI2563136	EPI2563137	EPI2563138	EPI2563139
A/Kamigoto/1036/2013	EPI ISL 17692004	EPI2563032	EPI2563033	EPI2563034	EPI2563035	EPI2563036	EPI2563037	EPI2563038	EPI2563039
A/Kamigoto/1035/2013	EPI ISL 17691998	EPI2563024	EPI2563025	EPI2563026	EPI2563027	EPI2563028	EPI2563029	EPI2563030	EPI2563031
A/Kamigoto/1026/2013	EPI ISL 17691980	EPI2563016	EPI2563017	EPI2563018	EPI2563019	EPI2563020	EPI2563021	EPI2563022	EPI2563023
A/Kamigoto/1020/2013	EPI ISL 17691968	EPI2563001	EPI2563004	EPI2563006	EPI2563008	EPI2563009	EPI2563011	EPI2563012	EPI2563014
A/Kamigoto/1006/2013	EPI ISL 17691966	EPI2562992	EPI2562993	EPI2562994	EPI2562995	EPI2562996	EPI2562997	EPI2562998	EPI2562999

A/Kamigoto/994/2013	EPI ISL 17691965	EPI2562984	EPI2562985	EPI2562986	EPI2562987	EPI2562988	EPI2562989	EPI2562990	EPI2562991
A/Kamigoto/992/2013	EPI ISL 17689263	EPI2562656	EPI2562657	EPI2562658	EPI2562659	EPI2562660	EPI2562661	EPI2562662	EPI2562663
A/Kamigoto/920/2013	EPI ISL 17684817	EPI2562648	EPI2562649	EPI2562650	EPI2562651	EPI2562652	EPI2562653	EPI2562654	EPI2562655
A/Kamigoto/878/2013	EPI ISL 17684804	EPI2562640	EPI2562641	EPI2562642	EPI2562643	EPI2562644	EPI2562645	EPI2562646	EPI2562647
A/Kamigoto/817/2013	EPI ISL 17684803	NA	NA	NA	EPI2562635	EPI2562636	EPI2562637	EPI2562638	EPI2562639
A/Kamigoto/805/2013	EPI ISL 17684787	NA	NA	NA	EPI2562630	EPI2562631	EPI2562632	EPI2562633	EPI2562634
A/Kamigoto/722/2013	EPI ISL 17684786	EPI2562622	EPI2562623	EPI2562624	EPI2562625	EPI2562626	EPI2562627	EPI2562628	EPI2562629
A/Kamigoto/707/2013	EPI ISL 17684785	EPI2562606	EPI2562607	EPI2562608	EPI2562609	EPI2562610	EPI2562612	EPI2562614	EPI2562616
A/Kamigoto/667/2013	EPI ISL 17684676	EPI2562597	EPI2562598	EPI2562599	EPI2562600	EPI2562601	EPI2562602	EPI2562603	EPI2562604
A/Kamigoto/666/2013	EPI ISL 17684609	EPI2562584	EPI2562585	EPI2562587	EPI2562588	EPI2562589	EPI2562590	EPI2562591	EPI2562593
A/Kamigoto/665/2013	EPI ISL 17684607	EPI2562575	EPI2562576	EPI2562578	EPI2562579	EPI2562580	EPI2562581	EPI2562582	EPI2562583
A/Kamigoto/635/2013	EPI ISL 17684606	EPI2562567	EPI2562568	EPI2562569	EPI2562570	EPI2562571	EPI2562572	EPI2562573	EPI2562574
A/Kamigoto/624/2013	EPI ISL 17684520	EPI2562559	EPI2562560	EPI2562561	EPI2562562	EPI2562563	EPI2562564	EPI2562565	EPI2562566
A/Kamigoto/618/2013	EPI ISL 17684519	EPI2562551	EPI2562552	EPI2562553	EPI2562554	EPI2562555	EPI2562556	EPI2562557	EPI2562558
A/Kamigoto/617/2013	EPI ISL 17684518	EPI2562543	EPI2562544	EPI2562545	EPI2562546	EPI2562547	EPI2562548	EPI2562549	EPI2562550
A/Kamigoto/616/2013	EPI ISL 17683953	EPI2562535	EPI2562536	EPI2562537	EPI2562538	EPI2562539	EPI2562540	EPI2562541	EPI2562542
A/Kamigoto/615/2013	EPI ISL 17683857	EPI2562527	EPI2562528	EPI2562529	EPI2562530	EPI2562531	EPI2562532	EPI2562533	EPI2562534
A/Kamigoto/614/2013	EPI ISL 17683792	EPI2562519	EPI2562520	EPI2562521	EPI2562522	EPI2562523	EPI2562524	EPI2562525	EPI2562526
A/Kamigoto/612/2013	EPI ISL 17683791	EPI2562511	EPI2562512	EPI2562513	EPI2562514	EPI2562515	EPI2562516	EPI2562517	EPI2562518
A/Kamigoto/603/2013	EPI ISL 17683790	EPI2562503	EPI2562504	EPI2562505	EPI2562506	EPI2562507	EPI2562508	EPI2562509	EPI2562510
A/Kamigoto/600/2013	EPI ISL 17683728	EPI2562495	EPI2562496	EPI2562497	EPI2562498	EPI2562499	EPI2562500	EPI2562501	EPI2562502
A/Kamigoto/590/2013	EPI ISL 17683727	EPI2562487	EPI2562488	EPI2562489	EPI2562490	EPI2562491	EPI2562492	EPI2562493	EPI2562494
A/Kamigoto/561/2013	EPI ISL 17683726	NA	EPI2562480	EPI2562481	EPI2562482	EPI2562483	EPI2562484	EPI2562485	EPI2562486
A/Kamigoto/480/2013	EPI ISL 17683724	EPI2562463	EPI2562464	EPI2562465	EPI2562466	EPI2562467	EPI2562468	EPI2562469	EPI2562470
A/Kamigoto/475/2013	EPI ISL 17683723	EPI2562455	EPI2562456	EPI2562457	EPI2562458	EPI2562459	EPI2562460	EPI2562461	EPI2562462
A/Kamigoto/375/2013	EPI ISL 17683722	EPI2562447	EPI2562448	EPI2562449	EPI2562450	EPI2562451	EPI2562452	EPI2562453	EPI2562454
A/Kamigoto/369/2013	EPI ISL 17683294	NA	NA	NA	EPI2562442	NA	EPI2562444	EPI2562445	EPI2562446
A/Kamigoto/310/2013	EPI ISL 17683293	EPI2562434	EPI2562435	EPI2562436	EPI2562437	EPI2562438	EPI2562439	EPI2562440	EPI2562441

A/Kamigoto/296/2013	EPI ISL 17683292	NA	NA	EPI2562428	EPI2562429	EPI2562430	EPI2562431	EPI2562432	EPI2562433
A/Kamigoto/274/2013	EPI ISL 17683291	EPI2562420	EPI2562421	EPI2562422	EPI2562423	EPI2562424	EPI2562425	EPI2562426	EPI2562427
A/Kamigoto/273/2013	EPI ISL 17683048	EPI2562412	EPI2562413	EPI2562414	EPI2562415	EPI2562416	EPI2562417	EPI2562418	EPI2562419
A/Kamigoto/220/2013	EPI ISL 17683047	EPI2562404	EPI2562405	EPI2562406	EPI2562407	EPI2562408	EPI2562409	EPI2562410	EPI2562411
A/Kamigoto/216/2013	EPI ISL 17683046	EPI2562396	EPI2562397	EPI2562398	EPI2562399	EPI2562400	EPI2562401	EPI2562402	EPI2562403
A/Kamigoto/208/2013	EPI ISL 17683045	EPI2562388	EPI2562389	EPI2562390	EPI2562391	EPI2562392	EPI2562393	EPI2562394	EPI2562395
A/Kamigoto/1137/2012	EPI ISL 17296154	EPI2477423	EPI2477424	EPI2477425	EPI2477426	EPI2477427	EPI2477428	EPI2477429	EPI2477430
A/Kamigoto/1209/2012	EPI ISL 17296116	EPI2477415	EPI2477416	EPI2477417	EPI2477418	EPI2477419	EPI2477420	EPI2477421	EPI2477422
A/Kamigoto/1378/2012	EPI ISL 17296115	EPI2477407	EPI2477408	EPI2477409	EPI2477410	EPI2477411	EPI2477412	EPI2477413	EPI2477414
A/Kamigoto/1430/2012	EPI ISL 17296114	EPI2477399	EPI2477400	EPI2477401	EPI2477402	EPI2477403	EPI2477404	EPI2477405	EPI2477406
A/Kamigoto/1437/2012	EPI ISL 17296113	EPI2477391	EPI2477392	EPI2477393	EPI2477394	EPI2477395	EPI2477396	EPI2477397	EPI2477398
A/Kamigoto/1439/2012	EPI ISL 17296112	EPI2477383	EPI2477384	EPI2477385	EPI2477386	EPI2477387	EPI2477388	EPI2477389	EPI2477390
A/Kamigoto/1483/2012	EPI ISL 17296108	EPI2477375	EPI2477376	EPI2477377	EPI2477378	EPI2477379	EPI2477380	EPI2477381	EPI2477382
A/Kamigoto/1490/2012	EPI ISL 17296105	EPI2477367	EPI2477368	EPI2477369	EPI2477370	EPI2477371	EPI2477372	EPI2477373	EPI2477374
A/Kamigoto/1514/2012	EPI ISL 17296097	EPI2477359	EPI2477360	EPI2477361	EPI2477362	EPI2477363	EPI2477364	EPI2477365	EPI2477366
A/Kamigoto/1530/2012	EPI ISL 17296096	EPI2477351	NA	EPI2477353	EPI2477354	EPI2477355	EPI2477356	EPI2477357	EPI2477358
A/Kamigoto/894/2012	EPI ISL 17296073	EPI2477343	EPI2477344	EPI2477345	EPI2477346	EPI2477347	EPI2477348	EPI2477349	EPI2477350
A/Kamigoto/887/2012	EPI ISL 17296061	EPI2477335	EPI2477336	EPI2477337	EPI2477338	EPI2477339	EPI2477340	EPI2477341	EPI2477342
A/Kamigoto/886/2012	EPI ISL 17296025	EPI2477327	NA	EPI2477329	EPI2477330	EPI2477331	EPI2477332	EPI2477333	EPI2477334
A/Kamigoto/871/2012	EPI ISL 17295949	NA	EPI2477320	EPI2477321	EPI2477322	EPI2477323	EPI2477324	EPI2477325	EPI2477326
A/Kamigoto/805/2012	EPI ISL 17295903	NA	EPI2477312	EPI2477313	EPI2477314	EPI2477315	EPI2477316	EPI2477317	EPI2477318
A/Kamigoto/796/2012	EPI ISL 17295902	EPI2477303	NA	EPI2477305	EPI2477306	EPI2477307	EPI2477308	EPI2477309	EPI2477310
A/Kamigoto/784/2012	EPI ISL 17295671	EPI2477295	EPI2477296	EPI2477297	EPI2477298	EPI2477299	EPI2477300	EPI2477301	EPI2477302
A/Kamigoto/772/2012	EPI ISL 17104742	EPI2451325	EPI2451326	EPI2451327	EPI2451328	EPI2451329	EPI2451330	EPI2451331	EPI2451332
A/Kamigoto/771/2012	EPI ISL 17104741	EPI2451317	EPI2451318	EPI2451319	EPI2451320	EPI2451321	EPI2451322	EPI2451323	EPI2451324
A/Kamigoto/765/2012	EPI ISL 17104740	EPI2451309	EPI2451310	EPI2451311	EPI2451312	EPI2451313	EPI2451314	EPI2451315	EPI2451316
A/Kamigoto/763/2012	EPI ISL 17104739	EPI2451301	EPI2451302	EPI2451303	EPI2451304	EPI2451305	EPI2451306	EPI2451307	EPI2451308
A/Kamigoto/762/2012	EPI ISL 17104738	EPI2451293	EPI2451294	EPI2451295	EPI2451296	EPI2451297	EPI2451298	EPI2451299	EPI2451300

A/Kamigoto/757/2012	EPI ISL 17104737	EPI2451285	EPI2451286	EPI2451287	EPI2451288	EPI2451289	EPI2451290	EPI2451291	EPI2451292
A/Kamigoto/752/2012	EPI ISL 17104735	EPI2451277	EPI2451278	EPI2451279	EPI2451280	EPI2451281	EPI2451282	EPI2451283	EPI2451284
A/Kamigoto/1460/2012	EPI ISL 17103548	EPI2449375	EPI2449376	EPI2449377	EPI2449378	EPI2449379	EPI2449380	EPI2449381	EPI2449382
A/Kamigoto/749/2012	EPI ISL 17103148	EPI2449359	EPI2449360	EPI2449361	EPI2449362	EPI2449363	EPI2449364	EPI2449365	EPI2449366
A/Kamigoto/729/1012	EPI ISL 17103065	EPI2449342	EPI2449344	NA	EPI2449346	EPI2449347	EPI2449348	EPI2449349	EPI2449350
A/Kamigoto/728/2012	EPI ISL 17103063	EPI2449327	EPI2449328	EPI2449329	EPI2449330	EPI2449331	EPI2449332	EPI2449333	EPI2449334
A/Kamigoto/1075/2012	EPI ISL 17103062	EPI2449319	EPI2449320	EPI2449321	EPI2449322	EPI2449323	EPI2449324	EPI2449325	EPI2449326

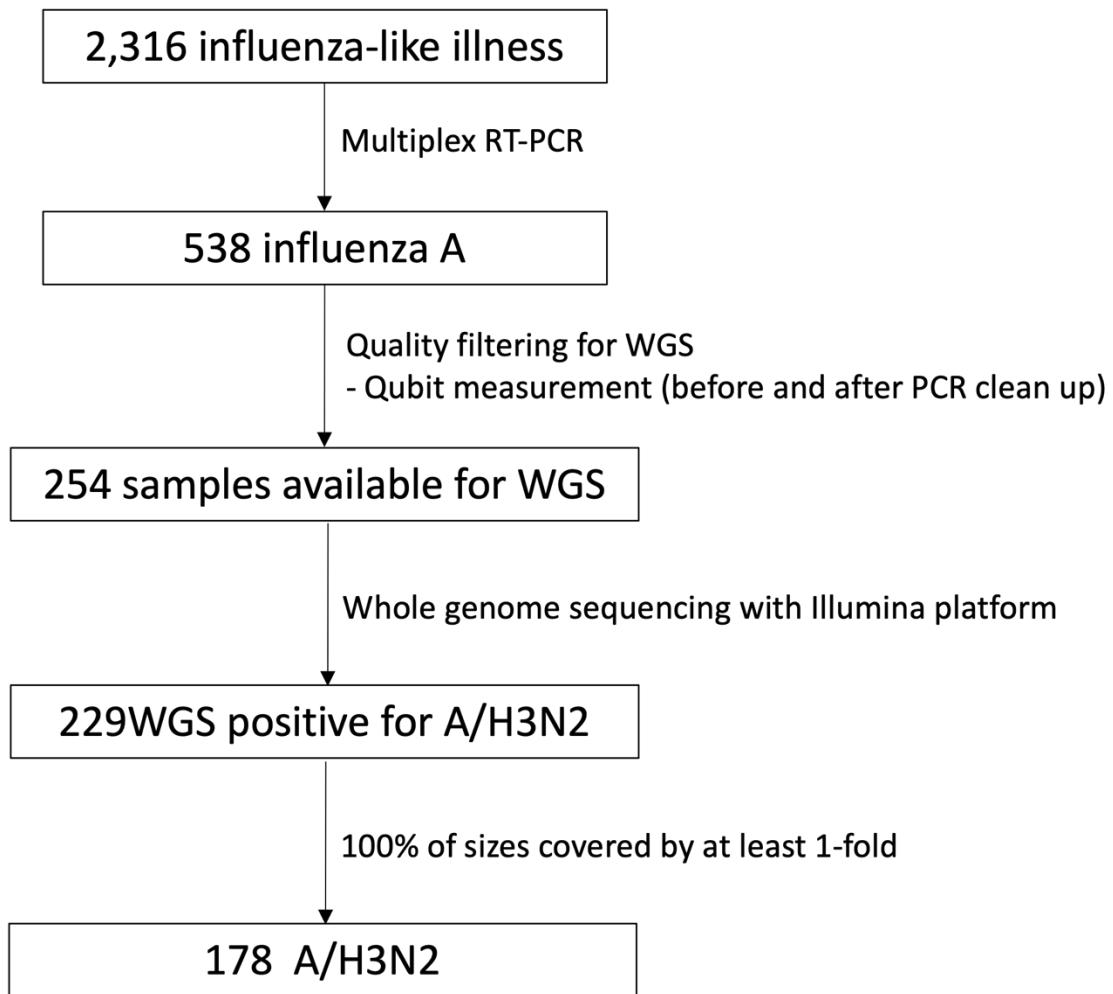


FIGURE S-1: Flowchart showing from samples collection to whole genome sequencing (WGS)

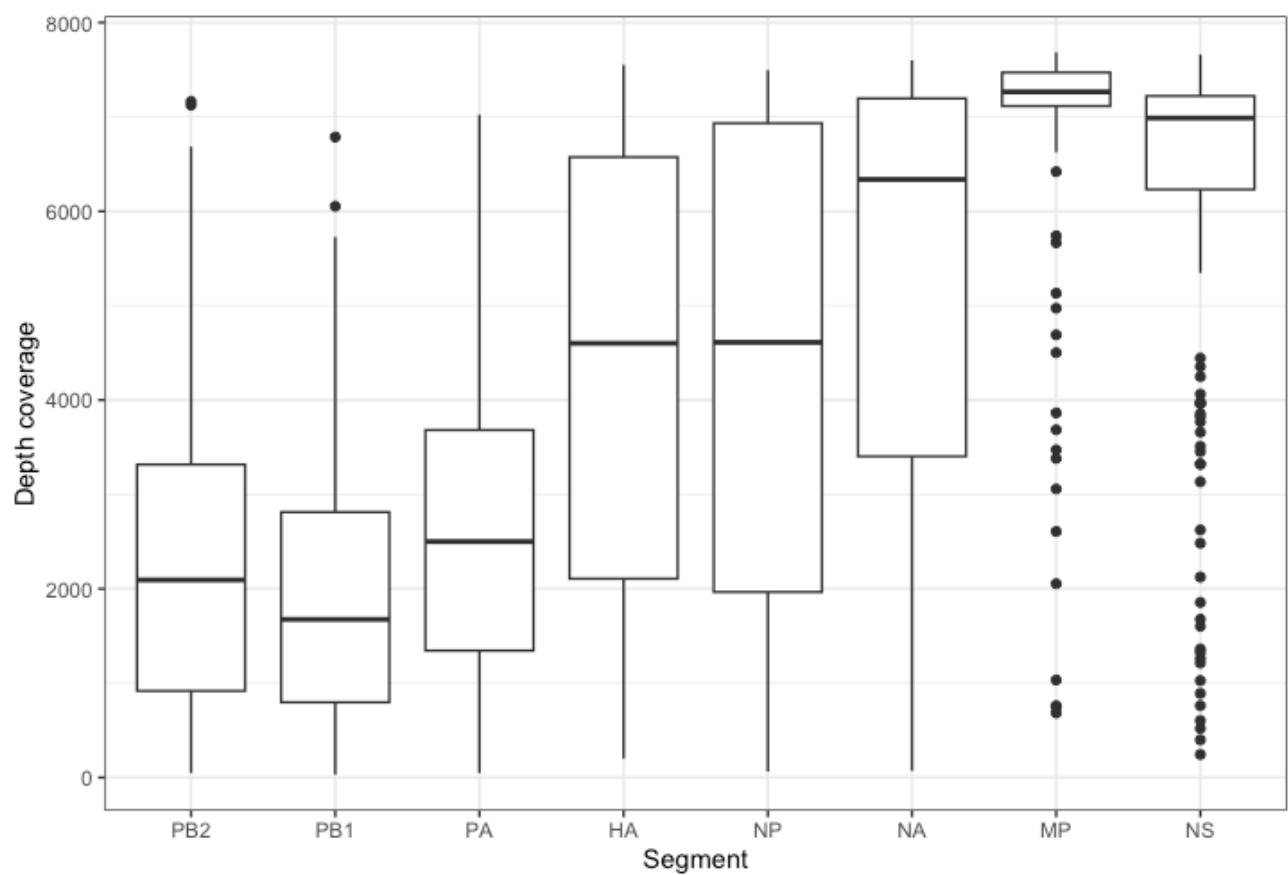


FIGURE S-2: Boxplots illustrating median read depth across each segment for A/H3N2 virus Boxes extend to the 1st and 3rd quartile.

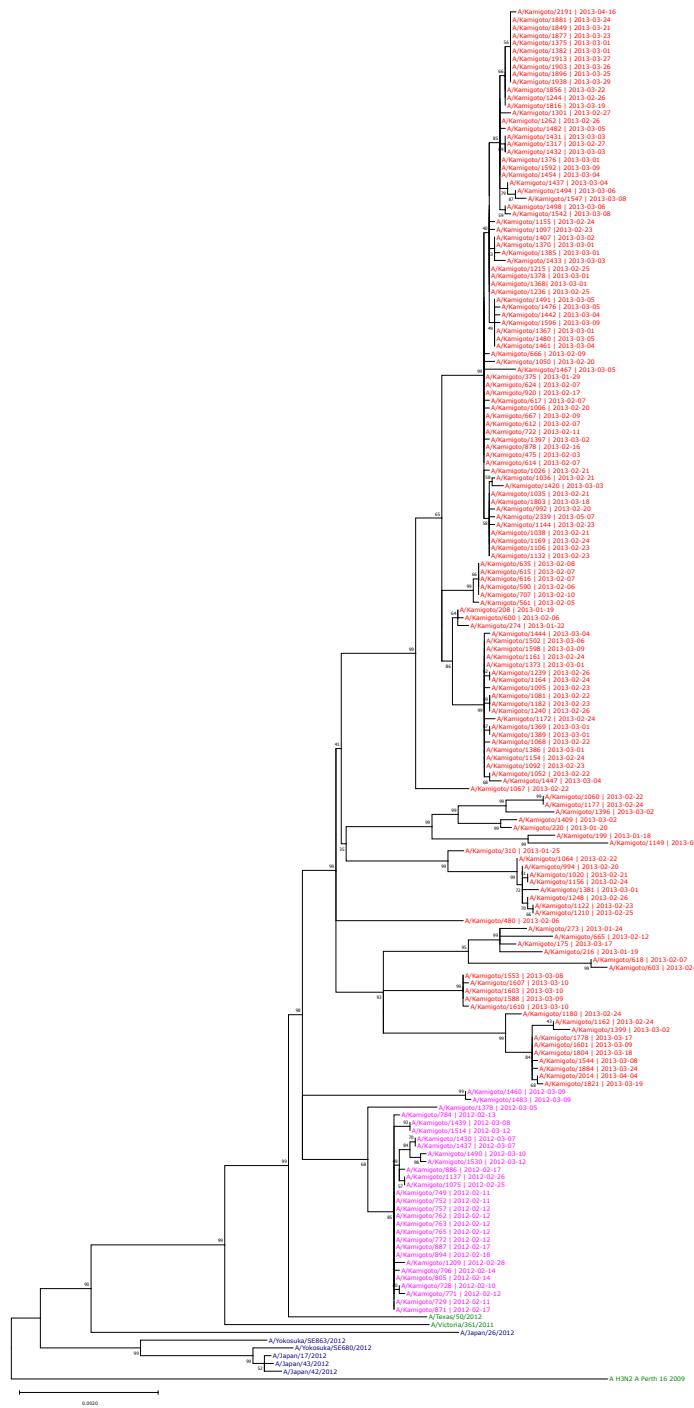


FIGURE S-3. The maximum likelihood phylogenetic tree includes 168 WGS collected during the 2011/12 (red) and 2012/13 (purple) influenza seasons alongside the WGS in Japan, that were available in the GISAID (blue), and the vaccine strains (green). For each sequence the date of the sample collection is mentioned (yyyy-mm-dd). WGS for 2012/2013 in Japan were not available during the study period.

The figure is in tiff file as separate document

FIGURE S-4. Time resolved phylogenetic tree of HA segments of Kamigoto island, Japan and global sequences (GISAID) as of 1st December 2022 submission date.

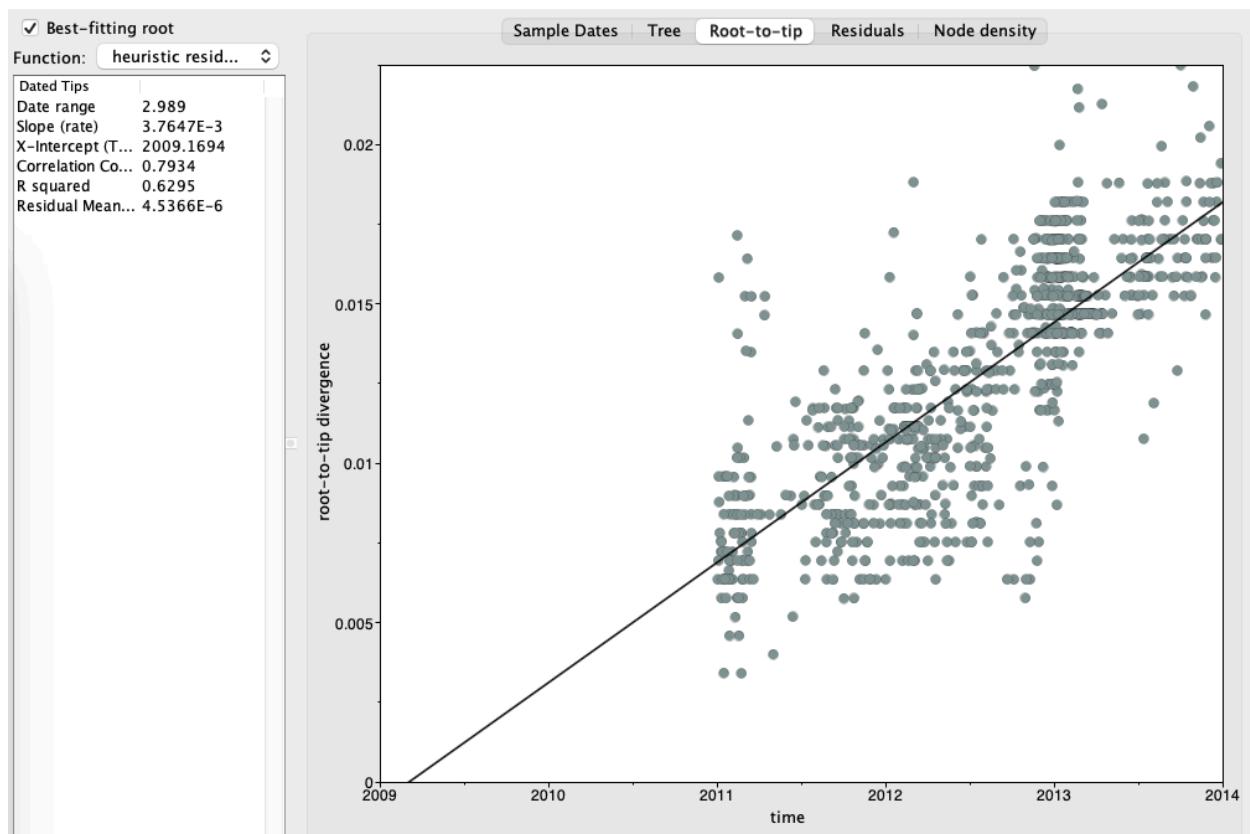


FIGURE S-5. Regression of root-to-tip genetic distances against sample collection dates.



Figure S-6: Maximum likelihood Phylogenetic tree of HA segments of A(H3N2) viruses from Kamigoto island, Japan

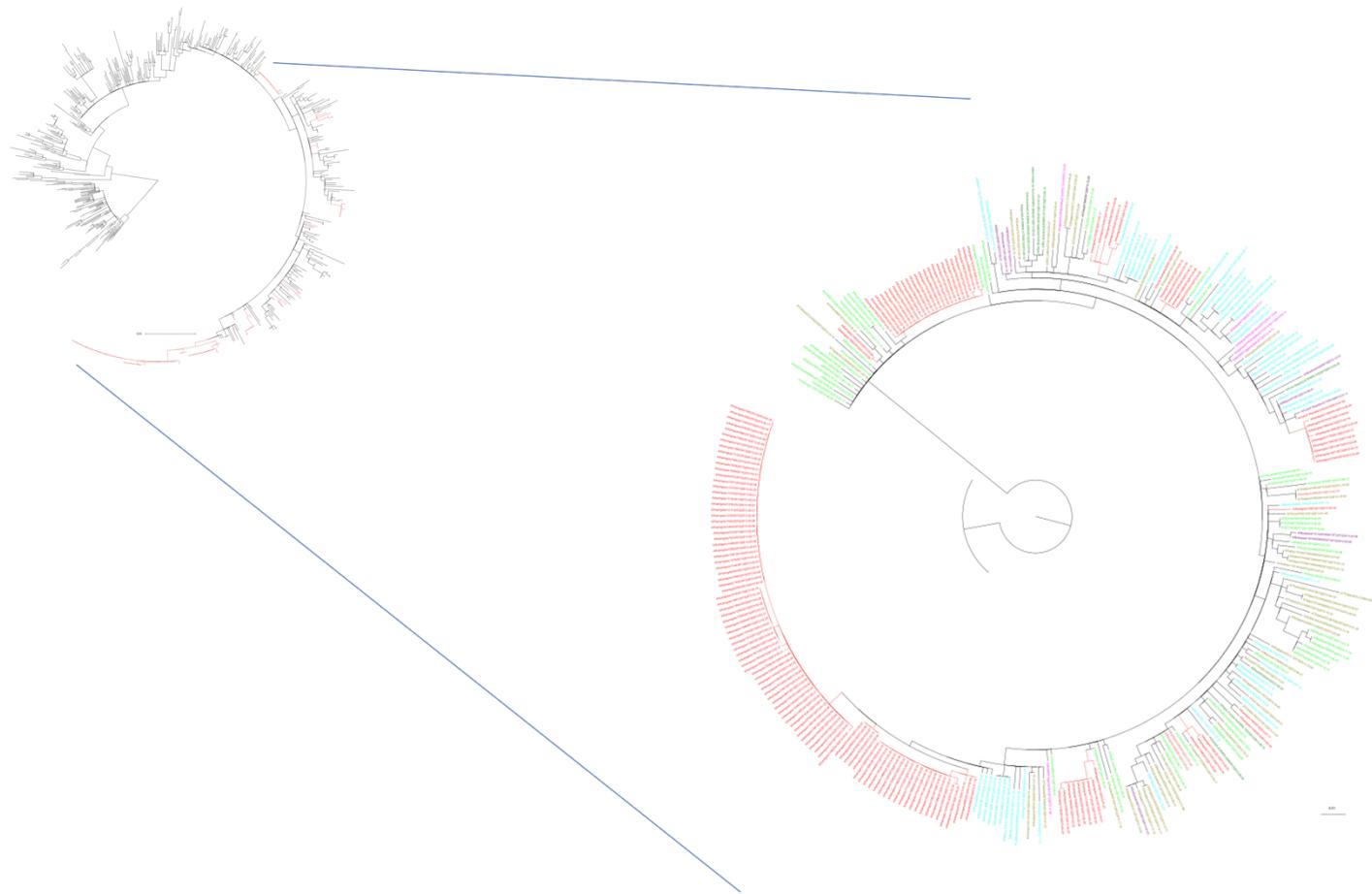


Figure S-7: Maximum-likelihood phylogenetic trees of PB2 segments of influenza A/H3N2 viruses circulating in Kamigoto and comparing sequences from strains isolated in Japan and other parts of the world from GISAID collected between 2011 and 2013.

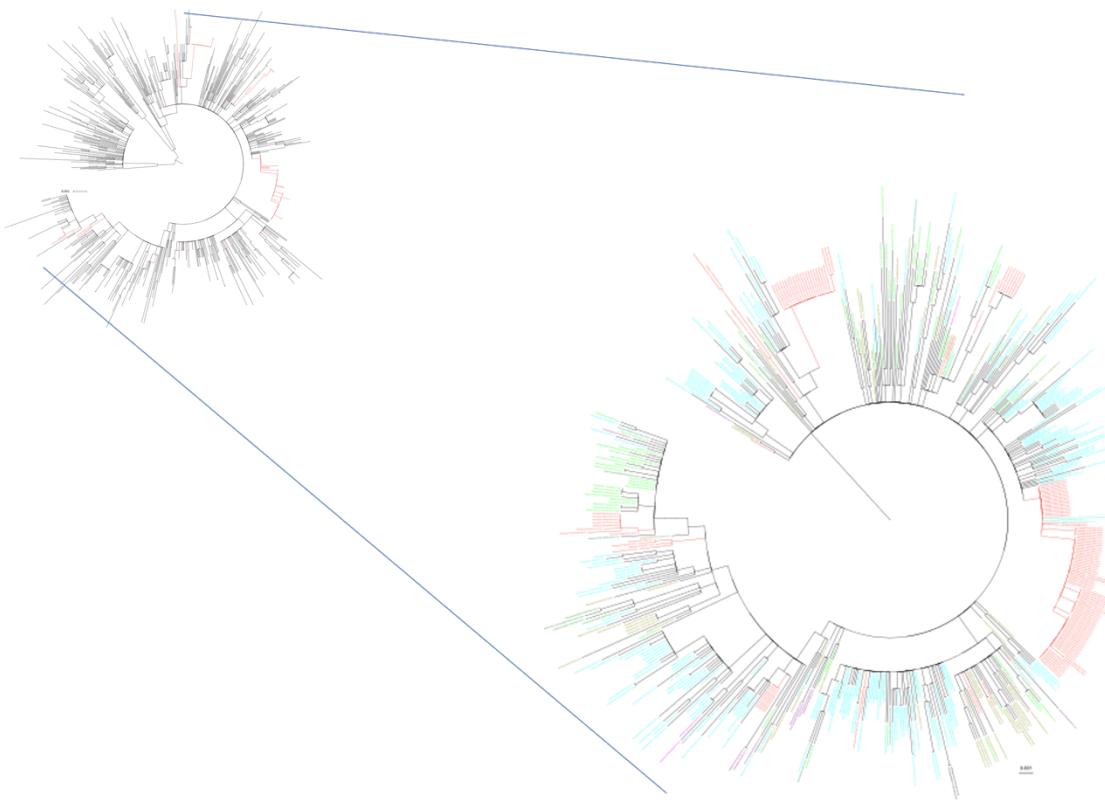


Figure S-8: Maximum-likelihood phylogenetic trees of PB1 segments of influenza A/H3N2 viruses circulating in Kamigoto and comparing sequences from strains isolated in Japan and other parts of the world from GISAID collected between 2011 and 2013.

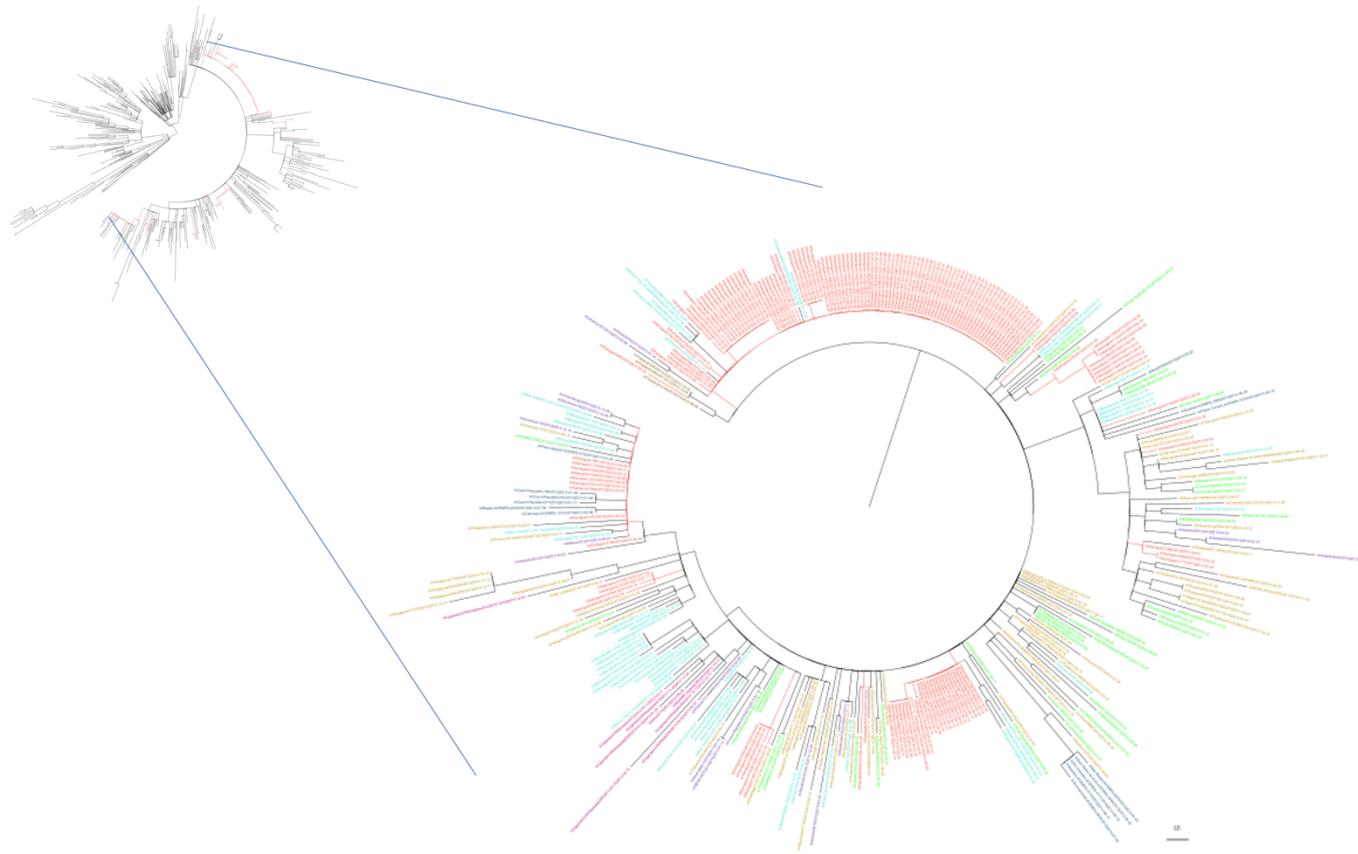


Figure S-9: Maximum-likelihood phylogenetic trees of PA segments of influenza A/H3N2 viruses circulating in Kamigoto and comparing sequences from strains isolated in Japan and other parts of the world from GISAID collected between 2011 and 2013.

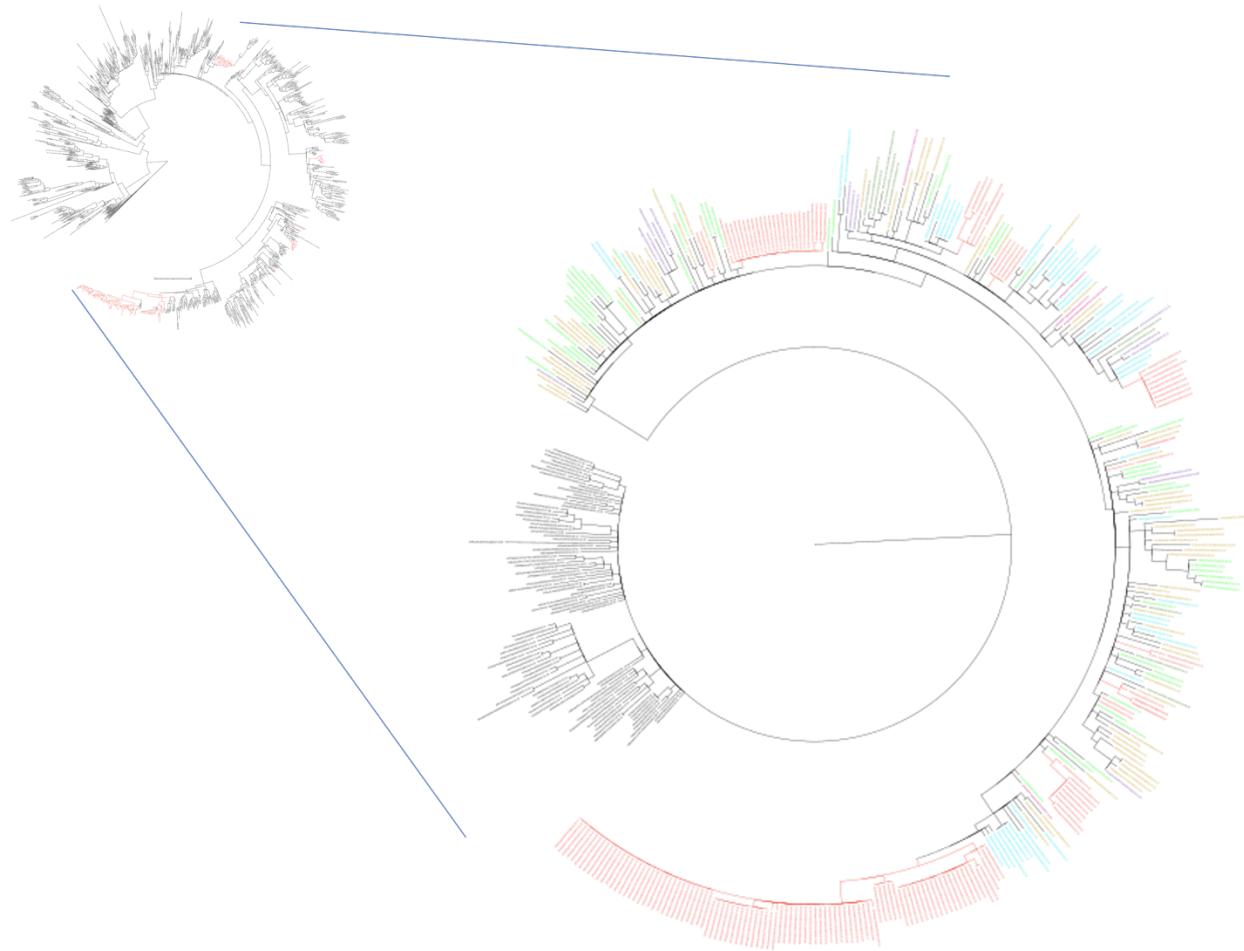


Figure S-10: Maximum-likelihood phylogenetic trees of HA segments of influenza A/H3N2 viruses circulating in Kamigoto and comparing sequences from strains isolated in Japan and other parts of the world from GISAID collected between 2011 and 2013.

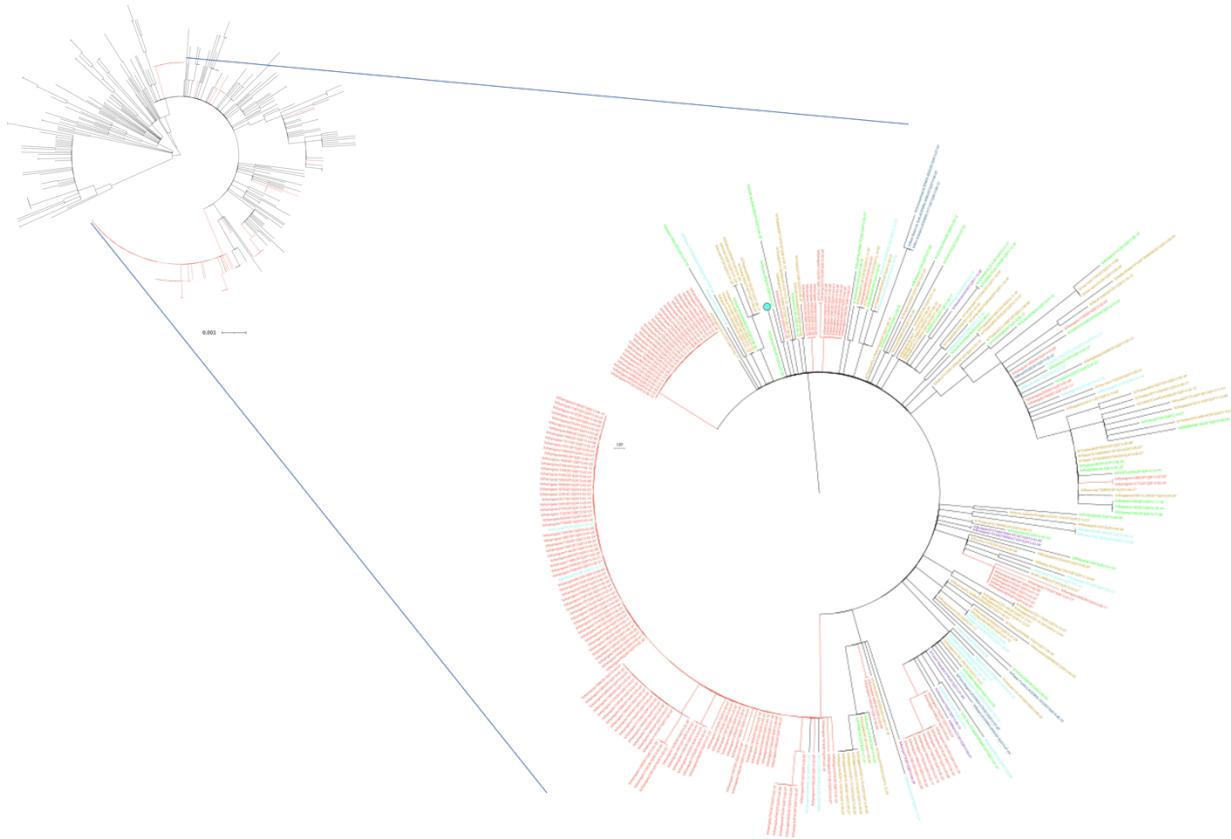


Figure S-11: Maximum-likelihood phylogenetic trees of NP segments of influenza A/H3N2 viruses circulating in Kamigoto and comparing sequences from strains isolated in Japan and other parts of the world from GISAID collected between 2011 and 2013.

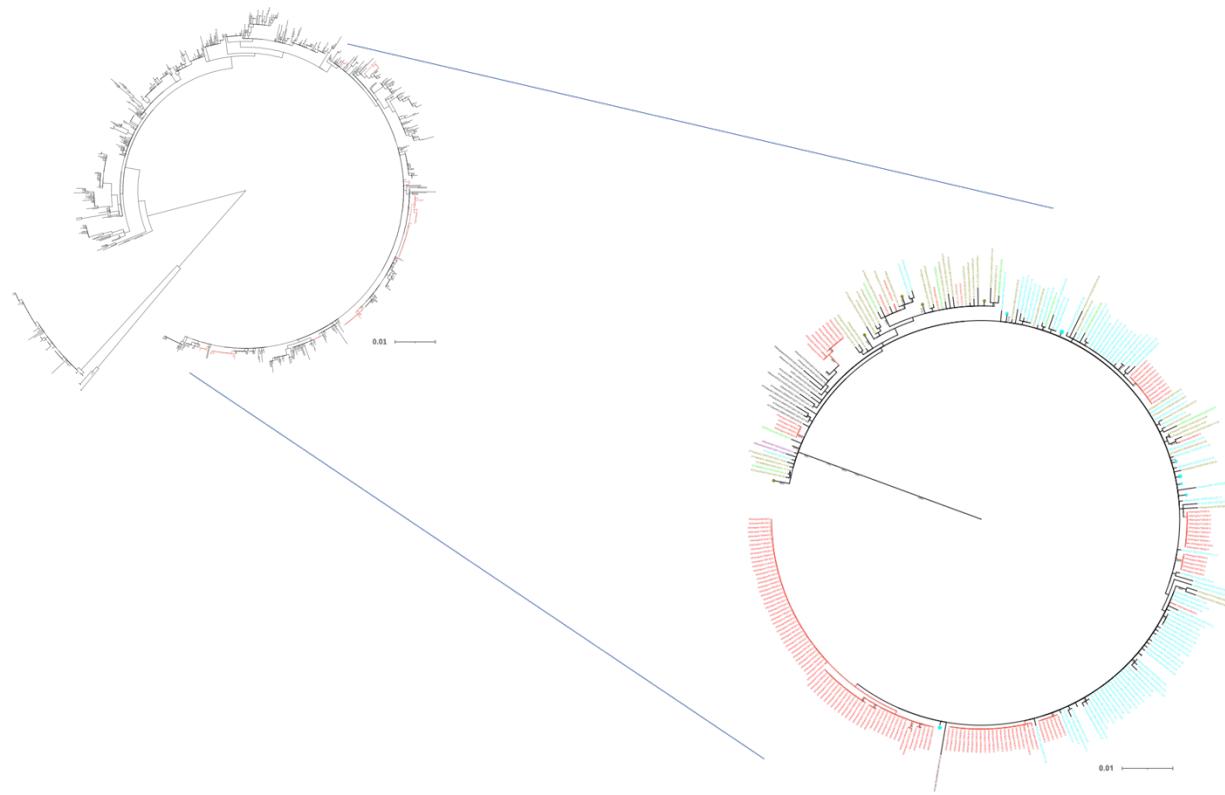


Figure S-12: Maximum-likelihood phylogenetic trees of NA segments of influenza A/H3N2 viruses circulating in Kamigoto and comparing sequences from strains isolated in Japan and other parts of the world from GISAID collected between 2011 and 2013.

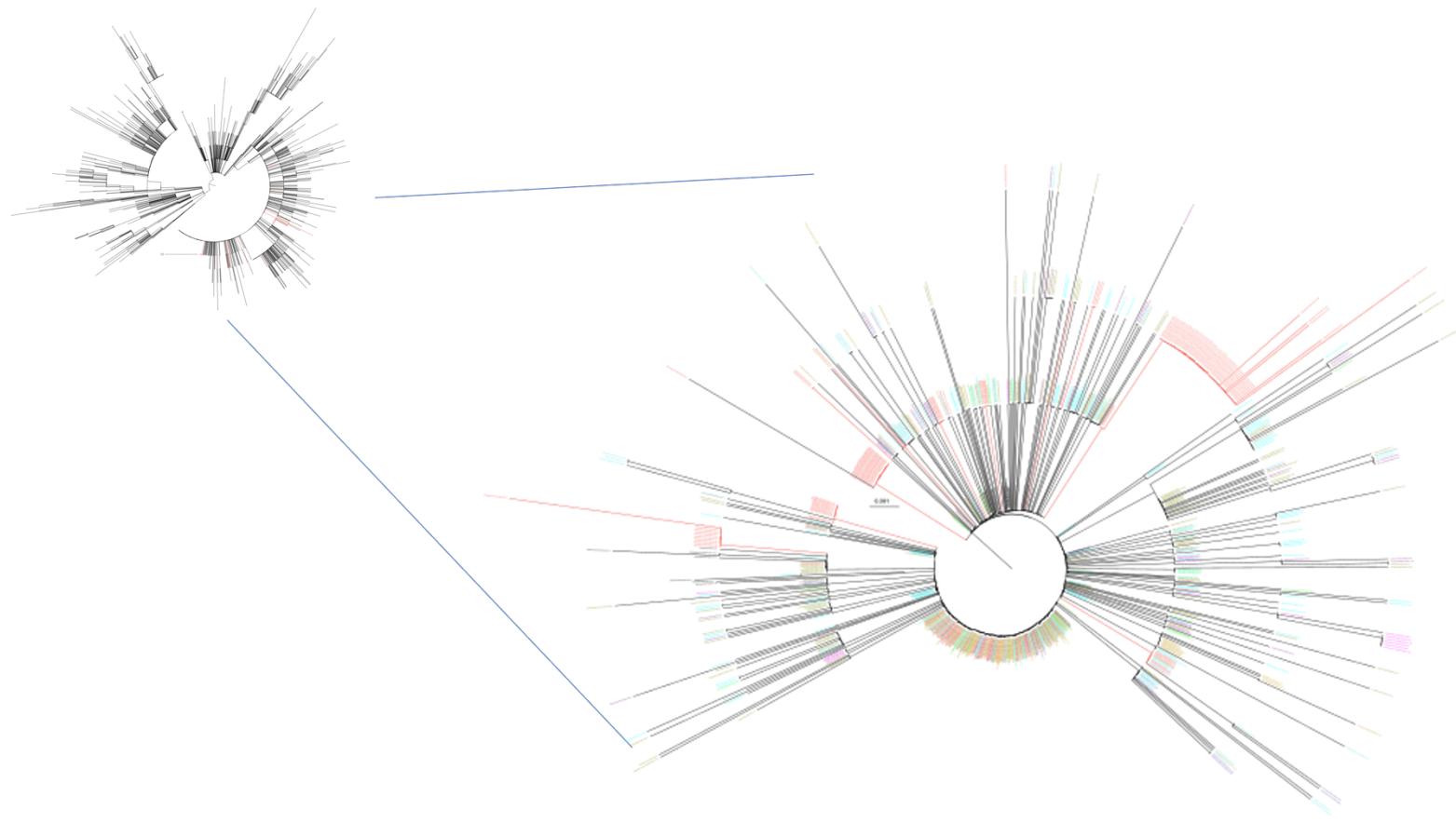


Figure S-13: Maximum-likelihood phylogenetic trees of MP segments of influenza A/H3N2 viruses circulating in Kamigoto and comparing sequences from strains isolated in Japan and other parts of the world from GISAID collected between 2011 and 2013.

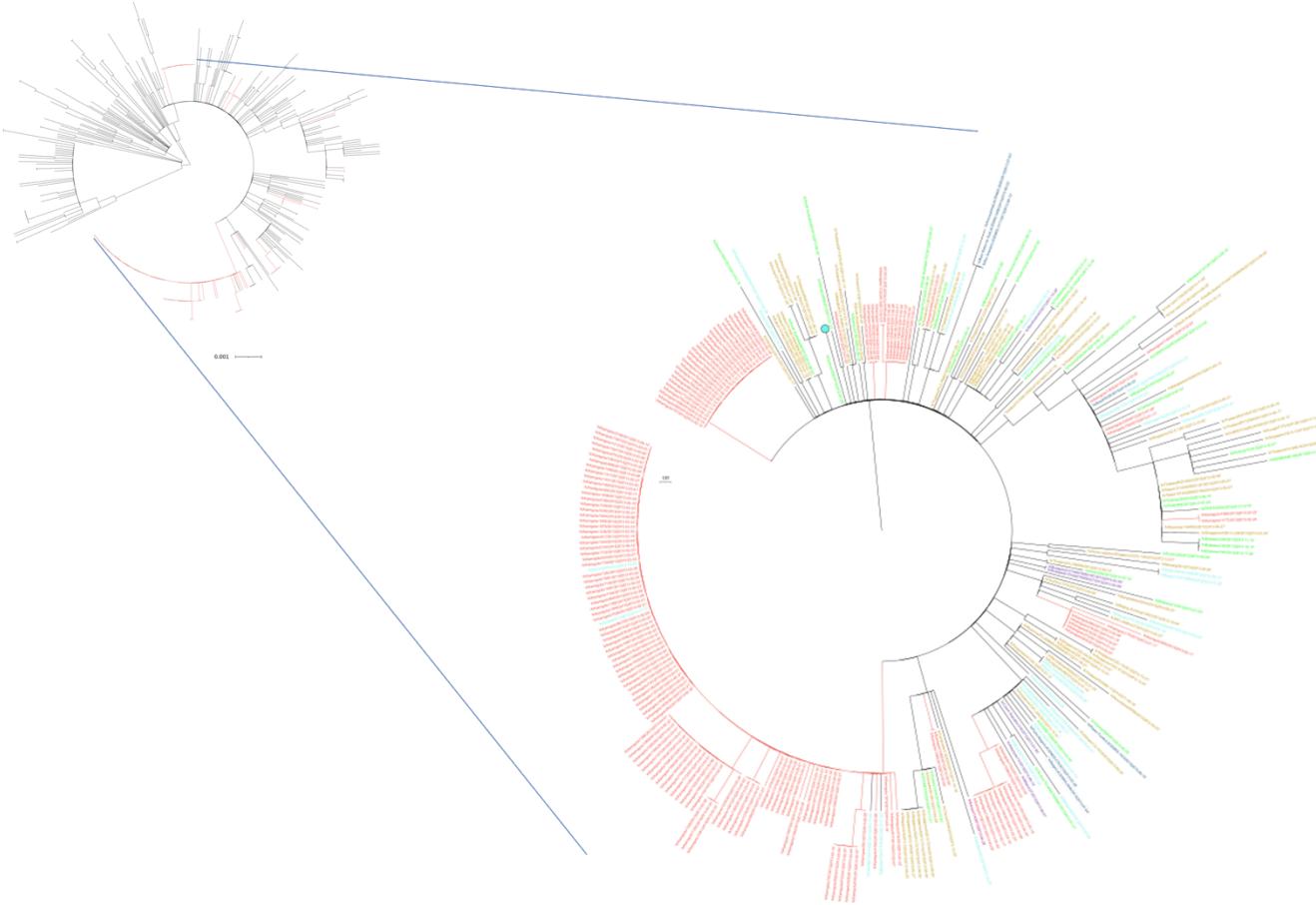


Figure S-14: Maximum-likelihood phylogenetic trees of NS segments of influenza A/H3N2 viruses circulating in Kamigoto and comparing sequences from strains isolated in Japan and other parts of the world from GISAID collected between 2011 and 2013

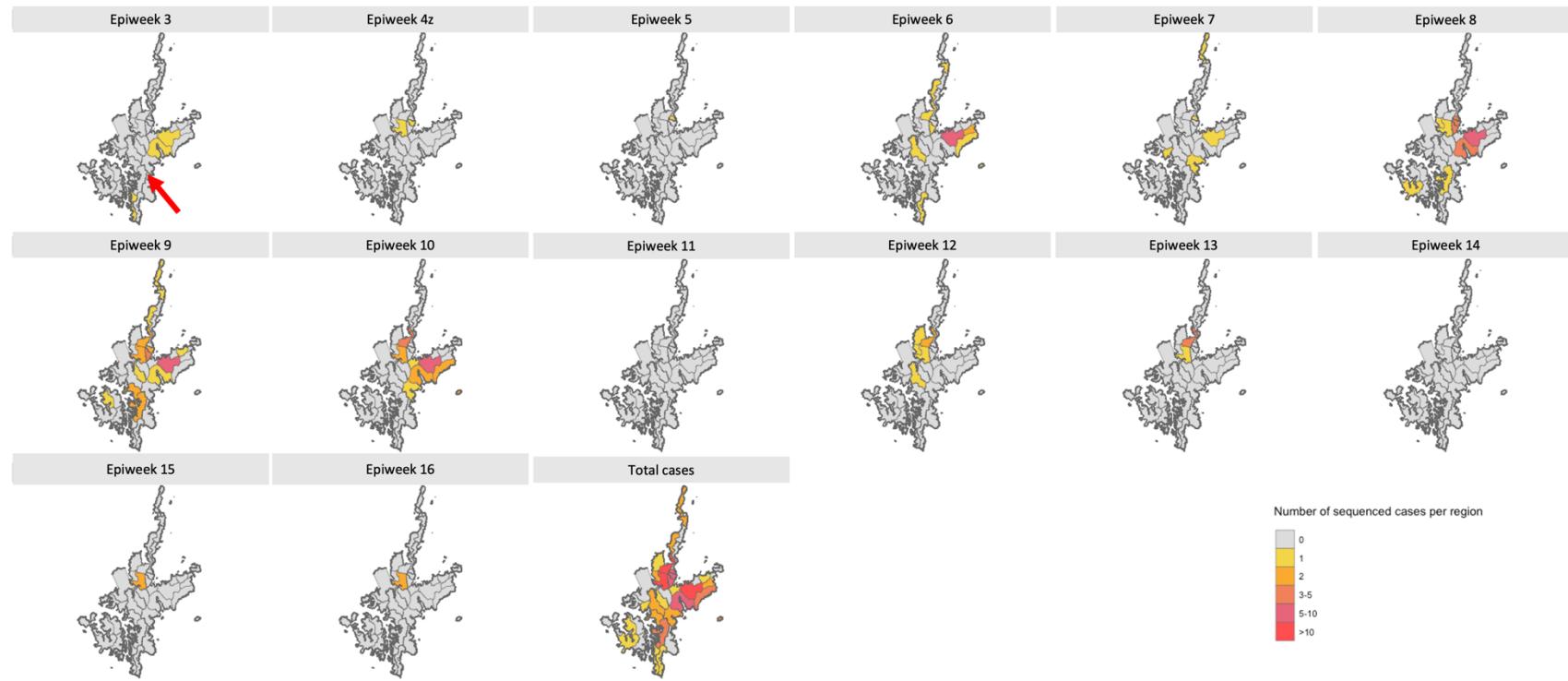
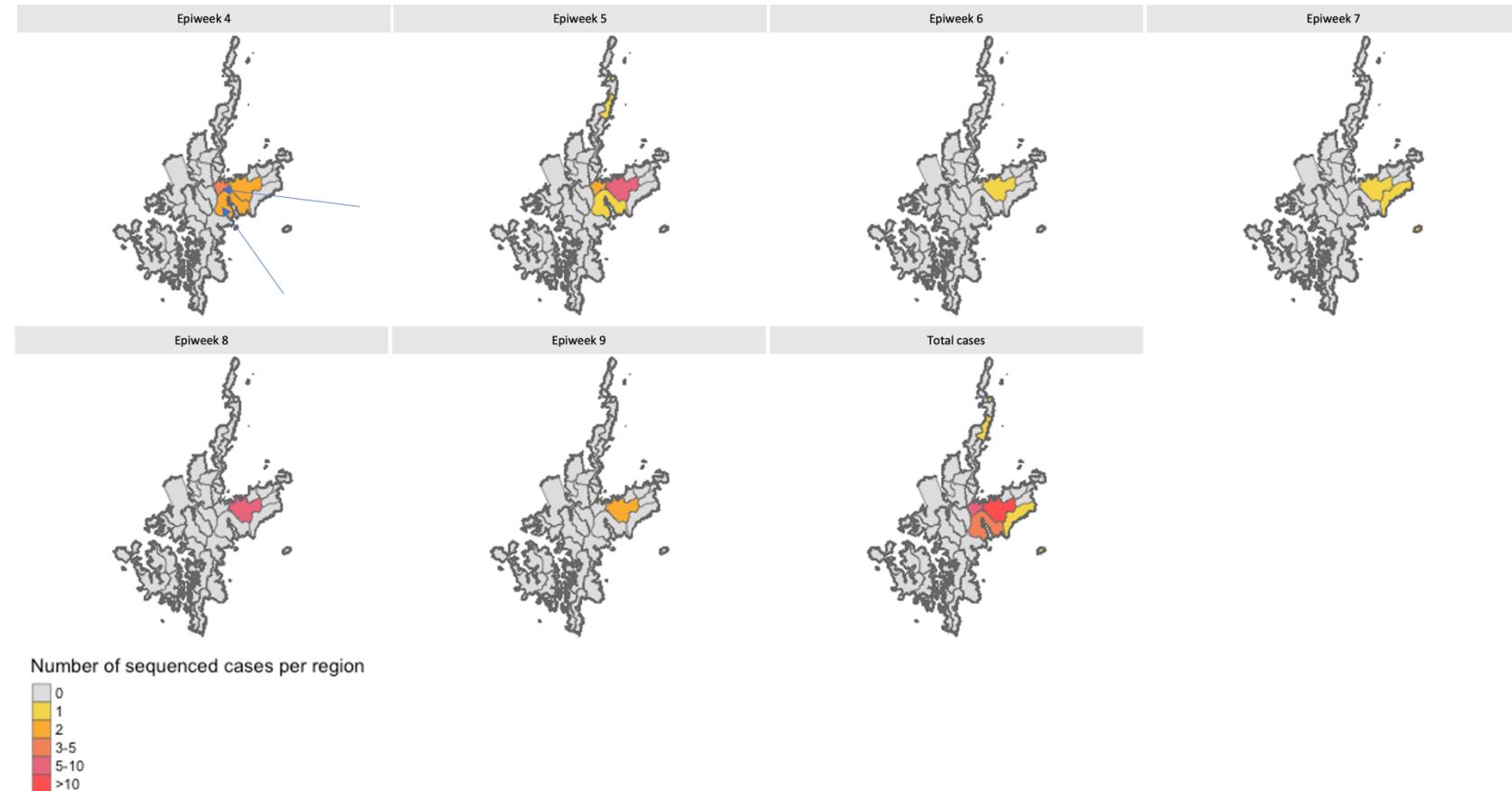


Figure S-15: Temporal and spatial distribution of the sequenced cases of cluster 5 (5A and 5B) (weekly)

1
2



3

4

5 **Figure S-16:** Temporal and spatial distribution of the sequenced cases of cluster 1 (weekly)

6

7 **Acknowledge table**

8 We gratefully acknowledge the authors, originating and submitting laboratories of the sequences from GISAID's
 9 EpiFlu™ Database on which this research is based. The list is detailed below. All submitters of data may be
 10 contacted directly via www.gisaid.org

Isolate-ID	Authors
EPI_ISL_393365	Liu,R.; Qian,Y.; Zhu,R.
EPI_ISL_393364	Liu,R.; Qian,Y.; Zhu,R.
EPI_ISL_393363	Liu,R.; Qian,Y.; Zhu,R.
EPI_ISL_393362	Liu,R.; Qian,Y.; Zhu,R.
EPI_ISL_393361	Liu,R.; Qian,Y.; Zhu,R.
EPI_ISL_393360	Liu,R.; Qian,Y.; Zhu,R.
EPI_ISL_393359	Liu,R.; Qian,Y.; Zhu,R.
EPI_ISL_393358	Liu,R.; Qian,Y.; Zhu,R.
EPI_ISL_393357	Liu,R.; Qian,Y.; Zhu,R.
EPI_ISL_209159	Lee,H.K.; Lee,C.K.; Koay,E.S.-C.
EPI_ISL_209158	Lee,H.K.; Lee,C.K.; Koay,E.S.-C.
EPI_ISL_209157	Lee,H.K.; Lee,C.K.; Koay,E.S.-C.
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EPI_ISL_94617	Lan,Yu;Wang,Dayan;Li,Xiyan;Huang,Weijuan;Zhao,Xiang;Chen,Yaoyao;Yang,Lei;Shu,Yuelong
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EPI_ISL_94615	Lan,Yu;Wang,Dayan;Li,Xiyan;Huang,Weijuan;Zhao,Xiang;Chen,Yaoyao;Yang,Lei;Shu,Yuelong
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EPI_ISL_94612	Lan,Yu;Wang,Dayan;Li,Xiyan;Huang,Weijuan;Zhao,Xiang;Chen,Yaoyao;Yang,Lei;Shu,Yuelong
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EPI_ISL_94610	Lan,Yu;Wang,Dayan;Li,Xiyan;Huang,Weijuan;Zhao,Xiang;Chen,Yaoyao;Yang,Lei;Shu,Yuelong
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EPI_ISL_169440	Chen,B.B.; Phuah,S.P.; Poh,M.K.; Chen,S.L.; Cui,L.
EPI_ISL_169439	Chen,B.B.; Phuah,S.P.; Poh,M.K.; Chen,S.L.; Cui,L.
EPI_ISL_169438	Chen,B.B.; Phuah,S.P.; Poh,M.K.; Chen,S.L.; Cui,L.
EPI_ISL_169437	Chen,B.B.; Phuah,S.P.; Poh,M.K.; Chen,S.L.; Cui,L.
EPI_ISL_169436	Chen,B.B.; Phuah,S.P.; Poh,M.K.; Chen,S.L.; Cui,L.
EPI_ISL_169435	Chen,B.B.; Phuah,S.P.; Poh,M.K.; Chen,S.L.; Cui,L.
EPI_ISL_169434	Chen,B.B.; Phuah,S.P.; Poh,M.K.; Chen,S.L.; Cui,L.
EPI_ISL_169433	Chen,B.B.; Phuah,S.P.; Poh,M.K.; Chen,S.L.; Cui,L.
EPI_ISL_169432	Chen,B.B.; Phuah,S.P.; Poh,M.K.; Chen,S.L.; Cui,L.
EPI_ISL_169431	Chen,B.B.; Phuah,S.P.; Poh,M.K.; Chen,S.L.; Cui,L.
EPI_ISL_169430	Chen,B.B.; Phuah,S.P.; Poh,M.K.; Chen,S.L.; Cui,L.
EPI_ISL_156805	NA
EPI_ISL_153537	NA
EPI_ISL_153076	Guo,X.; Cui,L.; Qi,X.; Zhao,K.; Yu,H.; Deng,F.; Qin,Y.; Shi,Z.; Zhou,M.
EPI_ISL_148747	Deng,Y-M., Iannello,P., Caldwell,N., Lau, H., Komadina,N.
EPI_ISL_128259	Lee,H.K.; Kong,D.H.L.; Tang,J.W.T.; Koay,E.S.C.
EPI_ISL_128258	Lee,H.K.; Kong,D.H.L.; Tang,J.W.T.; Koay,E.S.C.
EPI_ISL_128257	Lee,H.K.; Kong,D.H.L.; Tang,J.W.T.; Koay,E.S.C.
EPI_ISL_128256	Lee,H.K.; Kong,D.H.L.; Tang,J.W.T.; Koay,E.S.C.
EPI_ISL_128244	Lee,H.K.; Kong,D.H.L.; Tang,J.W.T.; Koay,E.S.C.
EPI_ISL_128243	Lee,H.K.; Kong,D.H.L.; Tang,J.W.T.; Koay,E.S.C.
EPI_ISL_128242	Lee,H.K.; Kong,D.H.L.; Tang,J.W.T.; Koay,E.S.C.
EPI_ISL_128241	Lee,H.K.; Kong,D.H.L.; Tang,J.W.T.; Koay,E.S.C.
EPI_ISL_128240	Lee,H.K.; Kong,D.H.L.; Tang,J.W.T.; Koay,E.S.C.
EPI_ISL_128239	Lee,H.K.; Kong,D.H.L.; Tang,J.W.T.; Koay,E.S.C.
EPI_ISL_99747	Deng,Y-M.; Iannello,P.; Caldwell,N.; Leang,S-K; Komadina,N.

EPI_ISL_96082	NA
EPI_ISL_399305	Ivan,F.X.; Zhou,X.; Lau,S.H.; Rashid,S.; Teo,J.S.; Lee,H.K.; Koay,E.S.; Chan,K.P.; Leo,Y.S.; Chen,M.I.; Kwoh,C.K.; Chow,V.T.
EPI_ISL_310576	Rahman,R.; Goswami,D.R.; Uddin,K.M.M.; Rahman,M.Z.; Hossain,M.E.; Brooks,W.A.
EPI_ISL_273221	Lee,H.S.; Noh,J.Y.; Song,J.Y.; Cheong,H.J.; Choi,W.S.; Jeong,H.W.; Wie,S.-H.; Kim,W.J.
EPI_ISL_273220	Lee,H.S.; Noh,J.Y.; Song,J.Y.; Cheong,H.J.; Choi,W.S.; Jeong,H.W.; Wie,S.-H.; Kim,W.J.
EPI_ISL_273214	Lee,H.S.; Noh,J.Y.; Song,J.Y.; Cheong,H.J.; Choi,W.S.; Jeong,H.W.; Wie,S.-H.; Kim,W.J.
EPI_ISL_273211	Lee,H.S.; Noh,J.Y.; Song,J.Y.; Cheong,H.J.; Choi,W.S.; Jeong,H.W.; Wie,S.-H.; Kim,W.J.
EPI_ISL_273210	Lee,H.S.; Noh,J.Y.; Song,J.Y.; Cheong,H.J.; Choi,W.S.; Jeong,H.W.; Wie,S.-H.; Kim,W.J.
EPI_ISL_257192	Cobbin,J.C.A.; Alfelali,M.; Barasheed,O.; Taylor,J.; Dwyer,D.E.; Booy,R.; Holmes,E.C.; Rashid,H.
EPI_ISL_257191	Cobbin,J.C.A.; Alfelali,M.; Barasheed,O.; Taylor,J.; Dwyer,D.E.; Booy,R.; Holmes,E.C.; Rashid,H.
EPI_ISL_257188	Cobbin,J.C.A.; Alfelali,M.; Barasheed,O.; Taylor,J.; Dwyer,D.E.; Booy,R.; Holmes,E.C.; Rashid,H.
EPI_ISL_182837	Rutvisuttinunt,W.; Chinnawirotisan,P.; Thaisomboonsuk,B.; Rodpradit,P.; Ajariyakhajorn,C.; Manasatiengkij,W.; Simasathien,S.; Shrestha,S.K.; Yoon,I.-K.; Klungthong,C.; Fernandez,S.
EPI_ISL_182836	Rutvisuttinunt,W.; Chinnawirotisan,P.; Thaisomboonsuk,B.; Rodpradit,P.; Ajariyakhajorn,C.; Manasatiengkij,W.; Simasathien,S.; Shrestha,S.K.; Yoon,I.-K.; Fernandez,S.; Klungthong,C.
EPI_ISL_162298	Rutvisuttinunt,W.; Chinnawirotisan,P.; Simasathien,S.; Shrestha,S.K.; Yoon,I.K.; Klungthong,C.; Fernandez,S.
EPI_ISL_162187	Rutvisuttinunt,W.; Chinnawirotisan,P.; Simasathien,S.; Shrestha,S.K.; Yoon,I.K.; Klungthong,C.; Fernandez,S.
EPI_ISL_162185	Rutvisuttinunt,W.; Chinnawirotisan,P.; Simasathien,S.; Shrestha,S.K.; Yoon,I.K.; Klungthong,C.; Fernandez,S.
EPI_ISL_161902	Deng,Y-M.; Iannello,P.; Spirason,N.; Jolley,L.; Lau,H.; Komadina,N.
EPI_ISL_161899	Deng,Y-M.; Iannello,P.; Spirason,N.; Jolley,L.; Lau,H.; Komadina,N.
EPI_ISL_161895	Deng,Y-M.; Iannello,P.; Spirason,N.; Jolley,L.; Lau,H.; Komadina,N.
EPI_ISL_161894	Deng,Y-M.; Iannello,P.; Spirason,N.; Jolley,L.; Lau,H.; Komadina,N.
EPI_ISL_149693	NA
EPI_ISL_145939	Lee,H.K.; Tang,J.W.-T.; Loh,T.P.; Kong,D.H.-L.; Yap,H.K.; Koay,E.S.-C.
EPI_ISL_141600	NA
EPI_ISL_101368	NA
EPI_ISL_14749584	Lu,L.; Robertson,G.; Ashworth,J.; Pham Hong,A.; Shi,T.; Ivens,A.; Thwaites,G.; Baker,S.; Woolhouse,M.
EPI_ISL_14749582	Lu,L.; Robertson,G.; Ashworth,J.; Pham Hong,A.; Shi,T.; Ivens,A.; Thwaites,G.; Baker,S.; Woolhouse,M.
EPI_ISL_14749581	Lu,L.; Robertson,G.; Ashworth,J.; Pham Hong,A.; Shi,T.; Ivens,A.; Thwaites,G.; Baker,S.; Woolhouse,M.
EPI_ISL_14749580	Lu,L.; Robertson,G.; Ashworth,J.; Pham Hong,A.; Shi,T.; Ivens,A.; Thwaites,G.; Baker,S.; Woolhouse,M.
EPI_ISL_208804	Khemnu,N.; Gaywee,J.; Bodhidatta,L.; Wacharaplaesadee,S.; Sirisopana,N.; Swierczewski,B.E.; Mason,C.J.
EPI_ISL_208803	Khemnu,N.; Gaywee,J.; Bodhidatta,L.; Wacharaplaesadee,S.; Sirisopana,N.; Swierczewski,B.E.; Mason,C.J.
EPI_ISL_208802	Khemnu,N.; Gaywee,J.; Bodhidatta,L.; Wacharaplaesadee,S.; Sirisopana,N.; Swierczewski,B.E.; Mason,C.J.
EPI_ISL_208801	Khemnu,N.; Gaywee,J.; Bodhidatta,L.; Wacharaplaesadee,S.; Sirisopana,N.; Swierczewski,B.E.; Mason,C.J.
EPI_ISL_208800	Khemnu,N.; Gaywee,J.; Bodhidatta,L.; Wacharaplaesadee,S.; Sirisopana,N.; Swierczewski,B.E.; Mason,C.J.
EPI_ISL_208794	Khemnu,N.; Gaywee,J.; Bodhidatta,L.; Wacharaplaesadee,S.; Sirisopana,N.; Swierczewski,B.E.; Mason,C.J.
EPI_ISL_208793	Khemnu,N.; Gaywee,J.; Bodhidatta,L.; Wacharaplaesadee,S.; Sirisopana,N.; Swierczewski,B.E.; Mason,C.J.
EPI_ISL_208792	Khemnu,N.; Gaywee,J.; Bodhidatta,L.; Wacharaplaesadee,S.; Sirisopana,N.; Swierczewski,B.E.; Mason,C.J.
EPI_ISL_208788	Khemnu,N.; Gaywee,J.; Bodhidatta,L.; Wacharaplaesadee,S.; Sirisopana,N.; Swierczewski,B.E.; Mason,C.J.
EPI_ISL_208787	Khemnu,N.; Gaywee,J.; Bodhidatta,L.; Wacharaplaesadee,S.; Sirisopana,N.; Swierczewski,B.E.; Mason,C.J.

EPI_ISL_208782	Khemnu,N.; Gaywee,J.; Bodhidatta,L.; Wacharaplaesadee,S.; Sirisopana,N.; Swierczewski,B.E.; Mason,C.J.
EPI_ISL_208781	Khemnu,N.; Gaywee,J.; Bodhidatta,L.; Wacharaplaesadee,S.; Sirisopana,N.; Swierczewski,B.E.; Mason,C.J.
EPI_ISL_208780	Khemnu,N.; Gaywee,J.; Bodhidatta,L.; Wacharaplaesadee,S.; Sirisopana,N.; Swierczewski,B.E.; Mason,C.J.
EPI_ISL_208779	Khemnu,N.; Gaywee,J.; Bodhidatta,L.; Wacharaplaesadee,S.; Sirisopana,N.; Swierczewski,B.E.; Mason,C.J.
EPI_ISL_208778	Khemnu,N.; Gaywee,J.; Bodhidatta,L.; Wacharaplaesadee,S.; Sirisopana,N.; Swierczewski,B.E.; Mason,C.J.
EPI_ISL_208777	Khemnu,N.; Gaywee,J.; Bodhidatta,L.; Wacharaplaesadee,S.; Sirisopana,N.; Swierczewski,B.E.; Mason,C.J.
EPI_ISL_143073	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143072	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143071	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143070	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143069	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143068	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143067	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143066	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143065	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143064	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143063	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143062	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143061	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143060	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143059	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143058	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143057	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143056	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143043	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143042	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143041	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143040	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143039	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143037	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143036	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143035	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143034	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143032	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143031	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143030	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143029	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143028	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143027	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.

EPI_ISL_143026	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143025	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143024	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143022	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143021	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_143020	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_118653	Deng,Y-M; Iannello,P; Caldwell,N; Komadina,N.
EPI_ISL_118600	Deng,Y-M; Iannello,P; Caldwell,N; Komadina,N.
EPI_ISL_118651	Deng,Y-M; Iannello,P; Caldwell,N; Komadina,N.
EPI_ISL_134828	NA
EPI_ISL_209160	Lee,H.K.; Lee,C.K.; Koay,E.S.-C.
EPI_ISL_399300	Ivan,F.X.; Zhou,X.; Lau,S.H.; Rashid,S.; Teo,J.S.; Lee,H.K.; Koay,E.S.; Chan,K.P.; Leo,Y.S.; Chen,M.I.; Kwoh,C.K.; Chow,V.T.
EPI_ISL_399298	Ivan,F.X.; Zhou,X.; Lau,S.H.; Rashid,S.; Teo,J.S.; Lee,H.K.; Koay,E.S.; Chan,K.P.; Leo,Y.S.; Chen,M.I.; Kwoh,C.K.; Chow,V.T.
EPI_ISL_399283	Ivan,F.X.; Zhou,X.; Lau,S.H.; Rashid,S.; Teo,J.S.; Lee,H.K.; Koay,E.S.; Chan,K.P.; Leo,Y.S.; Chen,M.I.; Kwoh,C.K.; Chow,V.T.; lee,H.K.
EPI_ISL_399281	Ivan,F.X.; Zhou,X.; Lau,S.H.; Rashid,S.; Teo,J.S.; Lee,H.K.; Koay,E.S.; Chan,K.P.; Leo,Y.S.; Chen,M.I.; Kwoh,C.K.; Chow,V.T.
EPI_ISL_399279	Ivan,F.X.; Zhou,X.; Lau,S.H.; Rashid,S.; Teo,J.S.; Lee,H.K.; Koay,E.S.; Chan,K.P.; Leo,Y.S.; Chen,M.I.; Kwoh,C.K.; Chow,V.T.
EPI_ISL_399276	Ivan,F.X.; Zhou,X.; Lau,S.H.; Rashid,S.; Teo,J.S.; Lee,H.K.; Koay,E.S.; Chan,K.P.; Leo,Y.S.; Chen,M.I.; Kwoh,C.K.; Chow,V.T.
EPI_ISL_399274	Ivan,F.X.; Zhou,X.; Lau,S.H.; Rashid,S.; Teo,J.S.; Lee,H.K.; Koay,E.S.; Chan,K.P.; Leo,Y.S.; Chen,M.I.; Kwoh,C.K.; Chow,V.T.
EPI_ISL_399272	Ivan,F.X.; Zhou,X.; Lau,S.H.; Rashid,S.; Teo,J.S.; Lee,H.K.; Koay,E.S.; Chan,K.P.; Leo,Y.S.; Chen,M.I.; Kwoh,C.K.; Chow,V.T.
EPI_ISL_399270	Ivan,F.X.; Zhou,X.; Lau,S.H.; Rashid,S.; Teo,J.S.; Lee,H.K.; Koay,E.S.; Chan,K.P.; Leo,Y.S.; Chen,M.I.; Kwoh,C.K.; Chow,V.T.
EPI_ISL_399268	Ivan,F.X.; Zhou,X.; Lau,S.H.; Rashid,S.; Teo,J.S.; Lee,H.K.; Koay,E.S.; Chan,K.P.; Leo,Y.S.; Chen,M.I.; Kwoh,C.K.; Chow,V.T.
EPI_ISL_399265	Ivan,F.X.; Zhou,X.; Lau,S.H.; Rashid,S.; Teo,J.S.; Lee,H.K.; Koay,E.S.; Chan,K.P.; Leo,Y.S.; Chen,M.I.; Kwoh,C.K.; Chow,V.T.
EPI_ISL_191167	Li,J.; Zhou,Y.Y.; Kou,Y.; Zheng,Z.B.; Yu,X.F.
EPI_ISL_191166	Li,J.; Zhou,Y.Y.; Kou,Y.; Zheng,Z.B.; Yu,X.F.
EPI_ISL_191165	Li,J.; Zhou,Y.Y.; Kou,Y.; Zheng,Z.B.; Yu,X.F.
EPI_ISL_218475	Timmermans,A.; Melendrez,M.C.; Se,Y.; Chuang,I.; Samon,N.; Uthaimongkol,N.; Klungthong,C.; Manasatienkij,W.; Thaisomboonsuk,B.; Tyner,S.D.; Rith,S.; Horm,V.S.; Jarman,R.G.; Bethell,D.; Chanarat,N.; Pavlin,J.; Wongstitwilaorong,T.; Saingam,P.; El,B.S.; Fukuda,M.M.; Touch,S.; Sovann,L.; Fernandez,S.; Buchy,P.; Chanthap,L.; Saunders,D.; Timmerman,A.
EPI_ISL_218474	Timmermans,A.; Melendrez,M.C.; Se,Y.; Chuang,I.; Samon,N.; Uthaimongkol,N.; Klungthong,C.; Manasatienkij,W.; Thaisomboonsuk,B.; Tyner,S.D.; Rith,S.; Horm,V.S.; Jarman,R.G.; Bethell,D.; Chanarat,N.; Pavlin,J.; Wongstitwilaorong,T.; Saingam,P.; El,B.S.; Fukuda,M.M.; Touch,S.; Sovann,L.; Fernandez,S.; Buchy,P.; Chanthap,L.; Saunders,D.; Timmerman,A.
EPI_ISL_218473	Timmermans,A.; Melendrez,M.C.; Se,Y.; Chuang,I.; Samon,N.; Uthaimongkol,N.; Klungthong,C.; Manasatienkij,W.; Thaisomboonsuk,B.; Tyner,S.D.; Rith,S.; Horm,V.S.; Jarman,R.G.; Bethell,D.; Chanarat,N.; Pavlin,J.; Wongstitwilaorong,T.; Saingam,P.; El,B.S.; Fukuda,M.M.; Touch,S.; Sovann,L.; Fernandez,S.; Buchy,P.; Chanthap,L.; Saunders,D.; Timmerman,A.
EPI_ISL_218472	Timmermans,A.; Melendrez,M.C.; Se,Y.; Chuang,I.; Samon,N.; Uthaimongkol,N.; Klungthong,C.; Manasatienkij,W.; Thaisomboonsuk,B.; Tyner,S.D.; Rith,S.; Horm,V.S.; Jarman,R.G.; Bethell,D.; Chanarat,N.; Pavlin,J.; Wongstitwilaorong,T.; Saingam,P.; El,B.S.; Fukuda,M.M.; Touch,S.; Sovann,L.; Fernandez,S.; Buchy,P.; Chanthap,L.; Saunders,D.; Timmerman,A.
EPI_ISL_218471	Timmermans,A.; Melendrez,M.C.; Se,Y.; Chuang,I.; Samon,N.; Uthaimongkol,N.; Klungthong,C.; Manasatienkij,W.; Thaisomboonsuk,B.; Tyner,S.D.; Rith,S.; Horm,V.S.; Jarman,R.G.; Bethell,D.; Chanarat,N.; Pavlin,J.; Wongstitwilaorong,T.; Saingam,P.; El,B.S.; Fukuda,M.M.; Touch,S.; Sovann,L.; Fernandez,S.; Buchy,P.; Chanthap,L.; Saunders,D.; Timmerman,A.
EPI_ISL_218470	Timmermans,A.; Melendrez,M.C.; Se,Y.; Chuang,I.; Samon,N.; Uthaimongkol,N.; Klungthong,C.; Manasatienkij,W.; Thaisomboonsuk,B.; Tyner,S.D.; Rith,S.; Horm,V.S.; Jarman,R.G.; Bethell,D.; Chanarat,N.; Pavlin,J.; Wongstitwilaorong,T.; Saingam,P.; El,B.S.; Fukuda,M.M.; Touch,S.; Sovann,L.; Fernandez,S.; Buchy,P.; Chanthap,L.; Saunders,D.; Timmerman,A.
EPI_ISL_161505	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161504	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161503	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.

EPI_ISL_161502	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161501	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161500	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161499	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161498	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161497	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161496	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161495	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161494	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161493	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161492	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161491	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161490	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161489	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161488	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161487	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161486	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161485	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161484	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161483	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161482	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161481	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161480	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161479	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161478	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161477	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161476	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_161475	Kumar,S.; Khare,S.; Saidullah,B.; Rai,A.
EPI_ISL_151808	NA
EPI_ISL_148097	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_148096	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_148095	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_148094	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_148093	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_148092	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_148078	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_144303	NA
EPI_ISL_143960	Bayasgalan,N; Naranzul,Ts; Nyamaa,G; Tsatsral,S; Darmaa,B; Nyimdawa,P
EPI_ISL_143959	Bayasgalan,N; Naranzul,Ts; Nyamaa,G; Tsatsral,S; Darmaa,B; Nyimdawa,P

EPI_ISL_143708	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_143707	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_143706	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_143705	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_143703	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_143702	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_143701	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_143662	Bayasgalan,N; Naranzul,Ts; Nyamaa,G; Tsatsral,S; Darmaa,B; Nyimdawa,P
EPI_ISL_140345	NA
EPI_ISL_140344	NA
EPI_ISL_140311	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_140309	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_140305	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_140300	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_140299	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_140298	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_140297	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_140296	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_140289	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_140282	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_140281	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_140280	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_135838	NA
EPI_ISL_135834	NA
EPI_ISL_132113	NA
EPI_ISL_132111	NA
EPI_ISL_132108	NA
EPI_ISL_127842	NA
EPI_ISL_127829	NA
EPI_ISL_127828	NA
EPI_ISL_127827	NA
EPI_ISL_127826	NA
EPI_ISL_123964	Mak,G.C.;Lo,J.Y.C.
EPI_ISL_123963	Mak,G.C.;Lo,J.Y.C.
EPI_ISL_123961	Mak,G.C.;Lo,J.Y.C.
EPI_ISL_123955	Mak,G.C.;Lo,J.Y.C.
EPI_ISL_123588	Mak,G.C.;Lo,J.Y.C.
EPI_ISL_123582	Mak,G.C.;Lo,J.Y.C.
EPI_ISL_123567	Mak,G.C.;Lo,J.Y.C.

EPI_ISL_123556	Mak,G.C.;Lo,J.Y.C.
EPI_ISL_123549	Mak,G.C.;Lo,J.Y.C.
EPI_ISL_123545	Mak,G.C.;Lo,J.Y.C.
EPI_ISL_119899	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_119897	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_119896	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_119895	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_119894	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_119893	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_119892	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_119891	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_119871	NA
EPI_ISL_119869	NA
EPI_ISL_111435	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_111434	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_111433	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_111432	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_111431	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_111430	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_111429	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_111428	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_111427	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_111426	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_111425	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_111424	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_111423	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_111422	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_111421	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_111420	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_111419	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_107036	NA
EPI_ISL_103313	NA
EPI_ISL_103312	NA
EPI_ISL_103311	NA
EPI_ISL_103310	NA
EPI_ISL_103309	NA
EPI_ISL_103308	NA
EPI_ISL_103307	NA
EPI_ISL_103306	NA

EPI_ISL_103293	NA
EPI_ISL_103292	NA
EPI_ISL_103291	NA
EPI_ISL_103290	NA
EPI_ISL_102989	NA
EPI_ISL_102985	NA
EPI_ISL_102982	NA
EPI_ISL_99061	NA
EPI_ISL_98822	NA
EPI_ISL_98636	NA
EPI_ISL_94885	Deng,Y-M.; Iannello,P.; Caldwell,N.; Leang,S-K; Komadina,N.
EPI_ISL_94868	Deng,Y-M.; Iannello,P.; Caldwell,N.; Leang,S-K; Komadina,N.
EPI_ISL_94857	Deng,Y-M.; Iannello,P.; Caldwell,N.; Leang,S-K; Komadina,N.
EPI_ISL_94818	Deng,Y-M.; Iannello,P.; Caldwell,N.; Leang,S-K; Komadina,N.
EPI_ISL_94817	Deng,Y-M.; Iannello,P.; Caldwell,N.; Leang,S-K; Komadina,N.
EPI_ISL_94774	NA
EPI_ISL_94358	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_94357	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_94355	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_94354	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_94353	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_94352	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_94351	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_94350	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_94349	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_94348	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_94347	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_94346	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_94345	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_94343	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_90817	NA
EPI_ISL_90810	NA
EPI_ISL_86073	NA
EPI_ISL_329617	Luvira,V.; Leaungwutiwong,P.; Iamsirithaworn,S.; Thippornchai,N.; Piroonamornpun,P.; Phumratanaaparin,W.; Davidson,A.D.
EPI_ISL_329616	Luvira,V.; Leaungwutiwong,P.; Iamsirithaworn,S.; Thippornchai,N.; Piroonamornpun,P.; Phumratanaaparin,W.; Davidson,A.D.
EPI_ISL_329615	Luvira,V.; Leaungwutiwong,P.; Iamsirithaworn,S.; Thippornchai,N.; Piroonamornpun,P.; Phumratanaaparin,W.; Davidson,A.D.
EPI_ISL_329614	Luvira,V.; Leaungwutiwong,P.; Iamsirithaworn,S.; Thippornchai,N.; Piroonamornpun,P.; Phumratanaaparin,W.; Davidson,A.D.
EPI_ISL_329613	Luvira,V.; Leaungwutiwong,P.; Iamsirithaworn,S.; Thippornchai,N.; Piroonamornpun,P.; Phumratanaaparin,W.; Davidson,A.D.
EPI_ISL_173210	Deng,Y-M.; Iannello,P.; JSpirason,N; Jolley,L; Lau,H; Komadina,N.

EPI_ISL_173209	Deng,Y-M; Iannello,P; Spirason,N; Jelley,L; Lau,H; Komadina,N.
EPI_ISL_157091	NA
EPI_ISL_157089	NA
EPI_ISL_157088	NA
EPI_ISL_157086	NA
EPI_ISL_157085	NA
EPI_ISL_157040	NA
EPI_ISL_153529	NA
EPI_ISL_153528	NA
EPI_ISL_153526	NA
EPI_ISL_153336	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153335	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153334	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153333	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153331	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153323	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153322	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153321	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153317	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153316	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153315	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153314	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153313	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153312	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153311	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153310	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153309	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153308	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153307	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153306	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153299	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153298	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153297	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153288	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153284	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153283	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153280	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Weijuan Huang,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_153219	NA
EPI_ISL_153213	NA

EPI_ISL_148679	Li,J
EPI_ISL_148678	Li,J
EPI_ISL_148677	Li,J
EPI_ISL_148676	Li,J
EPI_ISL_148675	Li,J
EPI_ISL_148674	Li,J
EPI_ISL_148673	Li,J
EPI_ISL_148672	Li,J
EPI_ISL_148671	Li,J
EPI_ISL_148670	Li,J
EPI_ISL_148669	Li,J
EPI_ISL_148668	Li,J
EPI_ISL_148667	Li,J
EPI_ISL_148666	Li,J
EPI_ISL_148665	Li,J
EPI_ISL_148664	Li,J
EPI_ISL_148663	Li,J
EPI_ISL_148662	Li,J
EPI_ISL_148661	Li,J
EPI_ISL_145312	Deng,Y-M., Iannello,P., Caldwell,N., Lau, H., Komadina,N.
EPI_ISL_145309	Deng,Y-M., Iannello,P., Caldwell,N., Lau, H., Komadina,N.
EPI_ISL_145110	NA
EPI_ISL_145041	NA
EPI_ISL_145039	NA
EPI_ISL_144998	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_144979	NA
EPI_ISL_144506	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_144505	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_144504	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_144500	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_144499	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_144498	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_144497	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_140929	Buchy,P.
EPI_ISL_140928	Buchy,P.
EPI_ISL_140927	Buchy,P.
EPI_ISL_140926	Buchy,P.
EPI_ISL_140925	Buchy,P.
EPI_ISL_136404	NA

EPI_ISL_132222	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_132221	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_132220	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_132219	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_132218	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_132217	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_132216	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_132215	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_132214	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_132213	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_132212	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_128748	Deng,Y-M; Iannello,P; Caldwell,N; Jelley,L; Komadina,N
EPI_ISL_128701	Deng,Y-M; Iannello,P; Caldwell,N; Jelley,L; Komadina,N
EPI_ISL_128686	Deng,Y-M; Iannello,P; Caldwell,N; Jelley,L; Komadina,N
EPI_ISL_128685	Deng,Y-M; Iannello,P; Caldwell,N; Jelley,L; Komadina,N
EPI_ISL_128679	Deng,Y-M; Iannello,P; Caldwell,N; Jelley,L; Komadina,N
EPI_ISL_128678	Deng,Y-M; Iannello,P; Caldwell,N; Jelley,L; Komadina,N
EPI_ISL_128677	Deng,Y-M; Iannello,P; Caldwell,N; Jelley,L; Komadina,N
EPI_ISL_128673	Deng,Y-M; Iannello,P; Caldwell,N; Jelley,L; Komadina,N
EPI_ISL_128669	Deng,Y-M; Iannello,P; Caldwell,N; Jelley,L; Komadina,N
EPI_ISL_128668	Deng,Y-M; Iannello,P; Caldwell,N; Jelley,L; Komadina,N
EPI_ISL_128667	Deng,Y-M; Iannello,P; Caldwell,N; Jelley,L; Komadina,N
EPI_ISL_128628	Deng,Y-M; Iannello,P; Caldwell,N; Jelley,L; Komadina,N
EPI_ISL_128337	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_128335	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_128334	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_128333	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_128332	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_128331	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_128330	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_128329	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_128328	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_128327	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_128318	NA
EPI_ISL_124529	NA
EPI_ISL_119906	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_119905	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_119904	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_119903	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'

EPI_ISL_119902	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_119901	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_119900	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_119898	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_116157	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_116156	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_116155	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_116154	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_116153	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_116152	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_116082	NA
EPI_ISL_116071	NA
EPI_ISL_107909	NA
EPI_ISL_107908	NA
EPI_ISL_107907	NA
EPI_ISL_107906	NA
EPI_ISL_107905	NA
EPI_ISL_107904	NA
EPI_ISL_107903	NA
EPI_ISL_107902	NA
EPI_ISL_107901	NA
EPI_ISL_107898	NA
EPI_ISL_107897	NA
EPI_ISL_107872	NA
EPI_ISL_107871	NA
EPI_ISL_107870	NA
EPI_ISL_107869	NA
EPI_ISL_107868	NA
EPI_ISL_107867	NA
EPI_ISL_107866	NA
EPI_ISL_107865	NA
EPI_ISL_107843	NA
EPI_ISL_107842	NA
EPI_ISL_107840	NA
EPI_ISL_107819	NA
EPI_ISL_107818	NA
EPI_ISL_104142	NA
EPI_ISL_104141	NA
EPI_ISL_104140	NA

EPI_ISL_99801	NA
EPI_ISL_99799	NA
EPI_ISL_99759	Deng,Y-M.; Iannello,P.; Caldwell,N.; Leang,S-K; Komadina,N.
EPI_ISL_99758	Deng,Y-M.; Iannello,P.; Caldwell,N.; Leang,S-K; Komadina,N.
EPI_ISL_99755	Deng,Y-M.; Iannello,P.; Caldwell,N.; Leang,S-K; Komadina,N.
EPI_ISL_96096	NA
EPI_ISL_96095	NA
EPI_ISL_96094	NA
EPI_ISL_96093	NA
EPI_ISL_96081	NA
EPI_ISL_95506	NA
EPI_ISL_14284852	NA
EPI_ISL_14284851	NA
EPI_ISL_260971	Li,J.; Gong,T.; Shi,Y.; Xiong,Y.
EPI_ISL_260961	Li,J.; Gong,T.; Shi,Y.; Xiong,Y.
EPI_ISL_260960	Li,J.; Gong,T.; Shi,Y.; Xiong,Y.
EPI_ISL_260959	Li,J.; Gong,T.; Shi,Y.; Xiong,Y.
EPI_ISL_260958	Li,J.; Gong,T.; Shi,Y.; Xiong,Y.
EPI_ISL_260957	Li,J.; Gong,T.; Shi,Y.; Xiong,Y.
EPI_ISL_260956	Li,J.; Gong,T.; Shi,Y.; Xiong,Y.
EPI_ISL_260955	Li,J.; Gong,T.; Shi,Y.; Xiong,Y.
EPI_ISL_260954	Li,J.; Gong,T.; Shi,Y.; Xiong,Y.
EPI_ISL_260953	Li,J.; Gong,T.; Shi,Y.; Xiong,Y.
EPI_ISL_260564	Hossain,M.M.; Jain,M.; Hasan,K.N.; Khaleque,A.; Ahsan,G.; Islam,S.
EPI_ISL_260563	Hossain,M.M.; Jain,M.; Hasan,K.N.; Khaleque,A.; Ahsan,G.; Islam,S.
EPI_ISL_260562	Hossain,M.M.; Jain,M.; Hasan,K.N.; Khaleque,A.; Ahsan,G.; Islam,S.
EPI_ISL_260561	Hossain,M.M.; Jain,M.; Hasan,K.N.; Khaleque,A.; Ahsan,G.; Islam,S.
EPI_ISL_165923	Deng,Y-M.; Iannello,P.; Spirason,N.; Jolley,L.; Lau,H.; Komadina,N.
EPI_ISL_165922	Deng,Y-M.; Iannello,P.; Spirason,N.; Jolley,L.; Lau,H.; Komadina,N.
EPI_ISL_162615	NA
EPI_ISL_162602	NA
EPI_ISL_161900	Deng,Y-M.; Iannello,P.; Spirason,N.; Jolley,L.; Lau,H.; Komadina,N.
EPI_ISL_161898	Deng,Y-M.; Iannello,P.; Spirason,N.; Jolley,L.; Lau,H.; Komadina,N.
EPI_ISL_158079	NA
EPI_ISL_158075	NA
EPI_ISL_158074	NA
EPI_ISL_155047	NA
EPI_ISL_155045	NA
EPI_ISL_154824	NA

EPI_ISL_154758	NA
EPI_ISL_154757	NA
EPI_ISL_154756	NA
EPI_ISL_154755	NA
EPI_ISL_154754	NA
EPI_ISL_154753	NA
EPI_ISL_154031	NA
EPI_ISL_154030	NA
EPI_ISL_154029	NA
EPI_ISL_154028	NA
EPI_ISL_154027	NA
EPI_ISL_154026	NA
EPI_ISL_154023	NA
EPI_ISL_153943	NA
EPI_ISL_153942	NA
EPI_ISL_150361	Yang,J.R.; Kuo,C.Y.; Huang,H.Y.; Wu,F.T.; Huang,Y.L.; Cheng,C.Y.; Su,Y.T.; Chang,F.Y.; Wu,H.S.; Liu,M.T.; Yang,J.-R.; Wu,H.-S.; Liu,M.-T.
EPI_ISL_150360	Yang,J.R.; Kuo,C.Y.; Huang,H.Y.; Wu,F.T.; Huang,Y.L.; Cheng,C.Y.; Su,Y.T.; Chang,F.Y.; Wu,H.S.; Liu,M.T.; Yang,J.-R.; Wu,H.-S.; Liu,M.-T.
EPI_ISL_150359	Yang,J.R.; Kuo,C.Y.; Huang,H.Y.; Wu,F.T.; Huang,Y.L.; Cheng,C.Y.; Su,Y.T.; Chang,F.Y.; Wu,H.S.; Liu,M.T.; Yang,J.-R.; Wu,H.-S.; Liu,M.-T.
EPI_ISL_150358	Yang,J.R.; Kuo,C.Y.; Huang,H.Y.; Wu,F.T.; Huang,Y.L.; Cheng,C.Y.; Su,Y.T.; Chang,F.Y.; Wu,H.S.; Liu,M.T.; Yang,J.-R.; Wu,H.-S.; Liu,M.-T.
EPI_ISL_150357	Yang,J.R.; Kuo,C.Y.; Huang,H.Y.; Wu,F.T.; Huang,Y.L.; Cheng,C.Y.; Su,Y.T.; Chang,F.Y.; Wu,H.S.; Liu,M.T.; Yang,J.-R.; Wu,H.-S.; Liu,M.-T.
EPI_ISL_150356	Yang,J.R.; Kuo,C.Y.; Huang,H.Y.; Wu,F.T.; Huang,Y.L.; Cheng,C.Y.; Su,Y.T.; Chang,F.Y.; Wu,H.S.; Liu,M.T.; Yang,J.-R.; Wu,H.-S.; Liu,M.-T.
EPI_ISL_150355	Yang,J.R.; Kuo,C.Y.; Huang,H.Y.; Wu,F.T.; Huang,Y.L.; Cheng,C.Y.; Su,Y.T.; Chang,F.Y.; Wu,H.S.; Liu,M.T.; Yang,J.-R.; Wu,H.-S.; Liu,M.-T.
EPI_ISL_150354	Yang,J.R.; Kuo,C.Y.; Huang,H.Y.; Wu,F.T.; Huang,Y.L.; Cheng,C.Y.; Su,Y.T.; Chang,F.Y.; Wu,H.S.; Liu,M.T.; Yang,J.-R.; Wu,H.-S.; Liu,M.-T.
EPI_ISL_150353	Yang,J.R.; Kuo,C.Y.; Huang,H.Y.; Wu,F.T.; Huang,Y.L.; Cheng,C.Y.; Su,Y.T.; Chang,F.Y.; Wu,H.S.; Liu,M.T.; Yang,J.-R.; Wu,H.-S.; Liu,M.-T.
EPI_ISL_150352	Yang,J.R.; Kuo,C.Y.; Huang,H.Y.; Wu,F.T.; Huang,Y.L.; Cheng,C.Y.; Su,Y.T.; Chang,F.Y.; Wu,H.S.; Liu,M.T.; Yang,J.-R.; Wu,H.-S.; Liu,M.-T.
EPI_ISL_150351	Yang,J.R.; Kuo,C.Y.; Huang,H.Y.; Wu,F.T.; Huang,Y.L.; Cheng,C.Y.; Su,Y.T.; Chang,F.Y.; Wu,H.S.; Liu,M.T.; Yang,J.-R.; Wu,H.-S.; Liu,M.-T.
EPI_ISL_150284	NA
EPI_ISL_150283	NA
EPI_ISL_150281	NA
EPI_ISL_150280	NA
EPI_ISL_150185	NA
EPI_ISL_150177	NA
EPI_ISL_150175	NA
EPI_ISL_150174	NA
EPI_ISL_150063	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_150062	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_150061	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_150060	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_150059	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato

EPI_ISL_150058	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_149682	NA
EPI_ISL_146075	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_146074	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_146072	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_146066	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_145640	NA
EPI_ISL_145639	NA
EPI_ISL_145566	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_145565	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_145564	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_145563	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_145561	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_145560	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_145559	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_145558	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_145557	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_145556	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_145555	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_145541	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_145516	NA
EPI_ISL_145512	NA
EPI_ISL_145486	NA
EPI_ISL_142610	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_142601	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_142600	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_142599	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_142598	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_142597	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_142596	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_142595	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_142583	NA
EPI_ISL_141554	Deng,Y-M., Iannello,P.,Caldwell,N., Jolley,L.,Komadina,N.
EPI_ISL_141553	Deng,Y-M., Iannello,P.,Caldwell,N., Jolley,L.,Komadina,N.
EPI_ISL_141552	Deng,Y-M., Iannello,P.,Caldwell,N., Jolley,L.,Komadina,N.
EPI_ISL_141548	Deng,Y-M; Iannello,P.;Caldwell,N; Jolley,L;Komadina,N.
EPI_ISL_138580	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_138579	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_138578	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato

EPI_ISL_138577	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_138576	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_138575	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_138574	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_138573	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_138572	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_138571	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_138482	NA
EPI_ISL_138481	NA
EPI_ISL_138477	NA
EPI_ISL_138476	NA
EPI_ISL_138456	NA
EPI_ISL_138454	NA
EPI_ISL_138453	NA
EPI_ISL_138006	NA
EPI_ISL_137649	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_137648	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_137647	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_137646	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_137645	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_137644	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_137643	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_137642	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_137641	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_137622	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_137446	NA
EPI_ISL_137439	NA
EPI_ISL_137435	NA
EPI_ISL_137259	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_137258	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_137256	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_134457	Deng,Y-M.; Iannello,P.; Caldwell,N.; Jolley,L.; Komadina,N.
EPI_ISL_134446	NA
EPI_ISL_134445	NA
EPI_ISL_134444	NA
EPI_ISL_133582	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato
EPI_ISL_133581	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato
EPI_ISL_133580	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato
EPI_ISL_133579	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato

EPI_ISL_133578	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato
EPI_ISL_133571	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato
EPI_ISL_133570	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato
EPI_ISL_133569	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato
EPI_ISL_133568	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato
EPI_ISL_133567	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato
EPI_ISL_133566	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato
EPI_ISL_133565	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato
EPI_ISL_133495	NA
EPI_ISL_133494	NA
EPI_ISL_133063	NA
EPI_ISL_129660	NA
EPI_ISL_125911	NA
EPI_ISL_122213	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_122212	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_122211	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_122210	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_122209	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_122208	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_122207	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_122206	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_122204	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_122199	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_122198	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_122134	NA
EPI_ISL_122132	NA
EPI_ISL_122130	NA
EPI_ISL_122129	NA
EPI_ISL_121884	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_121883	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_121882	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_121881	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_121880	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_121879	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_121878	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_121877	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_121876	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_121875	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_121874	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'

EPI_ISL_96818	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_96814	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_96813	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93029	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93028	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93026	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93025	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93024	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93023	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93021	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93020	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93019	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93018	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93015	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93014	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93013	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93011	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93010	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_163330	Meijer, A.;Overduin, P.
EPI_ISL_278405	Kim,J.-K.; Song,E.-J.
EPI_ISL_278404	Kim,J.-K.; Song,E.-J.
EPI_ISL_278403	Kim,J.-K.; Song,E.-J.
EPI_ISL_278402	Kim,J.-K.; Song,E.-J.
EPI_ISL_278401	Kim,J.-K.; Song,E.-J.
EPI_ISL_278400	Kim,J.-K.; Song,E.-J.
EPI_ISL_278399	Kim,J.-K.; Song,E.-J.
EPI_ISL_278398	Kim,J.-K.; Song,E.-J.
EPI_ISL_278397	Kim,J.-K.; Song,E.-J.
EPI_ISL_278396	Kim,J.-K.; Song,E.-J.
EPI_ISL_278395	Kim,J.-K.; Song,E.-J.
EPI_ISL_278394	Kim,J.-K.; Song,E.-J.
EPI_ISL_278393	Kim,J.-K.; Song,E.-J.
EPI_ISL_278392	Kim,J.-K.; Song,E.-J.
EPI_ISL_278391	Kim,J.-K.; Song,E.-J.
EPI_ISL_278390	Kim,J.-K.; Song,E.-J.
EPI_ISL_278389	Kim,J.-K.; Song,E.-J.
EPI_ISL_278388	Kim,J.-K.; Song,E.-J.
EPI_ISL_278387	Kim,J.-K.; Song,E.-J.
EPI_ISL_278386	Kim,J.-K.; Song,E.-J.

EPI_ISL_278385	Kim,J.-K.; Song,E.-J.
EPI_ISL_278384	Kim,J.-K.; Song,E.-J.
EPI_ISL_278383	Kim,J.-K.; Song,E.-J.
EPI_ISL_278382	Kim,J.-K.; Song,E.-J.
EPI_ISL_278381	Kim,J.-K.; Song,E.-J.
EPI_ISL_278380	Kim,J.-K.; Song,E.-J.
EPI_ISL_278379	Kim,J.-K.; Song,E.-J.
EPI_ISL_278378	Kim,J.-K.; Song,E.-J.
EPI_ISL_278377	Kim,J.-K.; Song,E.-J.
EPI_ISL_278376	Kim,J.-K.; Song,E.-J.
EPI_ISL_278375	Kim,J.-K.; Song,E.-J.
EPI_ISL_278374	Kim,J.-K.; Song,E.-J.
EPI_ISL_278373	Kim,J.-K.; Song,E.-J.
EPI_ISL_278372	Kim,J.-K.; Song,E.-J.
EPI_ISL_278371	Kim,J.-K.; Song,E.-J.
EPI_ISL_122542	Deng,Y-M; Iannello,P; Caldwell,N; Jolley,L; Komadina,N
EPI_ISL_122540	Deng,Y-M; Iannello,P; Caldwell,N; Jolley,L; Komadina,N
EPI_ISL_151510	Deng,Y-M; Iannello,P; Spirason,N; Jolley,L; Lau,H; Komadina,N
EPI_ISL_118577	Deng,Y-M; Iannello,P; Caldwell,N; Komadina,N.
EPI_ISL_118582	Deng,Y-M; Iannello,P; Caldwell,N; Komadina,N.
EPI_ISL_151505	Deng,Y-M; Iannello,P; Spirason,N; Jolley,L; Lau,H; Komadina,N
EPI_ISL_151504	Deng,Y-M; Iannello,P; Spirason,N; Jolley,L; Lau,H; Komadina,N
EPI_ISL_118652	Deng,Y-M; Iannello,P; Caldwell,N; Komadina,N.
EPI_ISL_134800	Fujisaki,Seiichiro; Kim,Namhee; Reiko,Itoh; Tashiro,Masato; Odagiri,Takato
EPI_ISL_134802	Fujisaki,Seiichiro; Kim,Namhee; Reiko,Itoh; Tashiro,Masato; Odagiri,Takato
EPI_ISL_134790	Fujisaki,Seiichiro; Kim,Namhee; Reiko,Itoh; Tashiro,Masato; Odagiri,Takato
EPI_ISL_101954	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_134799	Fujisaki,Seiichiro; Kim,Namhee; Reiko,Itoh; Tashiro,Masato; Odagiri,Takato
EPI_ISL_134785	Fujisaki,Seiichiro; Kim,Namhee; Reiko,Itoh; Tashiro,Masato; Odagiri,Takato
EPI_ISL_151441	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_151440	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_151439	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_134796	Fujisaki,Seiichiro; Kim,Namhee; Reiko,Itoh; Tashiro,Masato; Odagiri,Takato
EPI_ISL_134805	Fujisaki,Seiichiro; Kim,Namhee; Reiko,Itoh; Tashiro,Masato; Odagiri,Takato
EPI_ISL_101953	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_134791	Fujisaki,Seiichiro; Kim,Namhee; Reiko,Itoh; Tashiro,Masato; Odagiri,Takato
EPI_ISL_134804	Fujisaki,Seiichiro; Kim,Namhee; Reiko,Itoh; Tashiro,Masato; Odagiri,Takato
EPI_ISL_101955	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_151438	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato

EPI_ISL_134793	Fujisaki,Seiichiro; Kim,Namhee; Reiko,Itoh; Tashiro,Masato; Odagiri,Takato
EPI_ISL_134792	Fujisaki,Seiichiro; Kim,Namhee; Reiko,Itoh; Tashiro,Masato; Odagiri,Takato
EPI_ISL_134803	Fujisaki,Seiichiro; Kim,Namhee; Reiko,Itoh; Tashiro,Masato; Odagiri,Takato
EPI_ISL_101956	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_134798	Fujisaki,Seiichiro; Kim,Namhee; Reiko,Itoh; Tashiro,Masato; Odagiri,Takato
EPI_ISL_134878	NA
EPI_ISL_101920	NA
EPI_ISL_134860	NA
EPI_ISL_89826	NA
EPI_ISL_134827	NA
EPI_ISL_138720	NA
EPI_ISL_205597	Biswas,D.; Buragohain,M.; Dutta,M.; Sarmah,K.; Yadav,K.; Baruah,P.; Borkakoty,B.
EPI_ISL_205596	Biswas,D.; Buragohain,M.; Dutta,M.; Sarmah,K.; Yadav,K.; Baruah,P.; Borkakoty,B.
EPI_ISL_205595	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205440	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205439	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205438	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205437	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205436	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205435	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205434	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205433	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205432	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205431	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205430	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205429	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205428	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205427	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205426	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205425	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205424	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205423	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205422	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205421	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205420	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205419	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205418	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205417	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205416	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.

EPI_ISL_205415	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205414	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205413	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205412	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205411	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205410	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205409	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205408	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205407	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205406	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205405	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205404	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205403	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205402	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_205401	Tewawong,N.; Prachayangprecha,S.; Thongmee,T.; Vichiwattana,P.; Theamboonlers,A.; Poovorawan,Y.
EPI_ISL_201441	Peter,S.; Balakrishnan,A.; Potdar,V.A.; Chadha,M.S.; Jadhav,S.M.; Russell,C.; Smith,D.; Dakhave,M.; Anukumar,B.; Mishra,A.
EPI_ISL_201440	Peter,S.; Balakrishnan,A.; Potdar,V.A.; Chadha,M.S.; Jadhav,S.M.; Russell,C.; Smith,D.; Dakhave,M.; Anukumar,B.; Mishra,A.
EPI_ISL_201439	Peter,S.; Balakrishnan,A.; Potdar,V.A.; Chadha,M.S.; Jadhav,S.M.; Russell,C.; Smith,D.; Dakhave,M.; Anukumar,B.; Mishra,A.
EPI_ISL_201438	Peter,S.; Balakrishnan,A.; Potdar,V.A.; Chadha,M.S.; Jadhav,S.M.; Russell,C.; Smith,D.; Dakhave,M.; Anukumar,B.; Mishra,A.
EPI_ISL_201437	Peter,S.; Balakrishnan,A.; Potdar,V.A.; Chadha,M.S.; Jadhav,S.M.; Russell,C.; Smith,D.; Dakhave,M.; Anukumar,B.; Mishra,A.
EPI_ISL_201436	Peter,S.; Balakrishnan,A.; Potdar,V.A.; Chadha,M.S.; Jadhav,S.M.; Russell,C.; Smith,D.; Dakhave,M.; Anukumar,B.; Mishra,A.
EPI_ISL_201435	NA
EPI_ISL_201183	Rutvisuttinunt,W.; Chinnawirotisan,P.; Thaisomboonsuk,B.; Rodpradit,P.; Ajariyakhajorn,C.; Manasatiengkij,W.; Simasathien,S.; Shrestha,S.K.; Yoon,I.-K.; Klungthong,C.; Fernandez,S.
EPI_ISL_185283	Bedford,T.; Riley,S.; Barr,I.G.; Broor,S.; Chadha,M.; Cox,N.J.; Daniels,R.S.; Gunasekaran,C.P.; Hurt,A.C.; Kelso,A.; Klimov,A.; Lewis,N.S.; Li,X.; McCauley,J.W.; Odagiri,T.; Potdar,V.; Rambaut,A.; Shu,Y.; Skepner,E.; Smith,D.J.; Suchard,M.A.; Tashiro,M.; Wang,D.; Xu,X.; Lemey,P.; Russell,C.A.
EPI_ISL_185164	Bedford,T.; Riley,S.; Barr,I.G.; Broor,S.; Chadha,M.; Cox,N.J.; Daniels,R.S.; Gunasekaran,C.P.; Hurt,A.C.; Kelso,A.; Klimov,A.; Lewis,N.S.; Li,X.; McCauley,J.W.; Odagiri,T.; Potdar,V.; Rambaut,A.; Shu,Y.; Skepner,E.; Smith,D.J.; Suchard,M.A.; Tashiro,M.; Wang,D.; Xu,X.; Lemey,P.; Russell,C.A.
EPI_ISL_185065	Islam,M.A.; Shaha,M.; Islam,M.K.; Ahmed,M.F.; Rahman,M.M.; Rahman,S.R.
EPI_ISL_181321	Islam,M.A.; Shaha,M.; Islam,M.K.; Ahmed,M.F.; Rahman,M.M.; Rahman,S.R.
EPI_ISL_181320	Islam,M.A.; Shaha,M.; Islam,M.K.; Ahmed,M.F.; Rahman,M.M.; Rahman,S.R.
EPI_ISL_181319	Islam,M.A.; Shaha,M.; Islam,M.K.; Ahmed,M.F.; Rahman,M.M.; Rahman,S.R.
EPI_ISL_181318	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_176593	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_176592	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_176591	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_176590	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_176589	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_176588	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_176587	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato

EPI_ISL_176586	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_176585	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_176584	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_176583	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_176582	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_176581	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_176580	Deng,Y-M; Iannello,P; JSpirason,N; Jolley,L; Lau,H; Komadina,N. Saito, Reiko; Takemae, Nobuhiro; Saito, Takehiko; Shobugawa, Yugo; Kondo, Hiroki; Hibino, Akinobu; Yadanaar, Kyaw; Yi Yi, Myint; Khin Yi, Oo; Htay Htay, Tin
EPI_ISL_173204	
EPI_ISL_164975	NA
EPI_ISL_164923	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_164288	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_160153	Hibino, Akinobu
EPI_ISL_156851	NA
EPI_ISL_156639	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156638	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156637	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156636	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156635	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156634	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156633	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156632	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156631	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156630	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156629	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156628	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156627	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156626	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156625	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156624	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156623	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156622	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156621	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156620	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156619	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156618	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156617	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156616	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156615	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156614	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.

EPI_ISL_156613	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156612	Maitsetseg,C.; Burmaa,A.; Fuji,N.; Okamoto,M.; Bayasgalan,N.; Tsatsral,S.; Darma,B.; Oshitani,H.; Nymadawa,P.
EPI_ISL_156611	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_156584	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_156583	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_156582	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_155900	NA
EPI_ISL_155886	NA
EPI_ISL_155878	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_155838	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_155837	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_155836	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_155835	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_155834	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_155833	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_155832	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_155831	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_155830	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_155829	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_155828	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_155827	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_155826	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_155825	Wan,Y.
EPI_ISL_155729	Thammavong,H.; Balansay-Ames,M.; Hawksworth,A.; Myers,C.A.; Connors,B.; de Mattos,C.; Brice,G.
EPI_ISL_152046	Thammavong,H.; Balansay-Ames,M.; Hawksworth,A.; Myers,C.A.; Connors,B.; de Mattos,C.; Brice,G.
EPI_ISL_152043	Thammavong,H.; Balansay-Ames,M.; Hawksworth,A.; Myers,C.A.; Connors,B.; de Mattos,C.; Brice,G.
EPI_ISL_152008	Thammavong,H.; Balansay-Ames,M.; Hawksworth,A.; Myers,C.A.; Connors,B.; de Mattos,C.; Brice,G.
EPI_ISL_152006	Thammavong,H.; Balansay-Ames,M.; Hawksworth,A.; Myers,C.A.; Connors,B.; de Mattos,C.; Brice,G.
EPI_ISL_152004	NA
EPI_ISL_148477	NA
EPI_ISL_148472	NA
EPI_ISL_148470	NA
EPI_ISL_148469	NA
EPI_ISL_148465	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_148077	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_148076	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_148075	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_148074	Mak,G.C.;Lo,J.Y.C.
EPI_ISL_144524	Mak,G.C.;Lo,J.Y.C.

EPI_ISL_144523	Mak,G.C.;Lo,J.Y.C.
EPI_ISL_144521	Mak,G.C.;Lo,J.Y.C.
EPI_ISL_144520	Mak,G.C.;Lo,J.Y.C.
EPI_ISL_144519	Mak,G.C.;Lo,J.Y.C.
EPI_ISL_144518	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_144198	Connors,B.C.; Jones,S.L.; Sanow,A.D.; Bisaha,S.A.; Canas,L.C.; Baker,J.A.; Cosme,K.W.; Couch,M.R.; Garrett,C.M.; Weghorst,K.L.; Davis,M.G.; Hanson,J.F.; Yohannes,R.A.; Abshire,J.P.; DeMarcus,L.S.; Lloyd,L.V.; Seidel,A.K.; Smith,J.P.; Fumia,K.F.; Zorich,S.C.; Macias,E.A.; Noe,J.C.; Sjoberg,P.A.
EPI_ISL_144190	Connors,B.C.; Jones,S.L.; Sanow,A.D.; Bisaha,S.A.; Canas,L.C.; Baker,J.A.; Cosme,K.W.; Couch,M.R.; Garrett,C.M.; Weghorst,K.L.; Davis,M.G.; Hanson,J.F.; Yohannes,R.A.; Abshire,J.P.; DeMarcus,L.S.; Lloyd,L.V.; Seidel,A.K.; Smith,J.P.; Fumia,K.F.; Zorich,S.C.; Macias,E.A.; Noe,J.C.; Sjoberg,P.A.
EPI_ISL_144189	Connors,B.C.; Jones,S.L.; Sanow,A.D.; Bisaha,S.A.; Canas,L.C.; Baker,J.A.; Cosme,K.W.; Couch,M.R.; Garrett,C.M.; Weghorst,K.L.; Davis,M.G.; Hanson,J.F.; Yohannes,R.A.; Abshire,J.P.; DeMarcus,L.S.; Lloyd,L.V.; Seidel,A.K.; Smith,J.P.; Fumia,K.F.; Zorich,S.C.; Macias,E.A.; Noe,J.C.; Sjoberg,P.A.
EPI_ISL_144187	Connors,B.C.; Jones,S.L.; Sanow,A.D.; Bisaha,S.A.; Canas,L.C.; Baker,J.A.; Cosme,K.W.; Couch,M.R.; Garrett,C.M.; Weghorst,K.L.; Davis,M.G.; Hanson,J.F.; Yohannes,R.A.; Abshire,J.P.; DeMarcus,L.S.; Lloyd,L.V.; Seidel,A.K.; Smith,J.P.; Fumia,K.F.; Zorich,S.C.; Macias,E.A.; Noe,J.C.; Sjoberg,P.A.
EPI_ISL_144185	Connors,B.C.; Jones,S.L.; Sanow,A.D.; Bisaha,S.A.; Canas,L.C.; Baker,J.A.; Cosme,K.W.; Couch,M.R.; Garrett,C.M.; Weghorst,K.L.; Davis,M.G.; Hanson,J.F.; Yohannes,R.A.; Abshire,J.P.; DeMarcus,L.S.; Lloyd,L.V.; Seidel,A.K.; Smith,J.P.; Fumia,K.F.; Zorich,S.C.; Macias,E.A.; Noe,J.C.; Sjoberg,P.A.
EPI_ISL_144183	Connors,B.C.; Jones,S.L.; Sanow,A.D.; Bisaha,S.A.; Canas,L.C.; Baker,J.A.; Cosme,K.W.; Couch,M.R.; Garrett,C.M.; Weghorst,K.L.; Davis,M.G.; Hanson,J.F.; Yohannes,R.A.; Abshire,J.P.; DeMarcus,L.S.; Lloyd,L.V.; Seidel,A.K.; Smith,J.P.; Fumia,K.F.; Zorich,S.C.; Macias,E.A.; Noe,J.C.; Sjoberg,P.A.
EPI_ISL_144182	Connors,B.C.; Jones,S.L.; Sanow,A.D.; Bisaha,S.A.; Canas,L.C.; Baker,J.A.; Cosme,K.W.; Couch,M.R.; Garrett,C.M.; Weghorst,K.L.; Davis,M.G.; Hanson,J.F.; Yohannes,R.A.; Abshire,J.P.; DeMarcus,L.S.; Lloyd,L.V.; Seidel,A.K.; Smith,J.P.; Fumia,K.F.; Zorich,S.C.; Macias,E.A.; Noe,J.C.; Sjoberg,P.A.
EPI_ISL_144181	NA
EPI_ISL_143704	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_143560	NA
EPI_ISL_143557	Jain,A.; Dangi,T.; Jain,B.; Singh,A.; Mohan,M.; Dwivedi,M.; Prakash,S.; Singh,J.V.; Singh,K.P.; Kumar,A.; Sharma,P.; Upadhyaya,R.C.
EPI_ISL_143441	Jain,A.; Dangi,T.; Jain,B.; Singh,A.; Mohan,M.; Dwivedi,M.; Prakash,S.; Singh,J.V.; Singh,K.P.; Kumar,A.; Sharma,P.; Upadhyaya,R.C.
EPI_ISL_143440	Jain,A.; Dangi,T.; Jain,B.; Singh,A.; Mohan,M.; Dwivedi,M.; Prakash,S.; Singh,J.V.; Singh,K.P.; Kumar,A.; Sharma,P.; Upadhyaya,R.C.
EPI_ISL_143439	NA
EPI_ISL_140316	NA
EPI_ISL_140315	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_140314	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_140310	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_140308	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_139909	NA
EPI_ISL_132244	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_132243	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_132242	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_132241	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_132240	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_132239	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_132238	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_132237	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'

EPI_ISL_94342	NA
EPI_ISL_90619	NA
EPI_ISL_90618	NA
EPI_ISL_90617	NA
EPI_ISL_90616	NA
EPI_ISL_90615	NA
EPI_ISL_90609	NA
EPI_ISL_90608	Fujisaki,Seiichiro; Kim,Namhee; Tapiro,Masato; Odagiri,Takato'
EPI_ISL_86963	NA
EPI_ISL_223127	Liu,T.; Wang,X.; Li,Z.; Wu,J.
EPI_ISL_223126	Liu,T.; Wang,X.; Li,Z.; Wu,J.
EPI_ISL_223125	Chong,Y.; Ikematsu,H.
EPI_ISL_206669	Chong,Y.; Ikematsu,H.
EPI_ISL_206668	Chong,Y.; Ikematsu,H.
EPI_ISL_206667	Chong,Y.; Ikematsu,H.
EPI_ISL_206666	Chong,Y.; Ikematsu,H.
EPI_ISL_206665	Chong,Y.; Ikematsu,H.
EPI_ISL_206664	Chong,Y.; Ikematsu,H.
EPI_ISL_206663	Chong,Y.; Ikematsu,H.
EPI_ISL_206662	Chong,Y.; Ikematsu,H.
EPI_ISL_206661	Chong,Y.; Ikematsu,H.
EPI_ISL_206660	Chong,Y.; Ikematsu,H.
EPI_ISL_206659	Chong,Y.; Ikematsu,H.
EPI_ISL_206658	Chong,Y.; Ikematsu,H.
EPI_ISL_206657	Chong,Y.; Ikematsu,H.
EPI_ISL_206656	Chong,Y.; Ikematsu,H.
EPI_ISL_206655	Chong,Y.; Ikematsu,H.
EPI_ISL_206654	Chong,Y.; Ikematsu,H.
EPI_ISL_206653	Chong,Y.; Ikematsu,H.
EPI_ISL_206652	Chong,Y.; Ikematsu,H.
EPI_ISL_206651	Chong,Y.; Ikematsu,H.
EPI_ISL_206650	Chong,Y.; Ikematsu,H.
EPI_ISL_206649	Chong,Y.; Ikematsu,H.
EPI_ISL_206648	Chong,Y.; Ikematsu,H.
EPI_ISL_206647	Chong,Y.; Ikematsu,H.
EPI_ISL_206646	Chong,Y.; Ikematsu,H.
EPI_ISL_206645	Chong,Y.; Ikematsu,H.
EPI_ISL_206644	Chong,Y.; Ikematsu,H.
EPI_ISL_206643	Chong,Y.; Ikematsu,H.

EPI_ISL_206642	Chong,Y.; Ikematsu,H.
EPI_ISL_206641	Chong,Y.; Ikematsu,H.
EPI_ISL_206640	Chong,Y.; Ikematsu,H.
EPI_ISL_206639	Chong,Y.; Ikematsu,H.
EPI_ISL_206638	Chong,Y.; Ikematsu,H.
EPI_ISL_206637	Chong,Y.; Ikematsu,H.
EPI_ISL_206636	Chong,Y.; Ikematsu,H.
EPI_ISL_206635	Chong,Y.; Ikematsu,H.
EPI_ISL_206634	Chong,Y.; Ikematsu,H.
EPI_ISL_206633	Chong,Y.; Ikematsu,H.
EPI_ISL_206632	Chong,Y.; Ikematsu,H.
EPI_ISL_206631	Chong,Y.; Ikematsu,H.
EPI_ISL_206630	Chong,Y.; Ikematsu,H.
EPI_ISL_206629	Chong,Y.; Ikematsu,H.
EPI_ISL_206628	Chong,Y.; Ikematsu,H.
EPI_ISL_206627	Chong,Y.; Ikematsu,H.
EPI_ISL_206626	Chong,Y.; Ikematsu,H.
EPI_ISL_206625	Chong,Y.; Ikematsu,H.
EPI_ISL_206624	Chong,Y.; Ikematsu,H.
EPI_ISL_206623	Chong,Y.; Ikematsu,H.
EPI_ISL_206622	Chong,Y.; Ikematsu,H.
EPI_ISL_206621	Chong,Y.; Ikematsu,H.
EPI_ISL_206620	Chong,Y.; Ikematsu,H.
EPI_ISL_206619	Chong,Y.; Ikematsu,H.
EPI_ISL_206618	Chong,Y.; Ikematsu,H.
EPI_ISL_206617	Chong,Y.; Ikematsu,H.
EPI_ISL_206616	Chong,Y.; Ikematsu,H.
EPI_ISL_206615	Chong,Y.; Ikematsu,H.
EPI_ISL_206614	Chong,Y.; Ikematsu,H.
EPI_ISL_206613	Chong,Y.; Ikematsu,H.
EPI_ISL_206612	Chong,Y.; Ikematsu,H.
EPI_ISL_206611	Chong,Y.; Ikematsu,H.
EPI_ISL_206610	Chong,Y.; Ikematsu,H.
EPI_ISL_206609	Chong,Y.; Ikematsu,H.
EPI_ISL_206608	Chong,Y.; Ikematsu,H.
EPI_ISL_206607	Chong,Y.; Ikematsu,H.
EPI_ISL_206606	Chong,Y.; Ikematsu,H.
EPI_ISL_206605	Chong,Y.; Ikematsu,H.
EPI_ISL_206604	Chong,Y.; Ikematsu,H.

EPI_ISL_206603	Chong,Y.; Ikematsu,H.
EPI_ISL_206602	Chong,Y.; Ikematsu,H.
EPI_ISL_206601	Chong,Y.; Ikematsu,H.
EPI_ISL_206600	Chong,Y.; Ikematsu,H.
EPI_ISL_206599	Chong,Y.; Ikematsu,H.
EPI_ISL_206598	Chong,Y.; Ikematsu,H.
EPI_ISL_206597	Chong,Y.; Ikematsu,H.
EPI_ISL_206596	Chong,Y.; Ikematsu,H.
EPI_ISL_206595	Chong,Y.; Ikematsu,H.
EPI_ISL_206594	Chong,Y.; Ikematsu,H.
EPI_ISL_206593	Chong,Y.; Ikematsu,H.
EPI_ISL_206592	Chong,Y.; Ikematsu,H.
EPI_ISL_206591	Chong,Y.; Ikematsu,H.
EPI_ISL_206590	Chong,Y.; Ikematsu,H.
EPI_ISL_206589	Chong,Y.; Ikematsu,H.
EPI_ISL_206588	Chong,Y.; Ikematsu,H.
EPI_ISL_206587	Chong,Y.; Ikematsu,H.
EPI_ISL_206586	Chong,Y.; Ikematsu,H.
EPI_ISL_206585	Chong,Y.; Ikematsu,H.
EPI_ISL_206584	Chong,Y.; Ikematsu,H.
EPI_ISL_206583	Chong,Y.; Ikematsu,H.
EPI_ISL_206582	Chong,Y.; Ikematsu,H.
EPI_ISL_206581	Chong,Y.; Ikematsu,H.
EPI_ISL_206580	Chong,Y.; Ikematsu,H.
EPI_ISL_206579	Chong,Y.; Ikematsu,H.
EPI_ISL_206578	Chong,Y.; Ikematsu,H.
EPI_ISL_206577	Chong,Y.; Ikematsu,H.
EPI_ISL_206576	Chong,Y.; Ikematsu,H.
EPI_ISL_206575	Chong,Y.; Ikematsu,H.
EPI_ISL_206574	Tian,G.; Xiong,L.J.; Yong,S.; Ying,X.
EPI_ISL_190083	Tian,G.; Xiong,L.J.; Yong,S.; Ying,X.
EPI_ISL_190082	Tian,G.; Xiong,L.J.; Yong,S.; Ying,X.
EPI_ISL_190081	Tian,G.; Xiong,L.J.; Yong,S.; Ying,X.
EPI_ISL_190080	Tian,G.; Xiong,L.J.; Yong,S.; Ying,X.
EPI_ISL_190079	Tian,G.; Xiong,L.J.; Yong,S.; Ying,X.
EPI_ISL_190078	Bedford,T.; Riley,S.; Barr,I.G.; Broor,S.; Chadha,M.; Cox,N.J.; Daniels,R.S.; Gunasekaran,C.P.; Hurt,A.C.; Kelso,A.; Klimov,A.; Lewis,N.S.; Li,X.; McCauley,J.W.; Odagiri,T.; Potdar,V.; Rambaut,A.; Shu,Y.; Skepner,E.; Smith,D.J.; Suchard,M.A.; Tashiro,M.; Wang,D.; Xu,X.; Lemey,P.; Russell,C.A.
EPI_ISL_186766	Bedford,T.; Riley,S.; Barr,I.G.; Broor,S.; Chadha,M.; Cox,N.J.; Daniels,R.S.; Gunasekaran,C.P.; Hurt,A.C.; Kelso,A.; Klimov,A.; Lewis,N.S.; Li,X.; McCauley,J.W.; Odagiri,T.; Potdar,V.; Rambaut,A.; Shu,Y.; Skepner,E.; Smith,D.J.; Suchard,M.A.; Tashiro,M.; Wang,D.; Xu,X.; Lemey,P.; Russell,C.A.

EPI_ISL_186070	Bedford,T.; Riley,S.; Barr,I.G.; Broor,S.; Chadha,M.; Cox,N.J.; Daniels,R.S.; Gunasekaran,C.P.; Hurt,A.C.; Kelso,A.; Klimov,A.; Lewis,N.S.; Li,X.; McCauley,J.W.; Odagiri,T.; Potdar,V.; Rambaut,A.; Shu,Y.; Skepner,E.; Smith,D.J.; Suchard,M.A.; Tashiro,M.; Wang,D.; Xu,X.; Lemey,P.; Russell,C.A.
EPI_ISL_185993	Bedford,T.; Riley,S.; Barr,I.G.; Broor,S.; Chadha,M.; Cox,N.J.; Daniels,R.S.; Gunasekaran,C.P.; Hurt,A.C.; Kelso,A.; Klimov,A.; Lewis,N.S.; Li,X.; McCauley,J.W.; Odagiri,T.; Potdar,V.; Rambaut,A.; Shu,Y.; Skepner,E.; Smith,D.J.; Suchard,M.A.; Tashiro,M.; Wang,D.; Xu,X.; Lemey,P.; Russell,C.A.
EPI_ISL_185914	Bedford,T.; Riley,S.; Barr,I.G.; Broor,S.; Chadha,M.; Cox,N.J.; Daniels,R.S.; Gunasekaran,C.P.; Hurt,A.C.; Kelso,A.; Klimov,A.; Lewis,N.S.; Li,X.; McCauley,J.W.; Odagiri,T.; Potdar,V.; Rambaut,A.; Shu,Y.; Skepner,E.; Smith,D.J.; Suchard,M.A.; Tashiro,M.; Wang,D.; Xu,X.; Lemey,P.; Russell,C.A.
EPI_ISL_185826	Islam,M.A.; Shah,M.; Islam,M.K.; Ahmed,M.F.; Rahman,M.; Rahman,M.M.; Rahman,S.R.
EPI_ISL_182272	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181831	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181830	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181829	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181805	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181804	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181803	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181802	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181801	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181800	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181799	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181798	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181797	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181796	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181795	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181794	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181793	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181792	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181791	Zhu,R.; Qian,Y.; Sun,Y.; Wang,F.; Zhao,L.; Deng,J.
EPI_ISL_181790	NA
EPI_ISL_177620	NA
EPI_ISL_177619	NA
EPI_ISL_177618	NA
EPI_ISL_177617	NA
EPI_ISL_177616	NA
EPI_ISL_177560	NA
EPI_ISL_177559	NA
EPI_ISL_177557	NA
EPI_ISL_177556	NA
EPI_ISL_177555	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_173982	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_173981	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato

EPI_ISL_173980	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_173979	Saito, Reiko; Takemae, Nobuhiro; Saito, Takehiko; Shobugawa, Yugo; Kondo, Hiroki; Hibino, Akinobu
EPI_ISL_169391	NA
EPI_ISL_169389	NA
EPI_ISL_166232	Deng,Y-M.; Iannello,P.; Spirason,N.; Jolley,L.; Lau,H.; Komadina,N.
EPI_ISL_165442	Y,Yasui; S,Kobayashi; T,Yamashita; H,Minagawa
EPI_ISL_165441	Y,Yasui; S,Kobayashi; T,Yamashita; H,Minagawa
EPI_ISL_165440	Zhong,J.; Liang,L; Huang,P.; Zhu,X.; Zou,L.; Yu,S.; Zhang,X.; Zhang,Y.; Ni,H.; Yan,J.
EPI_ISL_165437	Zhong,J.; Liang,L; Huang,P.; Zhu,X.; Zou,L.; Yu,S.; Zhang,X.; Zhang,Y.; Ni,H.; Yan,J.
EPI_ISL_165436	Zhong,J.; Liang,L; Huang,P.; Zhu,X.; Zou,L.; Yu,S.; Zhang,X.; Zhang,Y.; Ni,H.; Yan,J.
EPI_ISL_165435	Zhong,J.; Liang,L; Huang,P.; Zhu,X.; Zou,L.; Yu,S.; Zhang,X.; Zhang,Y.; Ni,H.; Yan,J.
EPI_ISL_165434	Zhong,J.; Liang,L; Huang,P.; Zhu,X.; Zou,L.; Yu,S.; Zhang,X.; Zhang,Y.; Ni,H.; Yan,J.
EPI_ISL_165433	Zhong,J.; Liang,L; Huang,P.; Zhu,X.; Zou,L.; Yu,S.; Zhang,X.; Zhang,Y.; Ni,H.; Yan,J.
EPI_ISL_165432	Zhong,J.; Liang,L; Huang,P.; Zhu,X.; Zou,L.; Yu,S.; Zhang,X.; Zhang,Y.; Ni,H.; Yan,J.
EPI_ISL_165431	Zhong,J.; Liang,L; Huang,P.; Zhu,X.; Zou,L.; Yu,S.; Zhang,X.; Zhang,Y.; Ni,H.; Yan,J.
EPI_ISL_165430	Y,Yasui; S,Kobayashi; T,Yamashita; H,Minagawa
EPI_ISL_165351	Y,Yasui; S,Kobayashi; T,Yamashita; H,Minagawa
EPI_ISL_165350	Y,Yasui; S,Kobayashi; T,Yamashita; H,Minagawa
EPI_ISL_165349	Y,Yasui; S,Kobayashi; T,Yamashita; H,Minagawa
EPI_ISL_165348	Y,Yasui; S,Kobayashi; T,Yamashita; H,Minagawa
EPI_ISL_165347	Kondo,H.; Zaraket,H.; Saito,K.; Dapat,C.; Dapat,I.; Saito,R.
EPI_ISL_162217	Kondo,H.; Zaraket,H.; Saito,K.; Dapat,C.; Dapat,I.; Saito,R.
EPI_ISL_162216	Kondo,H.; Zaraket,H.; Saito,K.; Dapat,C.; Dapat,I.; Saito,R.
EPI_ISL_162215	Rutvisuttinunt,W.; Chinnawirotisan,P.; Simasathien,S.; Shrestha,S.K.; Yoon,I.K.; Klungthong,C.; Fernandez,S.
EPI_ISL_161376	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161375	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161374	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161373	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161372	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161371	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161370	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161369	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161368	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161367	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161366	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161365	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161364	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161363	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161362	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.

EPI_ISL_161361	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161360	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161359	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161358	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161357	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161356	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161355	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161354	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161353	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161352	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161351	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161350	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161349	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161348	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_161347	Deng,Y-D.; Iannello,P.; Spirason,N.; Jelley,L.; Lau,H.; Komadina,N.
EPI_ISL_161276	Deng,Y-D.; Iannello,P.; Spirason,N.; Jelley,L.; Lau,H.; Komadina,N.
EPI_ISL_161275	Deng,Y-D.; Iannello,P.; Spirason,N.; Jelley,L.; Lau,H.; Komadina,N.
EPI_ISL_161266	NA
EPI_ISL_156914	NA
EPI_ISL_156911	NA
EPI_ISL_156908	NA
EPI_ISL_156906	NA
EPI_ISL_156904	NA
EPI_ISL_156903	NA
EPI_ISL_156902	NA
EPI_ISL_156896	NA
EPI_ISL_156895	NA
EPI_ISL_153941	NA
EPI_ISL_153940	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153923	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153922	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153921	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153920	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153919	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153915	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153914	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153913	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153912	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153911	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato

EPI_ISL_153910	Connors,B.C.; Jones,S.L.; Bisaha,S.A.; Canas,L.C.; Baker,J.A.; Cosme,K.W.; Couch,M.R.; Garrett,C.M.; Weghorst,K.L.; Davis,M.G.; Hanson,J.F.; Yohannes,R.A.; Abshire,J.P.; DeMarcus,L.S.; Smith,J.P.; Fumia,K.F.; Zorich,S.C.; Macias,E.A.; Noe,J.C.; Sjoberg,P.A.
EPI_ISL_153645	NA
EPI_ISL_153063	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153062	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153061	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153060	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153059	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153058	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153057	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153056	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153055	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153054	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153053	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153052	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153051	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153050	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153049	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153048	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153047	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_153046	Wang,Z.-G.; Yang,T.-T.; Qing,C.
EPI_ISL_152962	Wang,Z.-G.; Yang,T.-T.; Qing,C.
EPI_ISL_152961	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_152911	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_152909	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_152908	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_152905	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_152904	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_152900	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_152897	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_152896	Yasui,Y; Kobayashi,S; Yamashita,T; Minagawa,H
EPI_ISL_152871	Yasui,Y; Kobayashi,S; Yamashita,T; Minagawa,H
EPI_ISL_152870	Yasui,Y; Kobayashi,S; Yamashita,T; Minagawa,H
EPI_ISL_152869	Yasui,Y; Kobayashi,S; Yamashita,T; Minagawa,H
EPI_ISL_152868	Yasui,Y; Kobayashi,S; Yamashita,T; Minagawa,H
EPI_ISL_152867	Yasui,Y; Kobayashi,S; Yamashita,T; Minagawa,H
EPI_ISL_152866	Yasui,Y; Kobayashi,S; Yamashita,T; Minagawa,H
EPI_ISL_152865	Deng,Y-M; Iannello,P; Spirason,N; Jolley,L; Lau,H; Komadina,N
EPI_ISL_152847	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149951	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.

EPI_ISL_149950	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149949	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149948	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149947	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149946	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149945	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149944	NA
EPI_ISL_145801	Fang,Q.X.; Gao,Y.; Yang,X.H.; Chen,M.F.; Guo,X.L.; Wei,L.
EPI_ISL_145787	Fang,Q.X.; Gao,Y.; Yang,X.H.; Chen,M.F.; Guo,X.L.; Wei,L.
EPI_ISL_145786	Fang,Q.X.; Gao,Y.; Yang,X.H.; Chen,M.F.; Guo,X.L.; Wei,L.
EPI_ISL_145765	Fang,Q.X.; Gao,Y.; Yang,X.H.; Chen,M.F.; Guo,X.L.; Wei,L.
EPI_ISL_145764	Fang,Q.X.; Gao,Y.; Yang,X.H.; Chen,M.F.; Guo,X.L.; Wei,L.
EPI_ISL_145763	Fang,Q.X.; Gao,Y.; Yang,X.H.; Chen,M.F.; Guo,X.L.; Wei,L.
EPI_ISL_145762	Fang,Q.X.; Gao,Y.; Yang,X.H.; Chen,M.F.; Guo,X.L.; Wei,L.
EPI_ISL_145761	Fang,Q.X.; Gao,Y.; Yang,X.H.; Chen,M.F.; Guo,X.L.; Wei,L.
EPI_ISL_145760	Fang,Q.X.; Gao,Y.; Yang,X.H.; Chen,M.F.; Guo,X.L.; Wei,L.
EPI_ISL_145759	Fang,Q.X.; Gao,Y.; Yang,X.H.; Chen,M.F.; Guo,X.L.; Wei,L.
EPI_ISL_145758	Fang,Q.X.; Gao,Y.; Yang,X.H.; Chen,M.F.; Guo,X.L.; Wei,L.
EPI_ISL_145757	Fang,Q.X.; Gao,Y.; Yang,X.H.; Chen,M.F.; Guo,X.L.; Wei,L.
EPI_ISL_145755	Fang,Q.X.; Gao,Y.; Yang,X.H.; Chen,M.F.; Guo,X.L.; Wei,L.
EPI_ISL_145754	NA
EPI_ISL_145550	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_144969	NA
EPI_ISL_141663	NA
EPI_ISL_140903	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140902	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140901	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140900	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140899	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140898	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140897	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140896	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140895	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140894	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140893	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140892	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140891	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140890	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140889	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.

EPI_ISL_140888	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140887	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140886	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140885	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140884	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140883	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140882	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140715	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140714	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140713	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140712	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140711	Mokhtari Azad,T.; Shafiei Jandaghi,N.Z.; Rezaei,F.
EPI_ISL_140710	Kondo,H.; Zaraket,H.; Saito,K.; Dapat,C.; Dapat,I.; Saito,R.
EPI_ISL_140704	Kondo,H.; Zaraket,H.; Saito,K.; Dapat,C.; Dapat,I.; Saito,R.
EPI_ISL_140703	Kondo,H.; Zaraket,H.; Saito,K.; Dapat,C.; Dapat,I.; Saito,R.
EPI_ISL_140702	Kondo,H.; Zaraket,H.; Saito,K.; Dapat,C.; Dapat,I.; Saito,R.
EPI_ISL_140701	Kondo,H.; Zaraket,H.; Saito,K.; Dapat,C.; Dapat,I.; Saito,R.
EPI_ISL_140700	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_136540	NA
EPI_ISL_132808	Connors,B.C.; Jones,S.L.; Adams,J.E.; Bisaha,S.A.; Canas,L.C.; Cosme,K.W.; Davis,M.G.; Yohannes,R.A.; Abshire,J.P.; DeMarcus,L.S.; LLoyd,L.V.; Seidel,A.K.; Smith,J.P.; Macintosh,V.H.; Fumia,K.F.; Macias,E.A.; Noe,J.C.; Sjoberg,P.A.; Zorich,S.C.
EPI_ISL_132804	Connors,B.C.; Jones,S.L.; Adams,J.E.; Bisaha,S.A.; Canas,L.C.; Cosme,K.W.; Davis,M.G.; Yohannes,R.A.; Abshire,J.P.; DeMarcus,L.S.; LLoyd,L.V.; Seidel,A.K.; Smith,J.P.; Macintosh,V.H.; Fumia,K.F.; Macias,E.A.; Noe,J.C.; Sjoberg,P.A.; Zorich,S.C.
EPI_ISL_132803	Connors,B.C.; Jones,S.L.; Adams,J.E.; Bisaha,S.A.; Canas,L.C.; Cosme,K.W.; Davis,M.G.; Yohannes,R.A.; Abshire,J.P.; DeMarcus,L.S.; LLoyd,L.V.; Seidel,A.K.; Smith,J.P.; Macintosh,V.H.; Fumia,K.F.; Macias,E.A.; Noe,J.C.; Sjoberg,P.A.; Zorich,S.C.
EPI_ISL_132802	Connors,B.C.; Jones,S.L.; Adams,J.E.; Bisaha,S.A.; Canas,L.C.; Cosme,K.W.; Davis,M.G.; Yohannes,R.A.; Abshire,J.P.; DeMarcus,L.S.; LLoyd,L.V.; Seidel,A.K.; Smith,J.P.; Macintosh,V.H.; Fumia,K.F.; Macias,E.A.; Noe,J.C.; Sjoberg,P.A.; Zorich,S.C.
EPI_ISL_132801	Connors,B.C.; Jones,S.L.; Adams,J.E.; Bisaha,S.A.; Canas,L.C.; Cosme,K.W.; Davis,M.G.; Yohannes,R.A.; Abshire,J.P.; DeMarcus,L.S.; LLoyd,L.V.; Seidel,A.K.; Smith,J.P.; Macintosh,V.H.; Fumia,K.F.; Macias,E.A.; Noe,J.C.; Sjoberg,P.A.; Zorich,S.C.
EPI_ISL_132800	Connors,B.C.; Jones,S.L.; Adams,J.E.; Bisaha,S.A.; Canas,L.C.; Cosme,K.W.; Davis,M.G.; Yohannes,R.A.; Abshire,J.P.; DeMarcus,L.S.; LLoyd,L.V.; Seidel,A.K.; Smith,J.P.; Macintosh,V.H.; Fumia,K.F.; Macias,E.A.; Noe,J.C.; Sjoberg,P.A.; Zorich,S.C.
EPI_ISL_132799	Connors,B.C.; Jones,S.L.; Adams,J.E.; Bisaha,S.A.; Canas,L.C.; Cosme,K.W.; Davis,M.G.; Yohannes,R.A.; Abshire,J.P.; DeMarcus,L.S.; LLoyd,L.V.; Seidel,A.K.; Smith,J.P.; Macintosh,V.H.; Fumia,K.F.; Macias,E.A.; Noe,J.C.; Sjoberg,P.A.; Zorich,S.C.
EPI_ISL_132796	NA
EPI_ISL_129435	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_129434	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_129433	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_129035	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_129034	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_129033	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_129032	Deng,Y-M; Iannello,P; Caldwell,N; Jolley,L; Komadina,N
EPI_ISL_128336	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_107864	NA
EPI_ISL_107863	NA

EPI_ISL_107862	NA
EPI_ISL_107861	NA
EPI_ISL_107860	NA
EPI_ISL_107859	NA
EPI_ISL_107841	NA
EPI_ISL_107816	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tapiro,Masato; Odagiri,Takato'
EPI_ISL_100796	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_100795	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_100794	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_100793	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_99886	NA
EPI_ISL_99885	NA
EPI_ISL_99884	NA
EPI_ISL_99777	Deng,Y-M.; Iannello,P.; Caldwell,N.; Leang,S-K.; Komadina,N.
EPI_ISL_99739	Fujisaki,Seiichiro; Kim,Namhee; Tapiro,Masato; Odagiri,Takato'
EPI_ISL_99706	Fujisaki,Seiichiro; Kim,Namhee; Tapiro,Masato; Odagiri,Takato'
EPI_ISL_99705	NA
EPI_ISL_96023	NA
EPI_ISL_96022	NA
EPI_ISL_96021	NA
EPI_ISL_96020	NA
EPI_ISL_87753	Garner,J.L.; Connors,B.; Canas,L.; Melendez,D.; Herrera,K.; Cormier,T.; Lowman,A.; Guerrero,A.; Abshire,J.; Smith,J.P.; Compton,D.; Lopez,C.C.; Macintosh,V.; Macias,E.; Noe,J.C.; Sjoberg,P.
EPI_ISL_87752	Garner,J.L.; Connors,B.; Canas,L.; Melendez,D.; Herrera,K.; Cormier,T.; Lowman,A.; Guerrero,A.; Abshire,J.; Smith,J.P.; Compton,D.; Lopez,C.C.; Macintosh,V.; Macias,E.; Noe,J.C.; Sjoberg,P.
EPI_ISL_87751	Garner,J.L.; Connors,B.; Canas,L.; Melendez,D.; Herrera,K.; Cormier,T.; Lowman,A.; Guerrero,A.; Abshire,J.; Smith,J.P.; Compton,D.; Lopez,C.C.; Macintosh,V.; Macias,E.; Noe,J.C.; Sjoberg,P.
EPI_ISL_87750	Garner,J.L.; Connors,B.; Canas,L.; Melendez,D.; Herrera,K.; Cormier,T.; Lowman,A.; Guerrero,A.; Abshire,J.; Smith,J.P.; Compton,D.; Lopez,C.C.; Macintosh,V.; Macias,E.; Noe,J.C.; Sjoberg,P.
EPI_ISL_87749	Machabishvili,A.; Jashiashvili,T.; Tevdoradze,T.; Chanturia,G.; Zhgenti,E.; Maglakelidze,G.; Farlow,J.; Nikolic,M.; Lyons,A.; Houng,H.-S.
EPI_ISL_118481	Machabishvili,A.; Jashiashvili,T.; Tevdoradze,T.; Chanturia,G.; Zhgenti,E.; Maglakelidze,G.; Farlow,J.; Nikolic,M.; Lyons,A.; Houng,H.-S.
EPI_ISL_118482	Machabishvili,A.; Jashiashvili,T.; Tevdoradze,T.; Chanturia,G.; Zhgenti,E.; Maglakelidze,G.; Farlow,J.; Nikolic,M.; Lyons,A.; Houng,H.-S.
EPI_ISL_118483	Lee,H.K.; Tang,J.W.-T.; Kong,D.H.-L.; Koay,E.S.-C.
EPI_ISL_171008	Biswas,D.; Yadav,K.; Buragohain,M.; Dutta,M.; Sarmah,K.; Borkakoty,B.; Mahanta,J.
EPI_ISL_171009	Biswas,D.; Yadav,K.; Dutta,M.; Sarmah,K.; Borkakoty,B.; Mahanta,J.
EPI_ISL_171097	Biswas,D.; Yadav,K.; Dutta,M.; Sarmah,K.; Borkakoty,B.; Mahanta,J.
EPI_ISL_171098	Fang,Q.; Gao,Y.
EPI_ISL_171338	Fang,Q.; Gao,Y.
EPI_ISL_171339	Rutvisuttinunt,W.; Chinnawirotisan,P.; Thaisomboonsuk,B.; Rodpradit,P.; Ajariyahajorn,C.; Manasatienkij,W.; Simasathien,S.; Shrestha,S.K.; Yoon,I.-K.; Fernandez,S.; Klunghthong,C.
EPI_ISL_97284	Connors,B.C.; Jones,S.L.; Adams,J.E.; Bisaha,S.A.; Canas,L.C.; Cormier,T.L.; Cosmer,K.W.; Davis,M.G.; Leaver,M.M.; Okoro,B.N.; Yohannes,R.A.; Abshire,J.P.; Lloyd,L.V.; Schlorman,C.A.; Tastad,K.J.; Smith,J.P.; Macintosh,V.H.; Fumia,K.F.; Macias,E.A.; Noe,J.C.; Sjoberg,P.A.

EPI_ISL_139012	Tohma,K.; Suzuki,A.
EPI_ISL_139013	Tohma,K.; Suzuki,A.
EPI_ISL_139014	Tohma,K.; Suzuki,A.
EPI_ISL_139015	Tohma,K.; Suzuki,A.
EPI_ISL_139016	Tohma,K.; Suzuki,A.
EPI_ISL_139017	Tohma,K.; Suzuki,A.
EPI_ISL_139018	Tohma,K.; Suzuki,A.
EPI_ISL_139019	Tohma,K.; Suzuki,A.
EPI_ISL_139020	Tohma,K.; Suzuki,A.
EPI_ISL_139021	Tohma,K.; Suzuki,A.
EPI_ISL_139022	Tohma,K.; Suzuki,A.
EPI_ISL_139023	Tohma,K.; Suzuki,A.
EPI_ISL_139024	Tohma,K.; Suzuki,A.
EPI_ISL_139025	Tohma,K.; Suzuki,A.
EPI_ISL_139026	Tohma,K.; Suzuki,A.
EPI_ISL_139027	Tohma,K.; Suzuki,A.
EPI_ISL_139028	Tohma,K.; Suzuki,A.
EPI_ISL_139029	Tohma,K.; Suzuki,A.
EPI_ISL_139030	Tohma,K.; Suzuki,A.
EPI_ISL_139031	Tohma,K.; Suzuki,A.
EPI_ISL_139032	Tohma,K.; Suzuki,A.
EPI_ISL_139033	Tohma,K.; Suzuki,A.
EPI_ISL_139034	Tohma,K.; Suzuki,A.
EPI_ISL_139035	Tohma,K.; Suzuki,A.
EPI_ISL_139036	Tohma,K.; Suzuki,A.
EPI_ISL_139037	Tohma,K.; Suzuki,A.
EPI_ISL_139038	Tohma,K.; Suzuki,A.
EPI_ISL_139039	Tohma,K.; Suzuki,A.
EPI_ISL_139040	Tohma,K.; Suzuki,A.
EPI_ISL_139041	Tohma,K.; Suzuki,A.
EPI_ISL_139042	Tohma,K.; Suzuki,A.
EPI_ISL_139043	Tohma,K.; Suzuki,A.
EPI_ISL_139044	Tohma,K.; Suzuki,A.
EPI_ISL_139045	Tohma,K.; Suzuki,A.
EPI_ISL_139046	Tohma,K.; Suzuki,A.
EPI_ISL_139047	Tohma,K.; Suzuki,A.
EPI_ISL_139048	Tohma,K.; Suzuki,A.
EPI_ISL_139049	Tohma,K.; Suzuki,A.
EPI_ISL_139050	Tohma,K.; Suzuki,A.

EPI_ISL_139051	Tohma,K.; Suzuki,A.
EPI_ISL_139052	Tohma,K.; Suzuki,A.
EPI_ISL_139053	Tohma,K.; Suzuki,A.
EPI_ISL_139054	Tohma,K.; Suzuki,A.
EPI_ISL_139055	Tohma,K.; Suzuki,A.
EPI_ISL_139056	Tohma,K.; Suzuki,A.
EPI_ISL_139057	Tohma,K.; Suzuki,A.
EPI_ISL_139058	Lee,H.K.; Tang,J.W.-T.; Loh,T.P.; Kong,D.H.-L.; Yap,H.K.; Koay,E.S.-C.
EPI_ISL_149952	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149953	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149954	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149955	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149956	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149957	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149958	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149959	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149960	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149961	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149962	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149963	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149964	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149965	Jain,A.; Dangi,T.; Jain,B.; Singh,A.K.; Dwivedi,M.; Verma,A.K.; Singh,J.V.; Kumar,R.
EPI_ISL_149966	Yang,J.R.; Kuo,C.Y.; Huang,H.Y.; Wu,F.T.; Huang,Y.L.; Cheng,C.Y.; Su,Y.T.; Chang,F.Y.; Wu,H.S.; Liu,M.T.; Yang,J.-R.; Wu,H.-S.; Liu,M.-T.
EPI_ISL_154231	Noh,J.; Song,J.; Cheong,H.; Choi,W.; Lee,J.; Wie,S.; Kim,Y.; Jeong,H.; Kim,W.
EPI_ISL_154232	Wang,Z.-G.; Yang,T.-T.; Qing,C.
EPI_ISL_154295	Wang,Z.-G.; Yang,T.-T.; Qing,C.
EPI_ISL_154296	Connors,B.C.; Jones,S.L.; Sarria,S.H.; Bisaha,S.A.; Canas,L.C.; Baker,J.A.; Couch,M.R.; Garrett,C.M.; Powell,M.L.; Weghorst,K.L.; Davis,M.G.; Hanson,J.F.; Yohannes,R.A.; Abshire,J.P.; DeMarcus,L.S.; Smith,J.P.; Fumia,K.F.; Zorich,S.C.; Macias,E.A.; Noe,J.C.; Sjoberg,P.A.
EPI_ISL_159331	Rutvisuttinunt,W.; Chinnawirotisan,P.; Simasathien,S.; Shrestha,S.K.; Yoon,I.K.; Klungthong,C.; Fernandez,S.
EPI_ISL_186887	Bedford,T.; Riley,S.; Barr,I.G.; Broor,S.; Chadha,M.; Cox,N.J.; Daniels,R.S.; Gunasekaran,C.P.; Hurt,A.C.; Kelso,A.; Klimov,A.; Lewis,N.S.; Li,X.; McCauley,J.W.; Odagiri,T.; Potdar,V.; Rambaut,A.; Shu,Y.; Skepner,E.; Smith,D.J.; Suchard,M.A.; Tashiro,M.; Wang,D.; Xu,X.; Lemey,P.; Russell,C.A.
EPI_ISL_186908	Bedford,T.; Riley,S.; Barr,I.G.; Broor,S.; Chadha,M.; Cox,N.J.; Daniels,R.S.; Gunasekaran,C.P.; Hurt,A.C.; Kelso,A.; Klimov,A.; Lewis,N.S.; Li,X.; McCauley,J.W.; Odagiri,T.; Potdar,V.; Rambaut,A.; Shu,Y.; Skepner,E.; Smith,D.J.; Suchard,M.A.; Tashiro,M.; Wang,D.; Xu,X.; Lemey,P.; Russell,C.A.
EPI_ISL_187085	Bedford,T.; Riley,S.; Barr,I.G.; Broor,S.; Chadha,M.; Cox,N.J.; Daniels,R.S.; Gunasekaran,C.P.; Hurt,A.C.; Kelso,A.; Klimov,A.; Lewis,N.S.; Li,X.; McCauley,J.W.; Odagiri,T.; Potdar,V.; Rambaut,A.; Shu,Y.; Skepner,E.; Smith,D.J.; Suchard,M.A.; Tashiro,M.; Wang,D.; Xu,X.; Lemey,P.; Russell,C.A.
EPI_ISL_187114	Bedford,T.; Riley,S.; Barr,I.G.; Broor,S.; Chadha,M.; Cox,N.J.; Daniels,R.S.; Gunasekaran,C.P.; Hurt,A.C.; Kelso,A.; Klimov,A.; Lewis,N.S.; Li,X.; McCauley,J.W.; Odagiri,T.; Potdar,V.; Rambaut,A.; Shu,Y.; Skepner,E.; Smith,D.J.; Suchard,M.A.; Tashiro,M.; Wang,D.; Xu,X.; Lemey,P.; Russell,C.A.
EPI_ISL_187623	Bedford,T.; Riley,S.; Barr,I.G.; Broor,S.; Chadha,M.; Cox,N.J.; Daniels,R.S.; Gunasekaran,C.P.; Hurt,A.C.; Kelso,A.; Klimov,A.; Lewis,N.S.; Li,X.; McCauley,J.W.; Odagiri,T.; Potdar,V.; Rambaut,A.; Shu,Y.; Skepner,E.; Smith,D.J.; Suchard,M.A.; Tashiro,M.; Wang,D.; Xu,X.; Lemey,P.; Russell,C.A.

EPI_ISL_187672	Bedford,T.; Riley,S.; Barr,I.G.; Broor,S.; Chadha,M.; Cox,N.J.; Daniels,R.S.; Gunasekaran,C.P.; Hurt,A.C.; Kelso,A.; Klimov,A.; Lewis,N.S.; Li,X.; McCauley,J.W.; Odagiri,T.; Potdar,V.; Rambaut,A.; Shu,Y.; Skepner,E.; Smith,D.J.; Suchard,M.A.; Tashiro,M.; Wang,D.; Xu,X.; Lemey,P.; Russell,C.A.
EPI_ISL_187683	Bedford,T.; Riley,S.; Barr,I.G.; Broor,S.; Chadha,M.; Cox,N.J.; Daniels,R.S.; Gunasekaran,C.P.; Hurt,A.C.; Kelso,A.; Klimov,A.; Lewis,N.S.; Li,X.; McCauley,J.W.; Odagiri,T.; Potdar,V.; Rambaut,A.; Shu,Y.; Skepner,E.; Smith,D.J.; Suchard,M.A.; Tashiro,M.; Wang,D.; Xu,X.; Lemey,P.; Russell,C.A.
EPI_ISL_187821	Bedford,T.; Riley,S.; Barr,I.G.; Broor,S.; Chadha,M.; Cox,N.J.; Daniels,R.S.; Gunasekaran,C.P.; Hurt,A.C.; Kelso,A.; Klimov,A.; Lewis,N.S.; Li,X.; McCauley,J.W.; Odagiri,T.; Potdar,V.; Rambaut,A.; Shu,Y.; Skepner,E.; Smith,D.J.; Suchard,M.A.; Tashiro,M.; Wang,D.; Xu,X.; Lemey,P.; Russell,C.A.
EPI_ISL_187869	Bedford,T.; Riley,S.; Barr,I.G.; Broor,S.; Chadha,M.; Cox,N.J.; Daniels,R.S.; Gunasekaran,C.P.; Hurt,A.C.; Kelso,A.; Klimov,A.; Lewis,N.S.; Li,X.; McCauley,J.W.; Odagiri,T.; Potdar,V.; Rambaut,A.; Shu,Y.; Skepner,E.; Smith,D.J.; Suchard,M.A.; Tashiro,M.; Wang,D.; Xu,X.; Lemey,P.; Russell,C.A.
EPI_ISL_187979	Khemnu,N.; Gaywee,J.; Bodhidatta,L.; Wacharaplaesadee,S.; Sirisopana,N.; Swierczewski,B.E.; Mason,C.J.
EPI_ISL_217038	Liu,T.; Wang,X.; Li,Z.
EPI_ISL_217057	NA
EPI_ISL_150623	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_158841	NA
EPI_ISL_158842	NA
EPI_ISL_158843	NA
EPI_ISL_158844	NA
EPI_ISL_159629	NA
EPI_ISL_159630	NA
EPI_ISL_159631	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Odagiri,Takato
EPI_ISL_166849	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Odagiri,Takato
EPI_ISL_166850	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Odagiri,Takato
EPI_ISL_166923	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174821	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174822	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174823	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174824	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174825	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174826	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174827	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174828	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174829	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174830	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174831	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174832	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174833	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174834	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174835	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174836	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174837	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174838	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato

EPI_ISL_174839	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174840	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174841	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174842	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174843	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Watanabe,Shinji; Odagiri,Takato
EPI_ISL_174844	Li,J.; Zhou,Y.Y.; Kou,Y.; Zheng,Z.B.; Yu,X.F.
EPI_ISL_133583	Fujisaki,Seiichiro; Kim,Namhee; Reiko,Itoh; Tashiro,Masato; Odagiri,Takato
EPI_ISL_93017	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_150633	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93009	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_96811	Fujisaki,Seiichiro; Kim,Namhee; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_150070	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_150619	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_158162	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93003	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato
EPI_ISL_93007	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_158170	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_96817	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_150627	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_96812	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_158178	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_158887	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_158164	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93012	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_101351	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_101476	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_150634	Takashita,Emi; Fujisaki,Seiichiro; Ejima,Miho; Odagiri,Takato; Tashiro,Masato
EPI_ISL_158173	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_96824	Fujisaki,Seiichiro; Kim,Namhee; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_158159	Fujisaki,Seiichiro; Kim,Namhee; Itoh,Reiko; Tashiro,Masato; Odagiri,Takato
EPI_ISL_150621	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_158160	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_158171	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93002	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_158161	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_150618	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato
EPI_ISL_93005	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_93006	Fujisaki,Seiichiro; Kim,Namhee; Tahiro,Masato; Odagiri,Takato'
EPI_ISL_122205	Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Tashiro,Masato; Odagiri,Takato

EPI_ISL_90072	Fujisaki,Seiichiro; Kim,Namhee; Tapiro,Masato; Odagiri,Takato'
EPI_ISL_93004	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato'
EPI_ISL_133572	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato
EPI_ISL_133573	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato
EPI_ISL_133574	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato
EPI_ISL_133575	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato
EPI_ISL_133576	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato
EPI_ISL_133577	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tashiro,Masato; Odagiri,Takato
EPI_ISL_166373	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Odagiri,Takato
EPI_ISL_166374	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Odagiri,Takato
EPI_ISL_166375	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Odagiri,Takato
EPI_ISL_166376	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Odagiri,Takato
EPI_ISL_166377	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Odagiri,Takato
EPI_ISL_166378	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Odagiri,Takato
EPI_ISL_166379	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Odagiri,Takato
EPI_ISL_166380	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Odagiri,Takato
EPI_ISL_166851	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Odagiri,Takato
EPI_ISL_166852	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Odagiri,Takato
EPI_ISL_166853	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Odagiri,Takato
EPI_ISL_166854	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Odagiri,Takato
EPI_ISL_166855	Takashita,Emi; Fujisaki,Seiichiro; Shirakura,Masayuki; Odagiri,Takato
EPI_ISL_166856	Takashita,Emi; Fujisaki,Seiichiro; Itoh,Reiko; Miura,Mai; Ejima,Miho; Tashiro,Masato; Odagiri,Takato
EPI_ISL_151418	Deng,Y-M; Iannello,P; Caldwell,N; Komadina,N.
EPI_ISL_138455	NA
EPI_ISL_100822	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_100823	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_100824	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_100825	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_100826	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_100838	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_100839	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_100840	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_100841	NA
EPI_ISL_126266	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126269	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126274	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126276	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126278	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126279	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu

EPI_ISL_126283	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126287	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126289	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126292	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126294	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126297	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126299	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126300	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126304	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126310	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126318	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126319	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126323	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126327	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126328	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126329	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126335	Yu Lan,Xiyan Li,Xiang Zhao,Yanhui Cheng,minju Tan,Yaoyao Chen,Bin Liu,Dayan Wang,Dexin Li,Yuelong Shu
EPI_ISL_126341	NA
EPI_ISL_117488	NA
EPI_ISL_117489	NA
EPI_ISL_158822	Fujisaki,Seiichiro; Kim,Namhee; Tapiro,Masato; Odagiri,Takato'
EPI_ISL_154777	NA
EPI_ISL_154778	NA
EPI_ISL_154779	Deng,Y-M; Iannello,P; Spirason,N; Jelley,L; Lau,H; Komadina,N
EPI_ISL_158839	Fujisaki,Seiichiro; Kim,Namhee; Tapiro,Masato; Odagiri,Takato'
EPI_ISL_118647	Deng,Y-M; Iannello,P; Spirason,N; Jelley,L; Lau,H; Komadina,N
EPI_ISL_93022	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tapiro,Masato; Odagiri,Takato'
EPI_ISL_113373	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tapiro,Masato; Odagiri,Takato'
EPI_ISL_113374	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tapiro,Masato; Odagiri,Takato'
EPI_ISL_113375	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tapiro,Masato; Odagiri,Takato'
EPI_ISL_113376	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tapiro,Masato; Odagiri,Takato'
EPI_ISL_113377	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tapiro,Masato; Odagiri,Takato'
EPI_ISL_113378	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tapiro,Masato; Odagiri,Takato'
EPI_ISL_113379	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tapiro,Masato; Odagiri,Takato'
EPI_ISL_113380	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tapiro,Masato; Odagiri,Takato'
EPI_ISL_113381	Fujisaki,Seiichiro; Kim,Namhee; Tapiro,Masato; Odagiri,Takato'
EPI_ISL_122200	Fujisaki,Seiichiro; Kim,Namhee; Aya,Sato; Tapiro,Masato; Odagiri,Takato'
EPI_ISL_158163	NA
EPI_ISL_240511	Horm, S-V; Dussart,P

EPI_ISL_240510	Horm, S-V; Dussart,P
EPI_ISL_240509	Horm, S-V; Dussart,P
EPI_ISL_240508	Horm, S-V; Dussart,P
EPI_ISL_240507	Horm, S-V; Dussart,P
EPI_ISL_240506	Horm, S-V; Dussart,P
EPI_ISL_240505	Horm, S-V; Dussart,P
EPI_ISL_240504	Horm, S-V; Dussart,P
EPI_ISL_240503	Horm, S-V; Dussart,P
EPI_ISL_240502	Horm, S-V; Dussart,P
EPI_ISL_240501	Horm, S-V; Dussart,P
EPI_ISL_240500	Horm, S-V; Dussart,P
EPI_ISL_240499	NA
EPI_ISL_212166	NA
EPI_ISL_212165	NA
EPI_ISL_348528	NA
EPI_ISL_348527	NA
EPI_ISL_348424	NA
EPI_ISL_348423	NA
EPI_ISL_348422	NA
EPI_ISL_348421	NA
EPI_ISL_348420	NA
EPI_ISL_348419	NA
EPI_ISL_348418	NA
EPI_ISL_348417	NA
EPI_ISL_281402	NA
EPI_ISL_390872	NA
EPI_ISL_390871	NA
EPI_ISL_390870	NA
EPI_ISL_390869	NA
EPI_ISL_390868	NA
EPI_ISL_390867	NA
EPI_ISL_390866	NA
EPI_ISL_390865	NA
EPI_ISL_390864	NA
EPI_ISL_390863	NA
EPI_ISL_390862	NA
EPI_ISL_390861	NA
EPI_ISL_390860	NA
EPI_ISL_390859	NA

EPI_ISL_390858	NA
EPI_ISL_390857	Velasco,J.M.S.; Valderama,M.T.G.; Diones,P.C.S.; Leonardia,S.; Alcantara,S.; Chinnawirotisan,P.; Phonpakobsin,T.; Rodpradit,P.; Joonlasak,K.; Manasatienskij,W.; Klungthong,C.; Fernandez,S.
EPI_ISL_16854191	Velasco,J.M.S.; Valderama,M.T.G.; Diones,P.C.S.; Leonardia,S.; Alcantara,S.; Chinnawirotisan,P.; Phonpakobsin,T.; Rodpradit,P.; Joonlasak,K.; Manasatienskij,W.; Klungthong,C.; Fernandez,S.
EPI_ISL_16854190	Velasco,J.M.S.; Valderama,M.T.G.; Diones,P.C.S.; Leonardia,S.; Alcantara,S.; Chinnawirotisan,P.; Phonpakobsin,T.; Rodpradit,P.; Joonlasak,K.; Manasatienskij,W.; Klungthong,C.; Fernandez,S.
EPI_ISL_16854189	Velasco,J.M.S.; Valderama,M.T.G.; Diones,P.C.S.; Leonardia,S.; Alcantara,S.; Chinnawirotisan,P.; Phonpakobsin,T.; Rodpradit,P.; Joonlasak,K.; Manasatienskij,W.; Klungthong,C.; Fernandez,S.
EPI_ISL_16854188	Velasco,J.M.S.; Valderama,M.T.G.; Diones,P.C.S.; Leonardia,S.; Alcantara,S.; Chinnawirotisan,P.; Phonpakobsin,T.; Rodpradit,P.; Joonlasak,K.; Manasatienskij,W.; Klungthong,C.; Fernandez,S.
EPI_ISL_16854187	Velasco,J.M.S.; Valderama,M.T.G.; Diones,P.C.S.; Leonardia,S.; Alcantara,S.; Chinnawirotisan,P.; Phonpakobsin,T.; Rodpradit,P.; Joonlasak,K.; Manasatienskij,W.; Klungthong,C.; Fernandez,S.
EPI_ISL_16854186	Velasco,J.M.S.; Valderama,M.T.G.; Diones,P.C.S.; Leonardia,S.; Alcantara,S.; Chinnawirotisan,P.; Phonpakobsin,T.; Rodpradit,P.; Joonlasak,K.; Manasatienskij,W.; Klungthong,C.; Fernandez,S.
EPI_ISL_16854185	Lu,L.; Robertson,G.; Ashworth,J.; Pham Hong,A.; Shi,T.; Ivens,A.; Thwaites,G.; Baker,S.; Woolhouse,M. Manasatienskij,W.; Chinnawirotpaisan,P.; Kittichotirat,W.; Macareo,L.R.; Ellison,D.W.; Cheevadhanarak,S.; Chotpitayasanondh,T.; Suntarattiwong,P.; Fernandez,S.; Yoon,I.-K.; Olsen,S.J.; Kittikraisak,W.; Anderson,K.B.; Rutvisuttinunt,W.; Klungthong,C.
EPI_ISL_368343	Manasatienskij,W.; Chinnawirotpaisan,P.; Kittichotirat,W.; Macareo,L.R.; Ellison,D.W.; Cheevadhanarak,S.; Chotpitayasanondh,T.; Suntarattiwong,P.; Fernandez,S.; Yoon,I.-K.; Olsen,S.J.; Kittikraisak,W.; Anderson,K.B.; Rutvisuttinunt,W.; Klungthong,C.
EPI_ISL_368342	Manasatienskij,W.; Chinnawirotpaisan,P.; Kittichotirat,W.; Macareo,L.R.; Ellison,D.W.; Cheevadhanarak,S.; Chotpitayasanondh,T.; Suntarattiwong,P.; Fernandez,S.; Yoon,I.-K.; Olsen,S.J.; Kittikraisak,W.; Anderson,K.B.; Rutvisuttinunt,W.; Klungthong,C.
EPI_ISL_368334	Manasatienskij,W.; Chinnawirotpaisan,P.; Kittichotirat,W.; Macareo,L.R.; Ellison,D.W.; Cheevadhanarak,S.; Chotpitayasanondh,T.; Suntarattiwong,P.; Fernandez,S.; Yoon,I.-K.; Olsen,S.J.; Kittikraisak,W.; Anderson,K.B.; Rutvisuttinunt,W.; Klungthong,C.
EPI_ISL_368333	Manasatienskij,W.; Chinnawirotpaisan,P.; Kittichotirat,W.; Macareo,L.R.; Ellison,D.W.; Cheevadhanarak,S.; Chotpitayasanondh,T.; Suntarattiwong,P.; Fernandez,S.; Yoon,I.-K.; Olsen,S.J.; Kittikraisak,W.; Anderson,K.B.; Rutvisuttinunt,W.; Klungthong,C.
EPI_ISL_368332	Luvira,V.; Leaungwutiwong,P.; Iamsirithaworn,S.; Thippornchai,N.; Piroonamornpun,P.; Phumratanaaparin,W.; Davidson,A.D.
EPI_ISL_328954	Pan,Y.; Yang,P.; Shi,W.; Cui,S.; Peng,X.; Zhang,D.; Lu,G.; Liu,Y.; Zhao,J.; Wang,Q.
EPI_ISL_328953	Pan,Y.; Yang,P.; Shi,W.; Cui,S.; Peng,X.; Zhang,D.; Lu,G.; Liu,Y.; Zhao,J.; Wang,Q.
EPI_ISL_328952	Pan,Y.; Yang,P.; Shi,W.; Cui,S.; Peng,X.; Zhang,D.; Lu,G.; Liu,Y.; Zhao,J.; Wang,Q.
EPI_ISL_328951	Pan,Y.; Yang,P.; Shi,W.; Cui,S.; Peng,X.; Zhang,D.; Lu,G.; Liu,Y.; Zhao,J.; Wang,Q.
EPI_ISL_328950	Pan,Y.; Yang,P.; Shi,W.; Cui,S.; Peng,X.; Zhang,D.; Lu,G.; Liu,Y.; Zhao,J.; Wang,Q.
EPI_ISL_328949	Pan,Y.; Yang,P.; Shi,W.; Cui,S.; Peng,X.; Zhang,D.; Lu,G.; Liu,Y.; Zhao,J.; Wang,Q.
EPI_ISL_328948	Pan,Y.; Yang,P.; Shi,W.; Cui,S.; Peng,X.; Zhang,D.; Lu,G.; Liu,Y.; Zhao,J.; Wang,Q.
EPI_ISL_328947	Pan,Y.; Yang,P.; Shi,W.; Cui,S.; Peng,X.; Zhang,D.; Lu,G.; Liu,Y.; Zhao,J.; Wang,Q.
EPI_ISL_328946	Pan,Y.; Yang,P.; Shi,W.; Cui,S.; Peng,X.; Zhang,D.; Lu,G.; Liu,Y.; Zhao,J.; Wang,Q.
EPI_ISL_328936	Pan,Y.; Yang,P.; Shi,W.; Cui,S.; Peng,X.; Zhang,D.; Lu,G.; Liu,Y.; Zhao,J.; Wang,Q.
EPI_ISL_328935	Qian,X.
EPI_ISL_328899	Qian,X.
EPI_ISL_328898	Qian,X.
EPI_ISL_328897	Qian,X.
EPI_ISL_328896	Qian,X.
EPI_ISL_328845	Qian,X.
EPI_ISL_328844	Qian,X.
EPI_ISL_328843	Qian,X.
EPI_ISL_328842	Qian,X.
EPI_ISL_328841	Chan,M.; Wang,M.; Chen,Z.; Hui,D.; Kwok,A.; Yeung,A.; Liu,K.; Lee,N.; Chan,P.
EPI_ISL_327176	Chan,M.; Wang,M.; Chen,Z.; Hui,D.; Kwok,A.; Yeung,A.; Liu,K.; Lee,N.; Chan,P.
EPI_ISL_327175	Chan,M.; Wang,M.; Chen,Z.; Hui,D.; Kwok,A.; Yeung,A.; Liu,K.; Lee,N.; Chan,P.

EPI_ISL_327039	Chan,M.; Wang,M.; Chen,Z.; Hui,D.; Kwok,A.; Yeung,A.; Liu,K.; Lee,N.; Chan,P.
EPI_ISL_327026	Chan,M.; Wang,M.; Chen,Z.; Hui,D.; Kwok,A.; Yeung,A.; Liu,K.; Lee,N.; Chan,P.
EPI_ISL_327025	Chan,M.; Wang,M.; Chen,Z.; Hui,D.; Kwok,A.; Yeung,A.; Liu,K.; Lee,N.; Chan,P.
EPI_ISL_327024	Chan,M.; Wang,M.; Chen,Z.; Hui,D.; Kwok,A.; Yeung,A.; Liu,K.; Lee,N.; Chan,P.
EPI_ISL_327021	Chan,M.; Wang,M.; Chen,Z.; Hui,D.; Kwok,A.; Yeung,A.; Liu,K.; Lee,N.; Chan,P.
EPI_ISL_327020	Chan,M.; Wang,M.; Chen,Z.; Hui,D.; Kwok,A.; Yeung,A.; Liu,K.; Lee,N.; Chan,P.
EPI_ISL_327019	Chan,M.; Wang,M.; Chen,Z.; Hui,D.; Kwok,A.; Yeung,A.; Liu,K.; Lee,N.; Chan,P.
EPI_ISL_327018	Chan,M.; Wang,M.; Chen,Z.; Hui,D.; Kwok,A.; Yeung,A.; Liu,K.; Lee,N.; Chan,P.
EPI_ISL_327017	Chan,M.; Wang,M.; Chen,Z.; Hui,D.; Kwok,A.; Yeung,A.; Liu,K.; Lee,N.; Chan,P.
EPI_ISL_327016	Chan,M.; Wang,M.; Chen,Z.; Hui,D.; Kwok,A.; Yeung,A.; Liu,K.; Lee,N.; Chan,P.
EPI_ISL_327015	Chan,M.; Wang,M.; Chen,Z.; Hui,D.; Kwok,A.; Yeung,A.; Liu,K.; Lee,N.; Chan,P.
EPI_ISL_326988	Rahman,R.; Goswami,D.R.; Uddin,K.M.M.; Rahman,M.Z.; Hossain,M.E.; Brooks,W.A.
EPI_ISL_295449	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295448	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295447	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295446	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295445	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295444	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295443	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295442	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295441	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295440	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295439	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295438	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295437	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295436	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295435	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295434	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295433	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295432	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295431	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295430	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295429	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295428	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295427	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295426	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295418	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295417	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295412	Lee,H.S.; Noh,J.Y.; Kim,W.J.

EPI_ISL_295411	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295410	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295409	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295408	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295407	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295406	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295405	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295404	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295403	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295402	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295401	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295400	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295399	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295398	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295397	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295380	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295379	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295377	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295373	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295372	Lee,H.S.; Noh,J.Y.; Kim,W.J.
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EPI_ISL_295370	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295368	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295367	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295357	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295356	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295355	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295354	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295353	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295352	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295351	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295350	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295349	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295348	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295347	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295346	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295345	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295344	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295343	Lee,H.S.; Noh,J.Y.; Kim,W.J.

EPI_ISL_295342	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295341	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295340	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295339	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295338	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295337	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295336	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295335	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295334	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295333	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295332	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295331	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295330	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295186	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295180	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295179	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295162	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295161	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295160	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295159	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295158	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295156	Lee,H.S.; Noh,J.Y.; Kim,W.J.
EPI_ISL_295155	Kim,J.-K.; Song,E.-J.
EPI_ISL_272723	Huang,Z.; Liang,L.; Huang,P.
EPI_ISL_272722	Huang,Z.; Liang,L.; Huang,P.
EPI_ISL_272721	Huang,Z.; Liang,L.; Huang,P.
EPI_ISL_272720	Huang,Z.; Liang,L.; Huang,P.
EPI_ISL_272719	Huang,Z.; Liang,L.; Huang,P.
EPI_ISL_272718	Huang,Z.; Liang,L.; Huang,P.
EPI_ISL_272717	Li,J.; Gong,T.; Shi,Y.; Xiong,Y.
EPI_ISL_252688	SureshBabu B.,V.; Gunasekaran,P.; Kaveri,K.; Venkataraman,P.; Magesh,S.; Chadha M,S.; Varsha,P.; SenthilRaja,R.
EPI_ISL_252687	SureshBabu B.,V.; Gunasekaran,P.; Kaveri,K.; Venkataraman,P.; Magesh,S.; Chadha M,S.; Varsha,P.; SenthilRaja,R.
EPI_ISL_252686	SureshBabu B.,V.; Gunasekaran,P.; Kaveri,K.; Venkataraman,P.; Magesh,S.; Chadha M,S.; Varsha,P.; SenthilRaja,R.
EPI_ISL_252685	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244591	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244590	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244589	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244588	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244587	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.

EPI_ISL_244586	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244585	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244584	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244583	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244582	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244581	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244580	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244579	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244578	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244577	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244576	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244575	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244574	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244573	El Shesheny,R.; Halasa,N.B.; Kayali,G.; Khuri-Bulos,N.
EPI_ISL_244572	Jianga,L.; Puthavathana,P.
EPI_ISL_234764	Nandhini,G.; Sujatha,S.
EPI_ISL_230617	Nandhini,G.; Sujatha,S.
EPI_ISL_230616	Timmermans,A.; Melendrez,M.C.; Se,Y.; Chuang,I.; Samon,N.; Uthaimongkol,N.; Klungthong,C.; Manasatienkij,W.; Thaisomboonsuk,B.; Tyner,S.D.; Rith,S.; Horm,V.S.; Jarman,R.G.; Bethell,D.; Chanarat,N.; Pavlin,J.; Wongstitwilairoong,T.; Saingam,P.; El,B.S.; Fukuda,M.M.; Touch,S.; Sovann,L.; Fernandez,S.; Buchy,P.; Chanthap,L.; Saunders,D.; Timmerman,A.
EPI_ISL_206295	Chong,Y.; Ikematsu,H.
EPI_ISL_206294	Chong,Y.; Ikematsu,H.
EPI_ISL_206293	Chong,Y.; Ikematsu,H.
EPI_ISL_206292	Khin Thu Zar, Htwe; Dapat, Clyde; Saito, Reiko; Shobugawa, Yugo; Kondo, Hiroki
EPI_ISL_314980	Khin Thu Zar, Htwe; Dapat, Clyde; Saito, Reiko; Shobugawa, Yugo; Kondo, Hiroki
EPI_ISL_314979	Khin Thu Zar, Htwe; Saito, Reiko; Odagiri, Takashi; Hibino, Akinobu; Kondo, Hiroki; Yagami, Ren; Saito, Takehiko ; Takemae, Nobuhiro; Tamura, Tsutomu; Shobugawa, Yugo; Ishida, Junko; Watanabe,Hisami; Yadanar, Kyaw; Nay, Lin; Yi Yi, Myint; Htay Htay, Tin; Win,Thein; Latt Latt, Kyaw; Pan Ei ,Soe; Chan Myae, Aung
EPI_ISL_264543	Khin Thu Zar, Htwe; Saito, Reiko; Odagiri, Takashi; Hibino, Akinobu; Kondo, Hiroki; Yagami, Ren; Saito, Takehiko ; Takemae, Nobuhiro; Tamura, Tsutomu; Shobugawa, Yugo; Ishida, Junko; Watanabe,Hisami; Yadanar, Kyaw; Nay, Lin; Yi Yi, Myint; Htay Htay, Tin; Win,Thein; Latt Latt, Kyaw; Pan Ei ,Soe; Chan Myae, Aung
EPI_ISL_264542	Khin Thu Zar, Htwe; Saito, Reiko; Odagiri, Takashi; Hibino, Akinobu; Kondo, Hiroki; Yagami, Ren; Saito, Takehiko ; Takemae, Nobuhiro; Tamura, Tsutomu; Shobugawa, Yugo; Ishida, Junko; Watanabe,Hisami; Yadanar, Kyaw; Nay, Lin; Yi Yi, Myint; Htay Htay, Tin; Win,Thein; Latt Latt, Kyaw; Pan Ei ,Soe; Chan Myae, Aung
EPI_ISL_264541	Khin Thu Zar, Htwe; Saito, Reiko; Odagiri, Takashi; Hibino, Akinobu; Kondo, Hiroki; Yagami, Ren; Saito, Takehiko ; Takemae, Nobuhiro; Tamura, Tsutomu; Shobugawa, Yugo; Ishida, Junko; Watanabe,Hisami; Yadanar, Kyaw; Nay, Lin; Yi Yi, Myint; Htay Htay, Tin; Win,Thein; Latt Latt, Kyaw; Pan Ei ,Soe; Chan Myae, Aung
EPI_ISL_264540	Khin Thu Zar, Htwe; Saito, Reiko; Odagiri, Takashi; Hibino, Akinobu; Kondo, Hiroki; Yagami, Ren; Saito, Takehiko ; Takemae, Nobuhiro; Tamura, Tsutomu; Shobugawa, Yugo; Ishida, Junko; Watanabe,Hisami; Yadanar, Kyaw; Nay, Lin; Yi Yi, Myint; Htay Htay, Tin; Win,Thein; Latt Latt, Kyaw; Pan Ei ,Soe; Chan Myae, Aung
EPI_ISL_264539	Khin Thu Zar, Htwe; Saito, Reiko; Odagiri, Takashi; Hibino, Akinobu; Kondo, Hiroki; Yagami, Ren; Saito, Takehiko ; Takemae, Nobuhiro; Tamura, Tsutomu; Shobugawa, Yugo; Ishida, Junko; Watanabe,Hisami; Yadanar, Kyaw; Nay, Lin; Yi Yi, Myint; Htay Htay, Tin; Win,Thein; Latt Latt, Kyaw; Pan Ei ,Soe; Chan Myae, Aung
EPI_ISL_264538	Khin Thu Zar, Htwe; Saito, Reiko; Odagiri, Takashi; Hibino, Akinobu; Kondo, Hiroki; Yagami, Ren; Saito, Takehiko ; Takemae, Nobuhiro; Tamura, Tsutomu; Shobugawa, Yugo; Ishida, Junko; Watanabe,Hisami; Yadanar, Kyaw; Nay, Lin; Yi Yi, Myint; Htay Htay, Tin; Win,Thein; Latt Latt, Kyaw; Pan Ei ,Soe; Chan Myae, Aung
EPI_ISL_264265	Khin Thu Zar, Htwe; Saito, Reiko; Odagiri, Takashi; Hibino, Akinobu; Kondo, Hiroki; Yagami, Ren; Saito, Takehiko ; Takemae, Nobuhiro; Tamura, Tsutomu; Shobugawa, Yugo; Ishida, Junko; Watanabe,Hisami; Yadanar, Kyaw; Nay, Lin; Yi Yi, Myint; Htay Htay, Tin; Win,Thein; Latt Latt, Kyaw; Pan Ei ,Soe; Chan Myae, Aung

EPI_ISL_264264	Khin Thu Zar, Htwe; Saito, Reiko; Odagiri, Takashi; Hibino, Akinobu; Kondo, Hiroki; Yagami, Ren; Saito, Takehiko ; Takemae, Nobuhiro; Tamura, Tsutomu; Shobugawa, Yugo; Ishida, Junko; Watanabe,Hisami; Yadanar, Kyaw; Nay, Lin; Yi Yi, Myint; Htay Htay, Tin; Win,Thein; Latt Latt, Kyaw; Pan Ei ,Soe; Chan Myae, Aung
EPI_ISL_264263	Khin Thu Zar, Htwe; Saito, Reiko; Odagiri, Takashi; Hibino, Akinobu; Kondo, Hiroki; Yagami, Ren; Saito, Takehiko ; Takemae, Nobuhiro; Tamura, Tsutomu; Shobugawa, Yugo; Ishida, Junko; Watanabe,Hisami; Yadanar, Kyaw; Nay, Lin; Yi Yi, Myint; Htay Htay, Tin; Win,Thein; Latt Latt, Kyaw; Pan Ei ,Soe; Chan Myae, Aung
EPI_ISL_264262	Khin Thu Zar, Htwe; Saito, Reiko; Odagiri, Takashi; Hibino, Akinobu; Kondo, Hiroki; Yagami, Ren; Saito, Takehiko ; Takemae, Nobuhiro; Tamura, Tsutomu; Shobugawa, Yugo; Ishida, Junko; Watanabe,Hisami; Yadanar, Kyaw; Nay, Lin; Yi Yi, Myint; Htay Htay, Tin; Win,Thein; Latt Latt, Kyaw; Pan Ei ,Soe; Chan Myae, Aung
EPI_ISL_264261	NA
EPI_ISL_219328	NA
EPI_ISL_13871191	Deng, Yi-Mo.; Iannello,P.; Komadina,N
EPI_ISL_219299	Deng,Y-M.; Iannello,P.; Spirason,N.; Lau,H.; Komadina,N
EPI_ISL_219298	Deng,Y-M.; Iannello,P.; Spirason,N.; Lau,H.; Komadina,N
EPI_ISL_219297	Deng,Y-M.; Iannello,P.; Spirason,N.; Lau,H.; Komadina,N
EPI_ISL_219294	NA
EPI_ISL_15146254	NA
EPI_ISL_15146253	NA
EPI_ISL_15146252	NA
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EPI_ISL_5159650	Carolan,Louise
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EPI_ISL_5159643	Carolan,Louise
EPI_ISL_5159642	Carolan,Louise
EPI_ISL_5159641	Carolan,Louise
EPI_ISL_5159640	Carolan,Louise
EPI_ISL_5159639	Carolan,Louise
EPI_ISL_5159638	Lu,L.; Robertson,G.; Ashworth,J.; Pham Hong,A.; Shi,T.; Ivens,A.; Thwaites,G.; Baker,S.; Woolhouse,M.

12 **Chapter 6: Impact of viral co-detection on within-host**
13 **A/H3N2 influenza viral diversity**

14 **6.1 Research Paper cover sheet**



London School of Hygiene & Tropical Medicine 15
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1901561	Title	Dr
First Name(s)	Su Myat		
Surname/Family Name	Han		
Thesis Title	Unravelling transmission dynamics of influenza and its interaction with other respiratory viral pathogens in the population of Kamigoto island, Japan		
Primary Supervisor	Professor Koya Ariyoshi		

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?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Virus Evolution	
Please list the paper's authors in the intended authorship order:	Su Myat Han, Alexis Robert, Yoshiano Kubo, Peterson Gitonga Mathenge, Shingo Masuda, Takahiro Yasaka, Satoshi Kanda, Kazuhiri Komori, Lay Myint Yoshida, Chris Smith, Marc Baguelin, Koya Ariyoshi	

Stage of publication	Not yet submitted
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SECTION D – Multi-authored work

<p>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)</p>	<p>The candidate conceived the study, designed the study model, performed the analysis and wrote the original draft of the manuscript</p>
---	---

SECTION E

Student Signature	Su Myat Han
Date	10 November 2023

Supervisor Signature	Koya Ariyoshi
Date	10 November 2023

17 **6.2 Summary of the Chapter**

18 In this chapter, I attempted to explore the impact of virus-virus co-detection on the influenza
19 transmission dynamics. The existing papers documented the virus codetection with disease
20 severity, although the findings were not consistent. Some studies reported virus codetection in
21 association with disease severity while some studies report no association. Evidence of virus-
22 virus interaction was also reported extensively, however, the impact of these interaction on the
23 within host diversity of viral population is not well studied.

24 I performed the whole genome sequencing (WGS) by next generation sequencing (NGS), of
25 A/H3N2 influenza cases and identified whether these cases were co-detected with other respiratory
26 viruses. NGS allows us to do minor variant (iSNV) calling, a method to identify the within-host
27 viral diversity, which is important as it shapes the influenza virus global evolution. There are many
28 tools commonly used for detection of variants.¹ Measurement of within-host viral diversity is
29 reported to be sensitive to systemic errors during the performance of variant calling.² I tried various
30 cut-off criteria, and bioinformatics tools (Lauren pipeline, bcftools, varscans) to perform the minor
31 variants calling in order to reduce the false variant calls. I followed the cut-off criteria based on
32 the published studies on the within-host viral diversity of influenzas viruses.³⁻⁶

33 I developed the study design, performed the WGS, and bioinformatic analysis. I also wrote
34 the paper and made the figures. Throughout the process I received input/suggestions/edits from
35 both my supervisors, and external collaborators.

36 **Reference:**

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49 and pandemic human influenza A viruses in young children. *Elife* 2021; **10**.

50 **6.3 Manuscript draft**

51 **Impact of viral co-detection on within-host A/H3N2 influenza viral**
52 **diversity**

53
54 Su Myat Han^{1,2*}, Shingo Masuda^{1,3}, Alexis Robert^{2,4}, Yoshiano Kubo^{5,6}, Peterson Gitonga
55 Mathenge⁷, Takahiro Yasaka³, Satoshi Kanda³, Kazuhiri Komori³, Lay Myint Yoshida^{1,8}, Akira
56 Endo^{1,9}, Chris Smith^{1,10}, Teiichiro Shiino^{11,12}, Marc Baguelin^{2,13}, Koya Ariyoshi^{1,6}

- 57
58 1. School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan
59 2. Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London
60 School of Hygiene and Tropical Medicine, London, United Kingdom
61 3. Department of Internal Medicine, Kamigoto Hospital, Kamigoto, Japan
62 4. Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical
63 Medicine, Keppel Street, London, UK
64 5. Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan
65 6. Department of Clinical Medicine, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan
66 7. Dana Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts. USA
67 8. Department of Pediatric Infectious Diseases, Institute of Tropical Medicine, Nagasaki University,
68 Nagasaki, Japan
69 9. Saw Swee Hock School of Public Health, National University of Singapore and National University Health
70 System, Singapore, Singapore
71 10. Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene
72 & Tropical Medicine, London, UK
73 11. Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan
74 12. AIDS Research Center, National Institute of Infectious Diseases, Tokyo, Japan
75 13. MRC Centre for Global Infectious Disease Analysis; and the Abdul Latif Jameel Institute for Disease
76

77 **Abstract**

78 Numerous studies have documented the evidence of virus-virus interactions at the
79 population, host, and cellular levels. However, the impact of these interactions on the within-host
80 diversity of influenza viral populations remains unexplored.

81 Our study identified 13 respiratory viral pathogens from the nasopharyngeal swab samples
82 (NPS) of influenza-like-illness (ILI) patients during the 2012/13 influenza season using multiplex
83 RT-PCR. Subsequent next-generation sequencing (NGS) of RT-PCR-confirmed influenza A
84 infections revealed all samples as subtype A/H3N2. We also reconstructed transmission trees to
85 identify the transmission networks and possible direction transmission pairs. We performed
86 negative binomial regression to identify the factors associated with the number of iSNV detected
87 within the host.

88 Out of the 2,316 samples examined, 538 (23.2%) were positive for influenza A virus (IAV),
89 with rhinovirus (RV) and adenoviruses (Adv) being detected in 264 (11.4%) and 44 (1.9%)
90 samples, respectively. Among these, 96 samples exhibited co-detection of more than one virus,
91 and 5 samples had co-detections of more than two viruses, with the IAV-RV pairing being
92 predominant (48/96).150 samples were available for whole-genome sequencing (WGS), out of
93 which 132 passed the minor variants (iSNV) calling criteria. 397 unique iSNVs were identified
94 across the genome. Most samples exhibited fewer than 5 iSNVs at a frequency below 10%. Seven
95 samples have no iSNVs. Interestingly, the bulk of iSNVs were unique, with 86% appearing only
96 once and rarely shared across samples. Transmission tree reconstruction revealed a singular
97 transmission pair that shared all three identified iSNVs between the infector and infectee. Older
98 age groups were found to have association with higher number of iSNVs detected within the host
99 (incidence rate ratio IRR= 2.08 (95% confidence interval (CI) 1.22-3.68).

100 Our study did not identify a significant influence of virus-virus codetection on within-host
101 viral genetic diversity. Our findings suggest a minor or negligible contribution of these viral
102 codetections to the evolution of influenza viruses. However, the data available in this study may
103 not be exhaustive, warranting further, more in-depth investigations to conclusively determine the
104 impact of virus-virus interactions on influenza virus genetic diversity.

105 **Introduction**

106 Influenza virus is a negative-sense, segmented, single-stranded RNA virus under the
107 *Orthomyxoviridae* family, with an approximately 13.5-kilobase (kb) genome.¹ Influenza A viruses
108 (subtype: A/H3N2, A/H1N1) and influenza B viruses (lineages: Victoria and Yamagata) co-
109 circulate among the human population², leading to the annual seasonal influenza epidemic
110 worldwide. These seasonal influenza outbreaks remain a major public health threat, affecting 3-5
111 million people and causing an estimated 290,000-650,000 deaths annually.³

112 Like other RNA viruses, influenza replicates via an RNA-dependent RNA polymerase that
113 lacks proofreading ability, leading to high mutation rates and rapid evolutionary adaptation.^{1,4} As
114 a result, RNA viruses, including influenza, exist as "quasispecies" or mutant swarms within a host.
115 This within-host diversity, especially low-frequency mutations, is hypothesized to contribute to
116 virulence and immune evasion.⁵⁻⁸ Understanding the evolution of viruses, especially influenza,
117 is crucial because these mutations and resultant viral diversity can significantly impact viral
118 virulence, transmissibility, and susceptibility to immune responses, shaping the trajectory and
119 severity of outbreaks and influencing vaccine effectiveness.⁵⁻⁸

120 With advancements in virus sequencing technologies, studying within-host viral genetic
121 diversity has become feasible.⁹ The existing studies observed relatively limited within-host genetic
122 diversity during the acute infection.^{6,7,10-14} Existing studies have reported relatively few variants
123 per infection,¹⁰⁻¹⁴ suggesting that strong bottlenecks or selective pressures may limit the
124 accumulation of within-host diversity during the acute phase of influenza infection. However, the
125 factors that influence this diversity, especially in the context of interactions with other viruses,
126 remain underexplored.

127 The motivation for this study arises from accumulating evidence that virus-virus interactions,
128 particularly among respiratory pathogens, can influence viral replication dynamics and host
129 immune responses.^{7,15-18} An experimental study has shown that the presence of one virus may alter
130 the course of infection by another virus through mechanisms such as resource competition or
131 immune modulation.¹⁶ For instance, a recent ex-vivo study showed that prior infection with the
132 human rhinovirus (hRV) could provide protection against a subsequent influenza A virus (IAV)
133 infection for up to three days. This prior infection reduced the IAV viral RNA by approximately
134 50,000-fold on day five post-hRV infection.¹⁷ This protective effect is attributed to the hRV-
135 induced activation of interferon-stimulated gene (ISG) expression in the airway mucosa. ISGs
136 restrict influenza viral replication and spread, invoking immune responses in neighboring cells,
137 thereby safeguarding them from influenza virus invasion.^{17,18} Another study suggested that hRV
138 might suppress genes linked to viral mRNA processing, ribosomal proteins, translation, and
139 influenza infection.¹⁹ Furthermore, a ferret model revealed that either influenza or the human
140 respiratory syncytial virus (hRSV) could induce interferon γ -expressing cells that limit the
141 subsequent virus's infection or disease for up to 14 days.²⁰

142 The central hypothesis underpinning our study is that viral coinfection (or co-detection) may
143 influence the intra-host diversity of influenza by altering the selective pressures or replication
144 dynamics of the virus. We propose that coinfection could either increase diversity by providing
145 more opportunities for genetic variants to emerge due to reduced competition or decrease diversity
146 due to enhanced immune responses limiting viral replication.

147 To investigate the impact of viral co-detection on the intra-host diversity of influenza viruses,
148 we first identified influenza viruses (both A and B) and additional 11 respiratory viruses by
149 applying multiplex reverse transcriptase-polymerase chain reaction (RT-PCR). Then we

150 performed whole genome sequencing (WGS) of the RT-PCR confirmed influenza cases by
151 applying Next Generation Sequencing (NGS). We finally assessed the difference in the distribution
152 of within-host minor variants (iSNVs) between the influenza-only cases and virus co-detected
153 influenza cases.

154 **Methods**

155 **Study design**

156 This study was a retrospective observational study of the patients presenting with influenza-
157 like illness (ILI) symptoms during the influenza season, which was conducted October 2012
158 through June 2013 in a semi-isolated island population in Japan. The details of the study site were
159 described previously.²¹ Since 2007, all the ILI cases were registered and monitored as part of the
160 national surveillance system. ILI was defined if the patient presented with a sudden onset of fever
161 and at least at least one respiratory symptom of a runny nose, coughing, headache, sore throat,
162 myalgia, or fatigue. During the influenza season, all the ILI cases were tested with rapid influenza
163 diagnostic test (RIDT) for the influenza diagnosis. During the study period, the nasopharyngeal
164 swabs (NPS) from the RIDTs were placed in viral transport media (VTM) and temporarily stored
165 at -20°C in the laboratory department of the hospital after being used for the RIDTs. Within a
166 week, the samples were transported to the Institute of Tropical Medicine at Nagasaki University
167 for storage in a deep freezer (-80°C) until processing.

168 **Sample collection and virus identification**

169 Viral nucleic acid was extracted using a QIA viral RNA minikit (QIAGEN Inc., Valencia,
170 CA) following the manufacture instruction. Extracted RNA samples were further processed for
171 multiplex reverse transcriptase PCRs (RT-PCRs) to identify 13 respiratory viral pathogens:
172 influenza A (IAV), influenza B (IBV) viruses, human rhinovirus (hRV), human respiratory

173 syncytial virus (hRSV), parainfluenza viruses 1 to 4 (PIV 1-4), human coronaviruses (hCoV)
174 (OC43 and 229E), human metapneumovirus (hMPV), human adenoviruses (hAdB) and human
175 bocaviruses (hBoV) using inhouse multiplex panels. The protocol of the multiplex assay panels
176 was described elsewhere.²²

177 **Library preparation and whole genome sequencing**

178 We amplified all 8 segments of RT-PCR confirmed influenza samples following the
179 protocols of Zhou, B., et al. (2009)²³ and confirmed by gel electrophoresis. Each PCR product
180 was purified again using Ampure XP beads (Beckman Coulter) according to the manufacturer's
181 instructions. The purity was then assessed with Agilent Technology 2100 Bioanalyzer using a High
182 Sensitivity DNA chip and Qubit dsDNA HS Assay Kit (Life Technology). 1 ng of the DNA is
183 used for library preparation (Nextera XT Kit, Illumina) following manufacturer's instructions
184 (Illumina, CA, USA). After rigorous quality control, the prepared library was sequenced on MiSeq
185 platform (Illumina) using V2 2 × 250 bp reagents kit.

186 **Phylogenetic analysis**

187 Consensus nucleotide sequences for each segment as well as concatenated WGS were
188 aligned using MAFFT.²⁴ The aligned sequences were viewed and edited in AliView.²⁵ Maximum
189 likelihood phylogenetic trees were generated using IQTREE²⁶ with the best fit model was
190 determined by software. The non-parametric bootstrapping method was used with 100 replicates.
191 Sequences for vaccine strains were retrieved from GISAID as outgroups. Trees were visualized
192 and annotated using FigTree (v1.4.2).²⁷

193 **Identification of intra-host single nucleotide variants (iSNVs)**

194 The criteria for iSNV calling are (i) mapping quality of more than 30, (ii) base quality more
195 than 30, (iii) a minimum of 1000-fold depth of coverage and (iv) requires at least 10 reads

196 supporting an alternate allele within a single individual to evaluate the iSNV frequency. The iSNVs
197 are included in the analysis by cutoff frequency of 2%, following the criteria of published studies.
198 ²⁸ Above 50%, all single nucleotide variants were considered to be consensus-level singandle
199 nucleotide polymorphisms (i.e., SNPs) as it is a common threshold for consensus-calling in
200 genome assembly.²⁹

201 **Statistical Analysis**

202 We compared the observed and expected co-detections of the viruses. First, we counted the
203 single infections and co-infections for various combinations. Then we calculated the expected
204 number of co-infections in the absence of interaction between any of the pathogen pairs. This
205 expected co-detection was calculated by multiplying the incidence of virus 1 and virus 2 by the
206 total sample size. Then, we employed either the χ^2 test or Fisher's exact test (with a significance
207 level set at $p < 0.05$) to evaluate whether there were significant differences between the observed
208 and expected co-detections. We also computed odds ratios (OR) along with their corresponding
209 95% confidence intervals (CIs) for each virus pair's co-detection. If any values in the contingency
210 table were zero, we applied Haldane's correction to calculate the odds ratio.

211 **Data availability / Accession number(s).**

212 All consensus sequences generated here have been submitted to the GISAID database. All
213 the intra-host sequence data have been submitted to the Sequence Read Archive under BioProject
214 accession number **PRJNA941384**.

215 **Ethics**

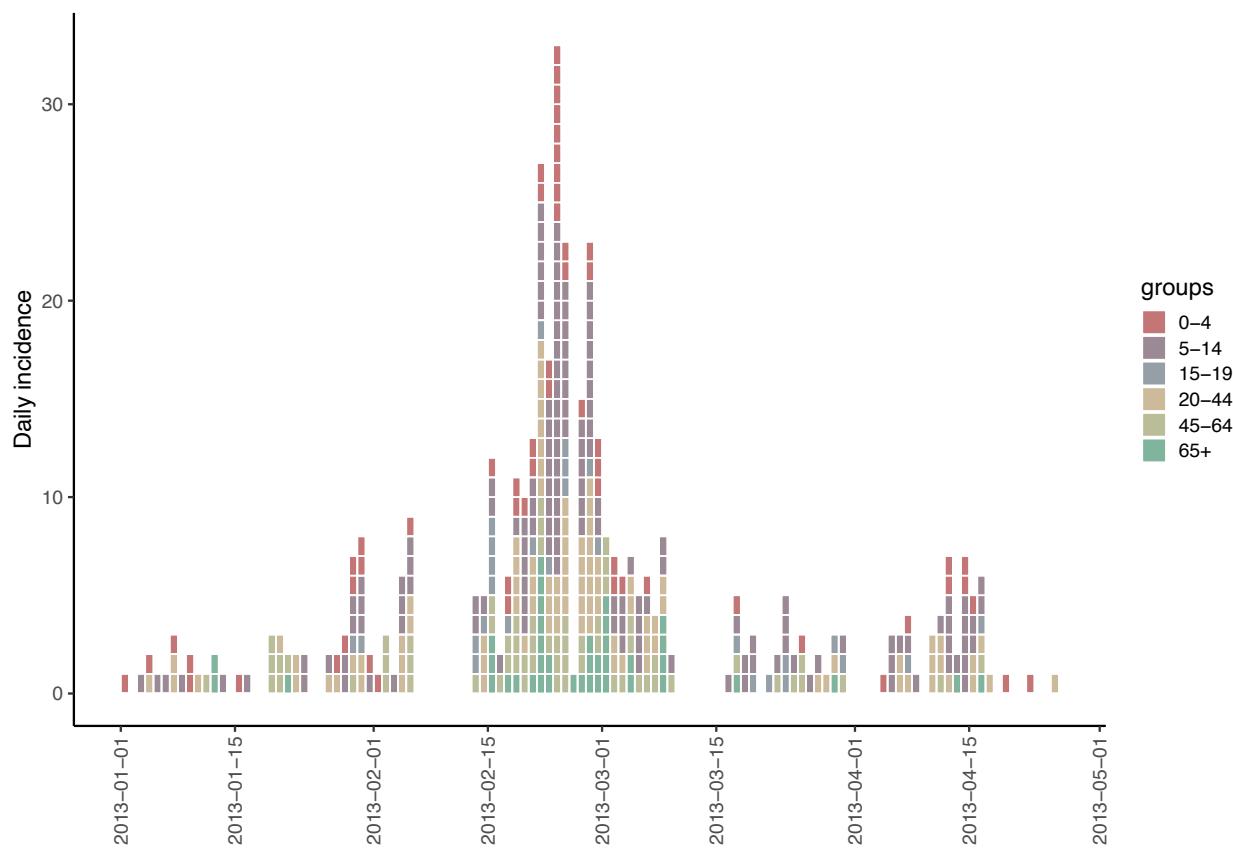
216 The research was approved by the institutional review boards of Kamigoto Hospital,
217 Nagasaki University Research Ethics Committee (reference number 200619236), and the London
218 School of Hygiene and Tropical Medicine Research Ethics Committee (reference number 26706).

219 Both Nagasaki University and London School of Hygiene and Tropical Medicine granted waivers
220 for obtaining informed consent due to the nature of this retrospective study and the preserved
221 anonymity of patients

222 **Results**

223 **Study Cohort and ILI Incidence**

224 A total of 2,407 ILI episodes were reported during the 2012/13 influenza season (from
225 October 2012 to June 2013). Figure 1 shows the distribution of ILI cases by age group during the
226 study period.



227
228 **Figure (1): Epidemic curve of the daily number of influenza-like illness (ILI) cases reported by the**
229 **Hospital influenza surveillance system.**

230

231 **Influenza and Rhinoviruses were most commonly detected and frequently co-detected pair**
232 **of viruses.**

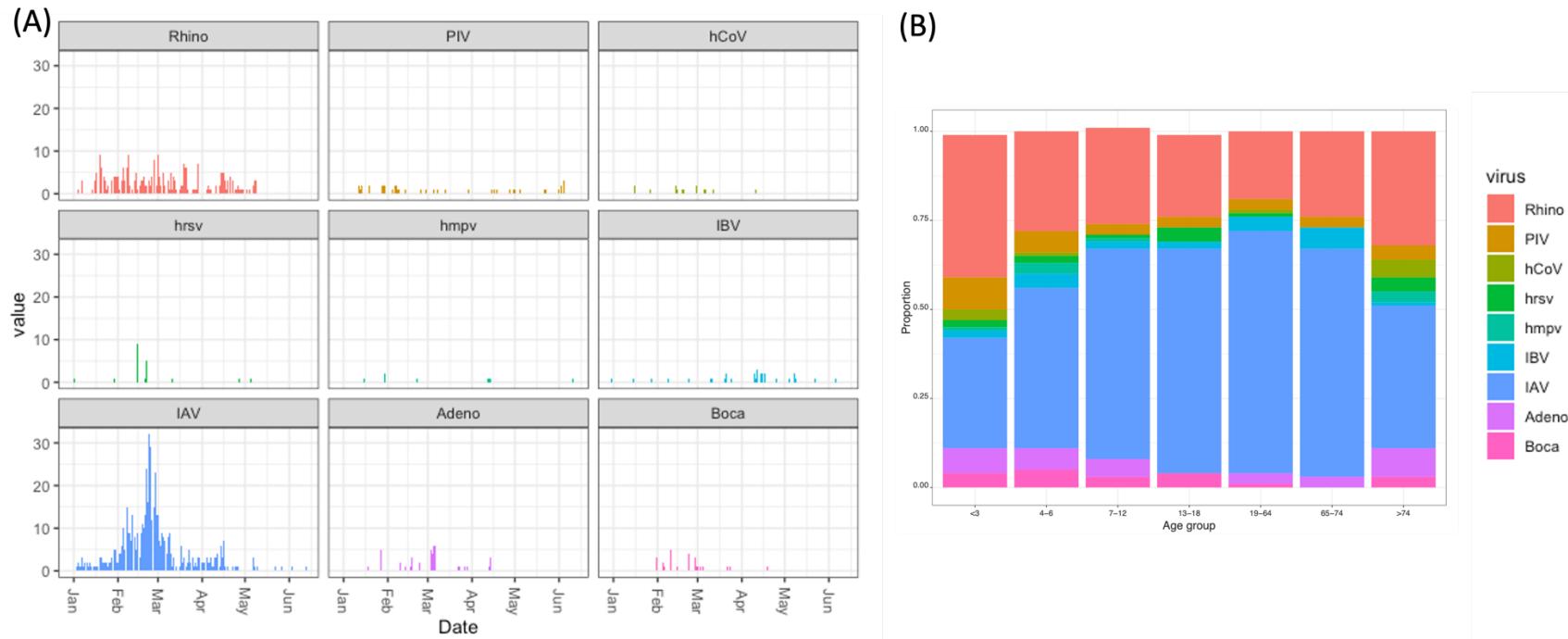
233 Table 1 displays the characteristics of the samples collected. Out of 2,410 ILI samples
 234 collected, 2,316 samples were available for molecular typing of the responsible viral pathogens.
 235 The most frequently detected virus was IAV (23.2%, 538/2316), followed by HRV (11.4%,
 236 264/2316). The other viruses detected were hAdV (1.9%, 44/2316), PIV (1.9%, 43/2316), BoV
 237 (1.1%, 26/2316), hRSV (0.9%, 20/2316), hCoV (0.6%, 14/2316), IBV (0.9%, 22/2316), and hMPV
 238 (0.3%, 8/2316). No viruses were detected in 1,427 samples. 105 samples were found to have more
 239 than one virus (96 samples with two viruses, 5 samples with more than two viruses). The finding
 240 of IAV was at its peak between late February and May, and RV was observed at almost the same
 241 frequency throughout the study period (Figure 2A). RV was the most common virus among the
 242 young age group (<3), and IAV was the most common virus among the other age groups (Figure
 243 2B, Supplementary Table S-1).

244 Table 1: Characteristics of the samples analyzed in 2012/2013 influenza season.

Characteristics	N (%)
Number of ILI episodes	2,407
Age group	
<6	546 (22.7)
6-18	707 (29.3)
19-64	693 (28.8)
>65	450 (18.7)
Total sampled	2,316
Influenza A	538 (23.2)
Influenza B	22 (0.9)
human Rhino virus	264 (11.4)
human metapneumovirus	8 (0.3)
Parainfluenza virus (I-IV)	43 (1.9)
human respiratory syncytial virus	20 (0.9)
human corona virus (OC43, 229E)	14 (0.6)
Adeno virus	44 (1.9)
Boca virus	26 (1.1)
Single virus infection	777 (33.5)

No virus detected	1,427 (61.6)
Multiple infection	
2 viruses	96 (4.1)
> 2 viruses	5 (0.2)
	245

246



247

248

249

250

Figure 2: Co-circulating viruses by season (A) and by age group (B)

259

251 IAV and RV were most commonly co-detected with other viruses and the most frequently
 252 co-detected pair of viruses Table 2. However, the expected number of co-detections for RV and
 253 IAV was 61, yet 48 co-detections were actually recorded (χ^2 p value = <0.001). The calculated
 254 odds ratio (OR) of Rhino and IAV co-detection was 0.16 (95% CI 0.09–0.28), indicating a strong
 255 negative association between the detection of IAV and RV. The other viral pairs did not have any
 256 significant difference between the observed and expected codetection, as well as the interaction
 257 between them.

258 Table 2: Observed detection of single and co-infection cases among influenza positive (538 IAV
 259 and one IBV) samples collected at the Kamigoto Hospital, Kamigoto, Japan 2012/2013 season.

Virus detected	Rhino	PIV	HCoV	MPV	RSV	IBV	Adeno	Boca	IAV
Rhino	264	5	0	1	0	6	8	4	48
PIV		42	0	0	0	0	0	0	4
HCoV			14	0	0	0	0	1	2
MPV				8	0	1	0	0	0
RSV					20	1	0	0	11
IBV						22	0	0	4
Adeno							44	0	7
Boca								26	3
IAV									538

260 Note: Rhino; rhinovirus, PIV; parainfluenza virus, HCoV; Human coronavirus, HMPV;
 261 metapneumovirus, RSV; respiratory syncytial virus, IBV; Influenza B virus, IAV; Influenza A virus,
 262 Adeno; Adenovirus, Boca; Boca virus

263

Table 3: Expected versus observed co-detections in virus pairs

Pair	observed	expected	Odd Ratios	p-value*
Rhino & PIV	5	5	0.90 (0.28-2.31)	1.000
Rhino & HCoV	0	2	0.27 (0.00-2.34)	0.391
Rhino & MPV	1	1	0.97 (0.02-7.26)	1.000
Rhino & RSV	0	2	0.19 (0.00-2.34)	0.156
Rhino & IBV	6	3	2.09 (0.69-5.38)	0.129
Rhino & Adeno	8	5	1.38 (0.64-2.96)	0.544
Rhino & Boca	4	3	1.18 (0.30-3.43)	0.772
Rhino & IAV	48	61	0.11 (0.08-0.14)	<0.001
PIV & Adeno	0	1	0.59 (0.00-4.85)	1.000
PIV & IAV	4	10	0.31 (0.11-0.86)	0.014
HCoV & Boca	1	0	6.24 (0.14-44.04)	0.162
HCoV & IAV	2	3	0.47 (0.05-2.05)	0.389
MPV & IBV	1	0	12.92 (0.28-103.77)	0.086
MPV & IAV	0	2	0.19 (0.00-1.93)	0.211
RSV & IBV	1	0	5.16 (0.12-35.31)	0.190
RSV & IAV	11	5	1.79 (0.85-3.75)	0.136
IBV & IAV	4	5	0.59 (0.20-1.73)	0.484
Adeno & IAV	7	10	0.51 (0.23-1.14)	0.131
Boca & IAV	3	6	0.38 (0.11-1.24)	0.121

264 IAV=influenza A virus. RSV=respiratory syncytial virus. hMPV=human metapneumovirus.

265 PIV=parainfluenza virus (I-IV). IBV=influenza B virus. Boca=Boca virus. Adeno=Adenovirus.

266 MPV=human metapneumovirus. HCoV=human coronavirus (OC43,229E) Rhino=Rhinovirus.

267 *Fisher's exact test or χ^2 test.

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269 **Whole genome sequencing of RT-PCR confirmed influenza A viruses.**

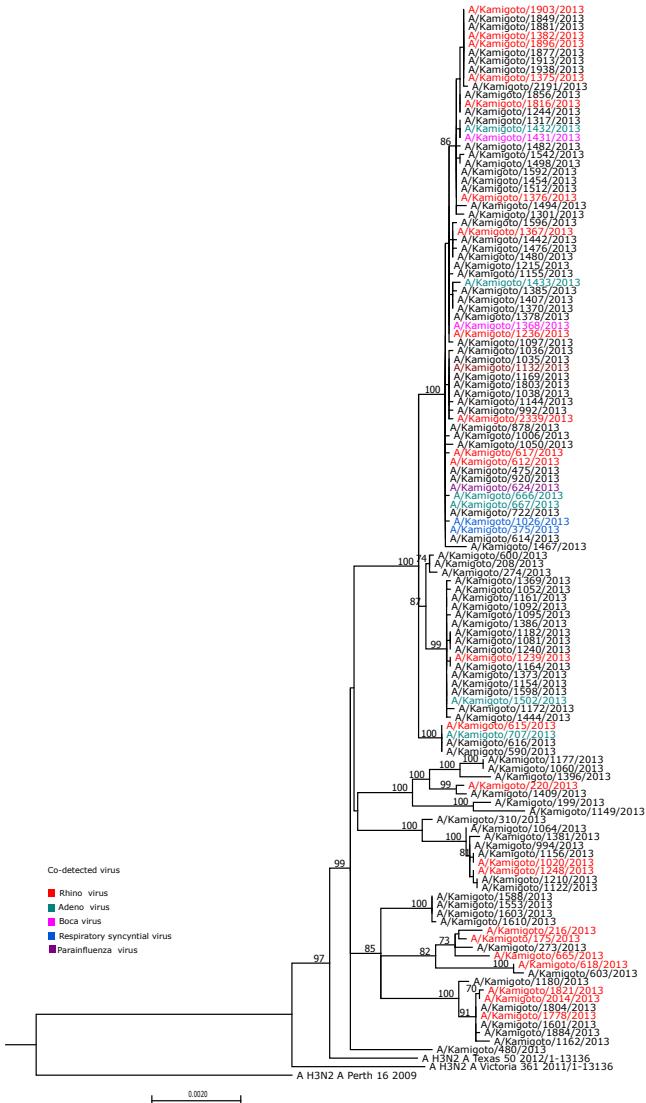
270 In this study, we aimed to explore the impact of respiratory virus codetection (or) co-
271 infection on the IAV within-host evolution. To do so, we first sequenced the RT-PCR-confirmed
272 influenza A viruses. We chose the IAV virus in this study due to its dominance during the studied
273 season. The flowchart of the sample collection to the sequencing is shown in the supplementary
274 Figure S-1. A total of 150 samples (only influenza =110, and viral-codetection=40) were
275 successfully sequenced for the whole genome, and all were identified as A/H3N2. In Table 4, we
276 compared the differences in demographic characteristics of influenza-only samples with IAV-virus
277 co-detected WGS samples. 60 RT-PCR positives were found to have viral-codetection, however,
278 only 41 of these samples were available for WGS due to the low DNA concentration
279 (Supplementary Figure S-2).

280 **Table 4: Characteristics of the Whole Genome Sequenced samples with co-detection status**

Characteristics	Only influenza (n= 110)	Viral-codetection (n= 40)
Age group		
<6	8	5
6-18	41	12
19-65	52	18
>65	6	4
Sex		
Male	52	15
Female	58	25
Vaccination status		
Vaccinated	80	26
Unvaccinated	29	14
Location/Region		
Narao	2	2
Arikawa	38	13
Shinuonome	23	4
Kamigoto	31	13
Wakamatsu	14	51
WGS (passed variant calling criteria)	99	33

282 **Identification of clustering by viral co-detection status on phylogeny**

283 We checked whether the A/H3N2 influenza cluster phylogenetically by codetection with
284 another respiratory virus. If the virus-virus codetection enhances the antigenic variations, we
285 would expect to see the antigenically distinct variants clustering together by the virus-influenza
286 codetection in phylogenetic trees. We therefore analyzed individual consensus sequences as well
287 as whole genome sequences from available 132 WGS cases (Figure 3, Supplementary Figure S-
288 3). There was very little diversity among the samples, and we found that all types of virus detection
289 (i.e influenza alone or influenza in co-detection with other respiratory viruses) were dispersed
290 throughout the phylogenetic tree.



291

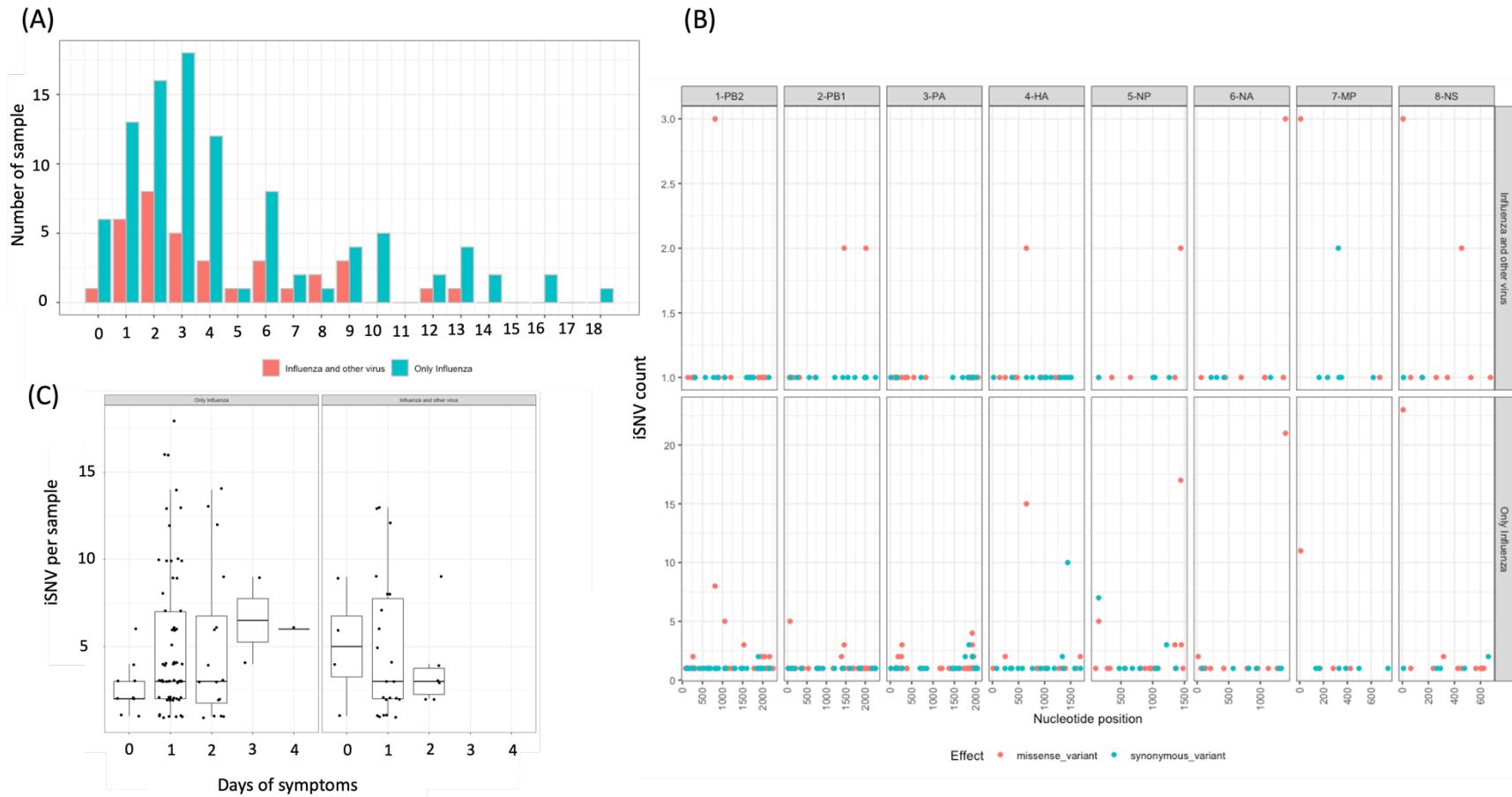
292 Figure 3: Maximum likelihood phylogenetic tree of WGS of A/H3N2 sequences in 2012/13
293 influenza season. The co-detected virus along with A/H3N2 was colored coded.

294 **Intra-host diversity in influenza-only cases versus virus-co-detected cases**

295 We next identified the iSNVs present in WGS samples. After filtering the criteria for
296 variant calling, 132 WGS A/H3N2 samples (99 only influenza cases and 33 co-detected cases)
297 were retained for further analysis. A total of 397 unique minority variants were identified across
298 the whole genome (Supplementary Figure -S4). Seven samples have no iSNVs identified. We did
299 not observe samples with many iSNV (more than 10 iSNVs/sample) or in higher frequencies iSNV
300 (>10% frequencies/iSNVs), which suggests that there were few if any, mixed lineage infections in
301 the samples from this season (Figure 4A, Supplementary Figure -S4). The average number of
302 iSNV per sample and the average frequency of occurrence of the iSNVs were similar across the
303 genome regardless of viral codetection group (Table 5, Figure 4B). Accounting for multiple testing
304 corrections using both Bonferroni and Benjamini-Hochberg methods, we did not identify any
305 significant difference in average number of iSNV as well as frequency of occurrence of iSNV
306 across all the segments. We did not identify any difference between influenza only cases and virus
307 codetection cases by the number of days post symptoms. (Figure 4C)

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312 Figure (4): number if iSNVs per sample (A), number of iSNVs by segment for influenza-only cases versus co-detected cases (B),
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Table 5: Average number and frequency of minor single-nucleotide variants (SNVs) detected on H3N2 sequences samples by coding region for each gene segment and viral co-detection groups.

Segment	Number of minor iSNVs				Mean (SD) minor iSNVs frequency of occurence (SD)					
	Flu-only(n=99)		Flu-other viruses(n=33)		Bonferroni Adjusted p-value	Flu-only(n=99)		Flu-other viruses (n=33)		Bonferroni Adjusted p-value
	Total Number	Mean (SD)/subject	Total Number	Mean (SD)/subject		Max Freq/site	Mean (SD)/site	Max Freq	Mean (SD)/site	
PB2	45	1.80 (0.99)	17	1.59 (0.71)	0.698	8	0.27 (0.68)	3	0.20 (0.46)	0.700
PB1	38	1.40 (0.75)	11	2.00 (1.00)	0.192	3	0.18 (0.45)	2	0.16 (0.39)	0.980
PA	51	1.78 (1.56)	18	1.44 (0.92)	0.219	3	0.31 (0.55)	1	0.19 (0.40)	0.328
HA	34	1.59 (0.93)	13	1.85 (1.57)	0.164	15	0.18 (1.03)	2	0.18 (0.40)	0.328
NP	41	1.95 (1.30)	9	1.44 (1.01)	0.416	19	0.27 (1.57)	3	0.10 (0.39)	0.576
NA	34	1.21 (0.41)	12	1.08 (0.29)	0.545	14	0.13 (0.94)	3	0.10 (0.37)	0.663
M	19	1.05 (0.23)	9	1.22 (0.44)	0.244	11	0.07 (0.66)	3	0.08 (0.37)	0.531
NS	33	1.24 (0.50)	11	1.18 (0.41)	0.802	23	0.14 (1.35)	3	0.10 (0.39)	0.629

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319 **Association factors to the number of iSNVs found in A/H3N2 WGS samples.**

320 We identified the factors associated with higher number of iSNVs found in A/H3N2 WGs
 321 samples (Table 6). The elderly age group (>64 years old) and school-age children group (6-18
 322 years old) were found to have association with a higher number of iSNV counts (Incidence rate
 323 ratio (IRR)=2.08 (95% confidence interval (CI) 1.22-3.68), and IRR= 1.38 (95% CI: 1.01- 1.90)
 324 respectively. However, after adjusting for multiple testing, the p-value is not statistically
 325 significant (adjusted p-value > 0.05). This suggests that the observed association could be due to
 326 chance rather than a true effect, and the evidence is not strong enough to rule out a random
 327 association. We did not find any other associating factors.

328 Table 4: Association factors to the number of iSNVs found in each sequenced sample.

Characteristics	N=132	IRR¹ (95 Confidence interval)	Bonferroni Adjusted p-value
Age group			
19-64	63	1	
<6	13	0.85 (0.51-1.43)	1.000
6-18	46	1.38 (1.01- 1.90)	0.280
>64	10	1.80 (1.09- 3.06)	0.173
Vaccination status			
Non vaccinated	37	1	
Vaccinated	94	0.94 (0.68-1.30)	1.000
Gender			
Female	62	1	
Male	70	0.98 (0.73- 1.30)	1.000
Days post symptoms		0.93 (0.83- 1.02)	0.547
Viral co-detection			
Only influenza	99	1	
Virus codetected	33	0.90 (0.65- 1.26)	1.000

329 ¹IRR=Incidence Rate Ratio

330 **Discussion**

331 Increased within-host diversity plays a vital role in viral evolution, enhancing the possibility
332 of novel variants that natural selection can act upon.^{5,6} Several factors may shape influenza A
333 viruses' within-host diversity and evolution. This study explores the relationship between viral
334 codetection and within-host influenza A virus diversity in the human host.

335 Many respiratory virus infections may present as influenza-like illnesses (ILI), and studies
336 reported the presence of more than single respiratory pathogens (viruses and bacteria) in the same
337 patients.^{22,34-36} From the existing studies, the virus's co-detection rate ranges from 11.6% to 15.7%.
338^{34,37,38} In our study, 15% (79/538) of IAV-positive samples were co-detected with other viral
339 pathogens. We identified rhinovirus as the most commonly co-detected respiratory viral pathogen
340 to influenza A viruses. Previous studies support our findings,^{22,34,35,37} where hRV was reported to
341 be the most frequently co-detected pathogen in the general population and respiratory syncytial
342 virus (RSVs) among hospitalized patients.^{22,34,35} None of the patients in the current study were
343 hospitalized, which may reflect the low amount of co-detection with RSV in our study.

344 Based on the findings of our study, the observed strong negative association between IAV
345 and RV co-detection suggests that the presence of one virus may inhibit the replication or detection
346 of the other. Although IAV and RV were the most commonly co-detected viruses, the observed
347 number of co-detections was significantly lower than expected (48 observed vs. 61 expected, χ^2 p
348 < 0.001). The calculated odds ratio of 0.16 (95% CI 0.09–0.28) reinforces this negative association,
349 indicating a reduced likelihood of both viruses being detected simultaneously in the same host.
350 Moreover, among the virus co-detected IAV positive samples, only 40 of samples could proceed
351 for the sequencing, due to the low cDNA values. These findings align with existing evidence of
352 respiratory virus interactions, such as resources competition or induction of antiviral immune

353 responses (e.g., ISG), leading to one virus inhibiting the infection with second virus.^{16,17,18} The
354 experimental studies reported the virus that infects the host cell earlier can block the entry of other
355 viruses or the dominant virus interferes with the replication of the co-existing viruses by triggering
356 antiviral responses in the airway mucosa through the activation of interferon-stimulated gene (ISG)
357 expression.^{16,17} This can result in a reduction of viral RNA from a subsequent infection. If this
358 hypothesis holds, the limited number of samples available for sequencing could be attributed to
359 the low RNA yield in co-detected virus samples. However, we could not identify whether influenza
360 or other viruses first infect the host in our study; thus, it is difficult to conclude. This warrants
361 further investigation into the mechanisms underlying their interaction.

362 Our analysis did not find evidence to suggest that viral co-detection significantly influences
363 the within-host diversity of influenza A. We did not find phylogenetic clustering of WGS, and
364 individual segments based on the virus co-detection status. Moreover, the majority of cases,
365 regardless of being solely influenza or co-detected with another virus, displayed minimal within-
366 host minor variants, less than ten iSNVs per segment with a frequency below 10%. Overall, the
367 findings from our study resonate with previous studies that acute viral infections typically have
368 limited viral diversity throughout their course.^{10,11,14,39-41}

369 Our study found thirteen samples with more than 10 iSNV counts and ten samples with
370 zero iSNVs. We identified that older age groups (over 64 years old) and school-aged children (6-
371 18 years old) were more likely to have higher iSNVs than younger ones. However, in those samples
372 with a higher number of iSNVs, the frequencies of the occurrence were less than 5%. The existing
373 studies of within-host diversity focused on the younger age groups or immunocompromised
374 groups; thus, it is worth further investigating to include the different age groups to have better
375 understanding on the within-host diversity of influenza viruses.

376 Almost 62% of the ILI samples included in this study were negative for any of the
377 respiratory viral pathogens. The multiplex assay panels we used in the study included 13
378 respiratory viruses, including influenza A and B viruses. All pathogen-negative samples may be
379 caused by bacteria or viruses that were not part of our assay panels (for example, enteroviruses or
380 HCoV-NL63). It is worth applying more extensive multiplex assays covering the broader range of
381 respiratory pathogens.

382 The study has a few limitations. First, multiple factors may influence the sensitivity and
383 specificity of the variant calling in our study. PCR and sequencing errors may lead to the false
384 positive variant's calls. However, to reduce these errors, we put the stringency criteria on the raw
385 reads (at least 1000 depth of coverage, 100x length coverage, and variants are identified if the call
386 is above 2% frequency). Second, our study lacks extensive longitudinal data for multiple study
387 participants.

388 **Conclusion**

389 In this study cohort of 132 A/H3N2 influenza WGS sequences, we found no evidence of a
390 specific impact of virus-virus codetection on the within-host diversity of the influenza viral
391 population in humans. Most of the cases, whether influenza alone or co-detected with another virus,
392 had low iSNVs, with five iSNVs per segment and relative frequencies between 1–5%. Our findings
393 suggest a minor or negligible contribution of these viral codetections to the evolution of influenza
394 viruses. However, the data available in this study may not be exhaustive, warranting further, more
395 in-depth investigations to conclusively determine the impact of virus-virus interactions on
396 influenza virus genetic diversity.

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6.4 Supplementary File

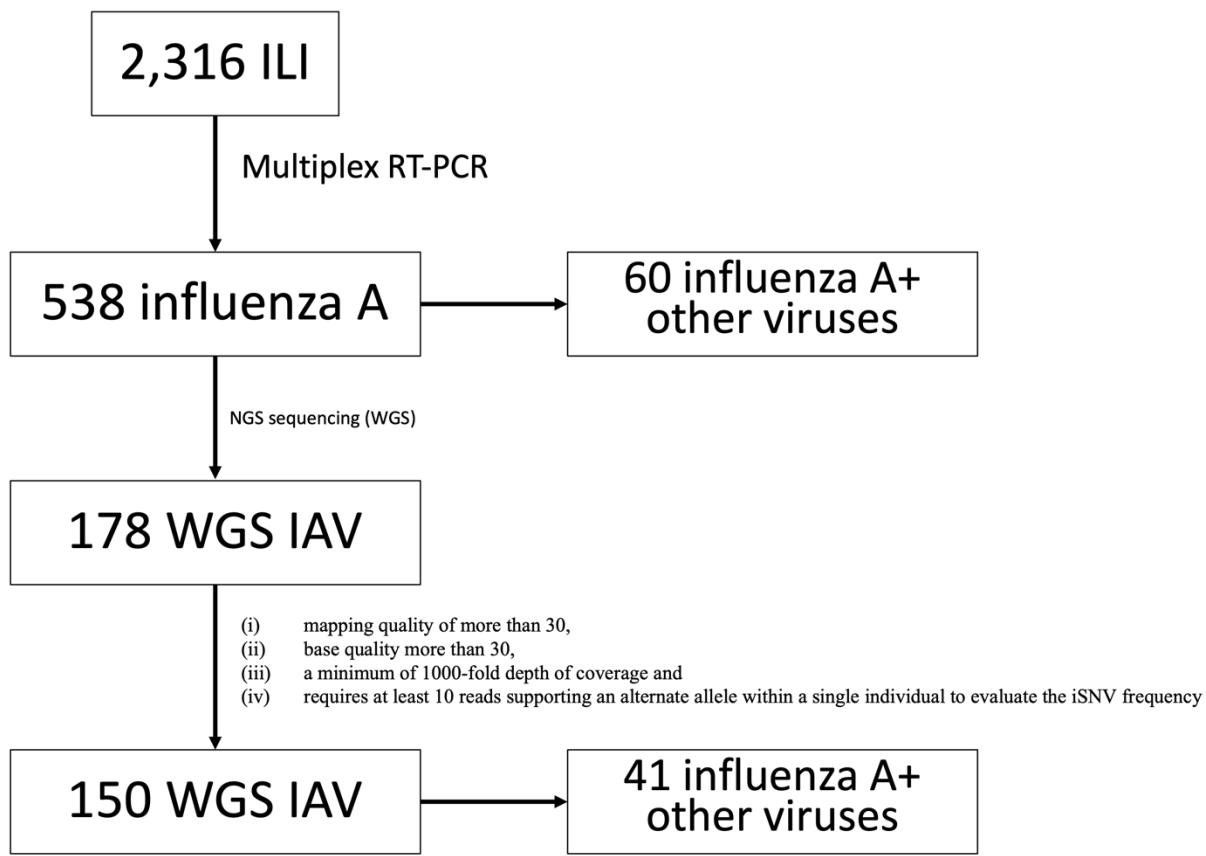
Impact of viral co-detection on within-host A/H3N2 influenza viral diversity

Su Myat Han^{1,2*}, Shingo Masuda^{1,3}, Alexis Robert^{2,4}, Yoshiano Kubo^{5,6}, Peterson Gitonga Mathenge⁷, Takahiro Yasaka³, Satoshi Kanda³, Kazuhiri Komori³, Lay Myint Yoshida^{1,8}, Akira Endo^{1,9}, Chris Smith^{1,10}, Teiichiro Shiino^{11,12}, Marc Baguelin^{2,13}, Koya Ariyoshi^{1,6}

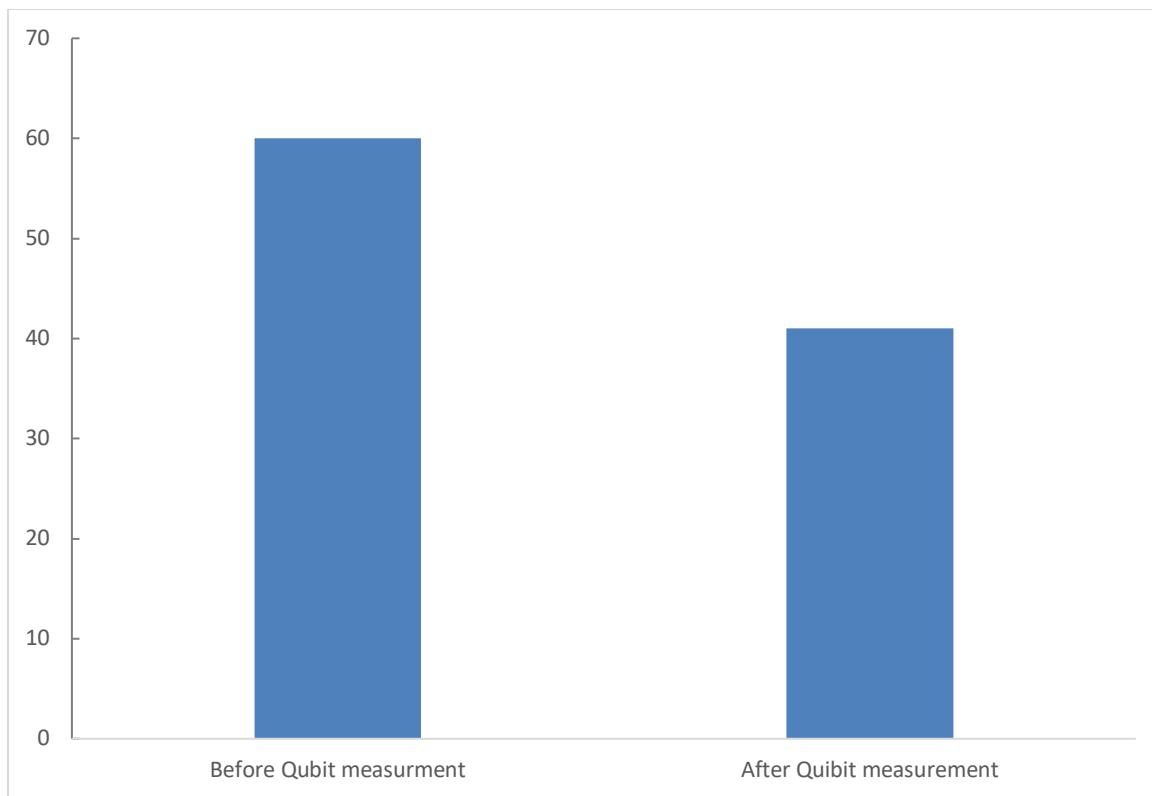
1. School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan
2. Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom
3. Department of Internal Medicine, Kamigoto Hospital, Kamigoto, Japan
4. Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, Keppel Street, London, UK
5. Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan
6. Department of Clinical Medicine, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan
7. Dana Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts. USA
8. Department of Pediatric Infectious Diseases, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan
9. Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore, Singapore
10. Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK
11. Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan
12. AIDS Research Center, National Institute of Infectious Diseases, Tokyo, Japan
13. MRC Centre for Global Infectious Disease Analysis; and the Abdul Latif Jameel Institute for Disease

Supplementary Table (1): Multiplex results of the respiratory pathogens (2012-13 season)

Age group	pop	ILI	IAV	IBV	PIV	RV	Adeno	Boca virus	hMPV	hCoV	hRSV	No pathogen detected
<5	479	444	62	5	20	77	15	7	2	5	5	271
5-10	686	328	108	4	3	42	10	5	3	1	2	163
11-15	845	289	70	4	5	35	2	6	1	0	2	176
16-20	607	164	44	3	2	18	2	3	0	0	4	100
21-25	114	40	9	0	0	6	2	0	0	0	1	27
26-30	227	62	18	0	0	7	0	0	0	0	0	39
31-35	329	100	28	4	1	7	1	0	0	0	0	63
36-40	500	101	33	1	1	9	1	0	0	1	2	56
41-45	555	90	30	2	1	9	0	0	0	2	0	50
46-50	615	85	36	1	3	9	3	2	0	1	0	36
51-55	675	60	23	1	0	2	1	1	0	0	1	34
56-60	770	59	21	1	1	8	0	0	0	0	0	33
61-65	920	46	12	1	1	2	0	0	0	0	0	30
66-70	869	53	12	1	1	6	1	0	0	0	0	34
71-75	1091	54	9	1	0	2	0	0	0	0	0	43
>75	3340	338	31	1	3	25	6	2	2	4	3	270

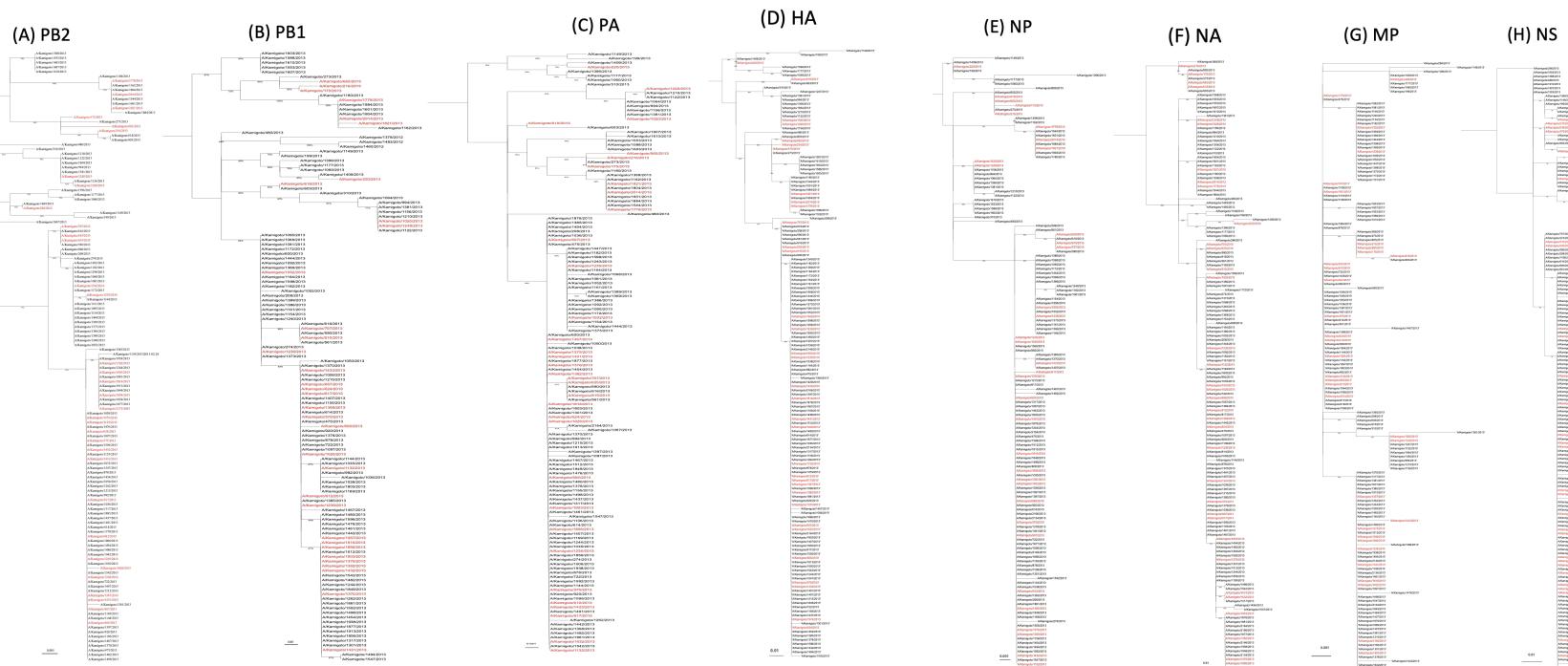


Supplementary Figure S-1: Flowchart showing the final results of WGS samples available for the downstream analysis in the study

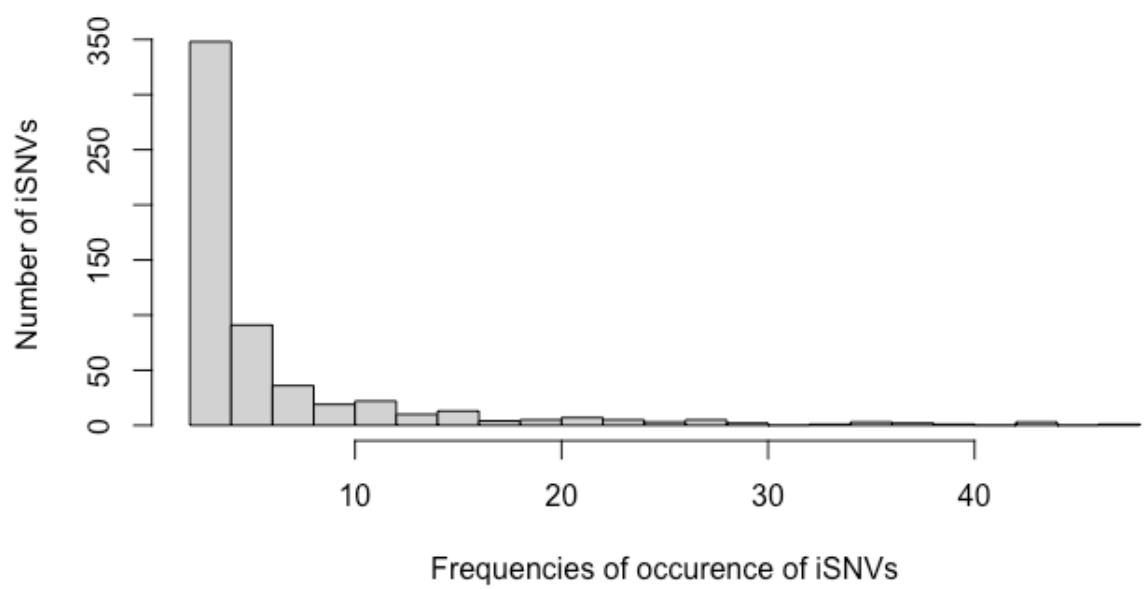


Supplementary Figure S-2: Number of codetection samples available for WGS (before and after measuring with Qubit for ng/ul)

**samples with at least 1ng/ul are used for further WGS

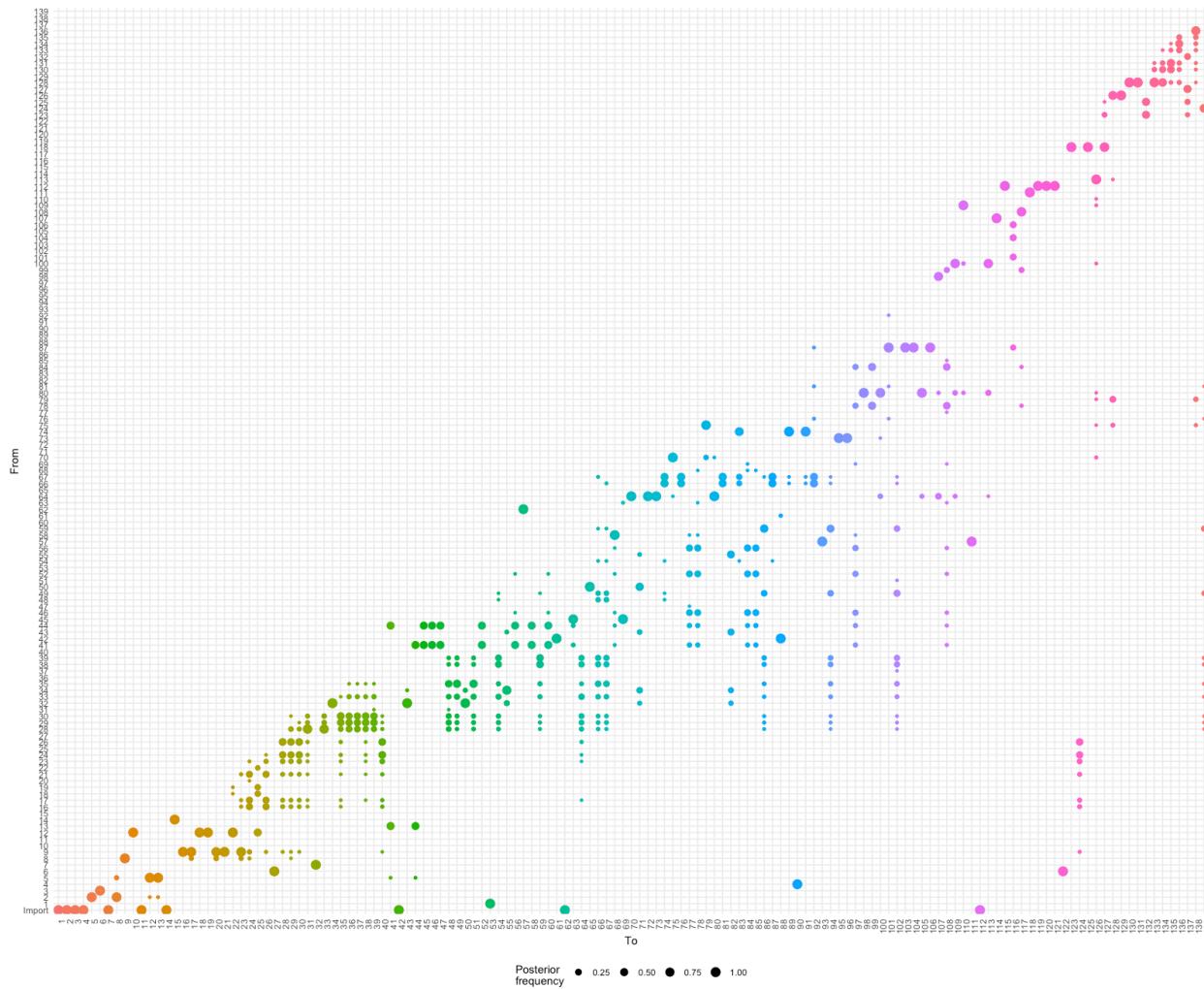


Supplementary Figure S-3: Maximum likelihood phylogenetic tree of (A) PB2, (B) PB1, (C) PA, (D) HA, (E) NP, (F) NA, (G) MP, (H) NS segment of A/H3N2 sequences in 2012/13 influenza season. The sequences in red color are virus-virus co-detected and black color are only influenza.



Supplementary Figure S-4: Number of occurrences of iSNV

1



2

3 Supplementary Figure S-5: The posterior support (the percentage of networks across all those sampled, where a given infector is
4 assigned to each case) for each potential transmission pairs.
5

6 **Reference**

- 7
- 8 1. Cori A, Valleron AJ, Carrat F, Scalia Tomba G, Thomas G, Boelle PY. Estimating influenza
9 latency and infectious period durations using viral excretion data. *Epidemics* 2012; **4**(3): 132-8.
- 10 2. Petrie JG, Ohmit SE, Cowling BJ, et al. Influenza transmission in a cohort of households
11 with children: 2010-2011. *PLoS One* 2013; **8**(9): e75339.

Chapter 7: Discussion and Conclusion

This chapter presents the discussion which includes the summary of main findings, with added values to the existing literature, strengths and limitations of the thesis, and implications for the future research studies.

7.1 Summary of main findings

This thesis focuses on the influenza transmission dynamics at the local community setting. **Chapter 4** worked to assess the temporo-spatial transmission patterns of influenza at Kamigoto island over eight influenza season and assessed the factors influencing the onwards local transmission. Younger children (below 19 years old) despite the higher vaccination coverage, were found to have higher relative illness ratio compared to the other age groups. These age groups were also found to have associated with higher number of secondary cases generated. This added the evidence of important role of children in the influenza outbreaks. The study also found that vaccination may reduce the chance of getting infected and severity once infected but may not protect against onward transmission from those who experienced a ‘breakthrough’ infection. Districts with lower vaccination coverage were associated with higher number of secondary cases generated, highlighting the needs of homogenously high vaccination across the community. Districts with higher number of population, and busy districts (which connects the islands to mainland Japan) were also found to have association with onwards transmission. Thus, my findings suggest improving the infection control intervention in the districts where the more interaction occurs (shopping districts or districts with ports in this island), and to achieve homogenous high vaccination coverage across the islands. The spatial heterogeneity of the median number of secondary cases per district shows

that active transmission clusters was only observed around a limited number of districts. More analysis, potentially using mechanistic transmission models, is needed to compare the impact of different vaccination strategies as the future work. The imports and secondary transmission patterns Kamigoto island were found to be consistent across the years studied.

Influenza has various types and subtypes that cannot be discerned solely through ILI surveillance data or RIDT results. While RIDT can distinguish between influenza A, B, or neither, many studies have used this data to predict influenza transmission dynamics. However, given that multiple influenza types and subtypes can co-circulate simultaneously, genomic analysis offers a more comprehensive understanding. In Chapter 5, I conducted whole genome sequencing on A/H3N2 samples from the 2011/12 and 12/13 influenza seasons in Kamigoto Island. I did phylogenetic analysis to examine the relationships between Kamigoto influenza strains and strains from mainland Japan and globally. The study identified that at least five distinct clusters co-circulated on the island. Without genomic data, these would appear as a single cluster. Being a semi-isolated region, most Kamigoto strains closely resembled those from mainland Japan. Some Kamigoto strains also showed similarities to strains outside Japan (North American strains). This underscores that respiratory viruses, like influenza, can traverse boundaries effortlessly. Adding the evidence to the **Chapter 4**, genomic analysis in **Chapter 5**, indicated that densely populated areas were often the initial outbreak sources and key in further transmission. **Chapter 5** further suggested that adults of working age were likely responsible for such importations. This is perhaps because they commute more frequently than the other age groups. The repeated introduction of similar strains also highlights the importance

of implementing control measures, especially at ports in Kamigoto Island, to curb the spread of influenza.

Many factors, including host, viral, and environmental elements, are known to influence influenza's transmission dynamics. Many of these factors, such as humidity, temperature, vaccination, innate/adaptive immune response, and human mobility, have been extensively studied. However, there's limited research on the interaction between multiple viruses and their impact on influenza transmission dynamics. Some evidence suggests competition between viruses within a host; an infection with one virus might interfere with another. Yet, the influence of these interactions on the within-host influenza viral diversity remains unclear. This diversity offers insights into global virus evolution, which in turn affects influenza's transmission dynamics. Hence, understanding within-host influenza viral diversity and its determinants is crucial. In **Chapter 6**, I began by exploring the viruses co-detected in each ILI host. Then, I performed NGS of the PCR confirmed influenza cases. In order to identify the within-host influenza diversity, I conducted variant calling for influenza sequences, both for influenza-only samples and influenza co-detected with other viruses samples. My findings indicated that within-host viral diversity is seemingly random. I didn't observe any strong evidence suggesting that virus co-detection influenced the variation in the number and frequencies of detected variants. Additionally, there were no unique iSNVs specific to either only-influenza cases or virus co-detected influenza cases. Factors like vaccination, sex, and viral co-detection status weren't associated with the number of iSNVs found in the samples. However, the elderly age group (over 74 years old) and school-aged children (6-18 years old) exhibited a higher number of iSNVs compared to the reference age group (19-64 years old).

This aspect of age-related differences in viral diversity hasn't been the focus of prior studies, emphasizing the need for further research in this aspect.

Chapter 3 outlines the laboratory methodologies and bioinformatics analyses I utilized to produce data for **Chapters 5 and 6**. Given the limited sequences available from Japan, especially the Kyushu region, in existing sources like the Influenza Research Database and GISAID, the data presented in **Chapter 3** enriches the research landscape for influenza viruses. This addition aids in discerning the intricate relationships of viruses from various geographical contexts.

7.2 Strength and limitations

In this study, I conducted multiplex RT-PCR assays to identify 13 respiratory viral pathogens (Chapter 3). These assays were developed and applied by the Nagasaki University research teams at the Department of Clinical Medicine, Institute of Tropical Medicine since 2010 [73]. The assays have been further developed to include enteroviruses in 2020/2021 [116]. Another study in the UK also developed multiplex RT-PCR assays to identify eleven respiratory viral pathogens, screening respiratory samples collected over multiple years. During the COVID-19 pandemic, numerous RT-PCR assays were developed to include COVID-19 in multiplex assays. To maintain methodological consistency throughout the study period, I refrained from changing the protocol or assays to include these alternative multiplex assays. In future research, I aim to compare and evaluate available multiplex RT-PCR assays and develop the optimal multiplex RT-PCR assay.

Secondly, I applied conventional RT-PCR in multiple assays, and thus, I couldn't measure the genome copy number as in qRT-PCR. Studies have emphasized the importance of viral

load (Ct values) in iSNV sensitivity and specificity. The current study is limited by the unavailability of viral loads or Ct values for the sequenced samples. However, I included samples with high cDNA concentration (measured by Qubit fluorometer) for sequencing. Additionally, I excluded sequence samples with depth coverage lower than 1000 from downstream analysis, and for iSNVs analysis, only samples with coverage (at least 100x) in all eight segments were included. This led to a reduced number of samples for Chapter 6, which investigated differences between influenza-only cases and those co-detected with other respiratory viral pathogens at the iSNVs level. For future research, I ideally want to use qRT-PCR and develop an optimal sequencing protocol for better sequence coverage.

Lastly, Chapters 5 and 6 focused only on A/H3N2 due to its dominance during the study period. It would be interesting to explore whether similar results apply to A/H1N1 or influenza B viruses. This aspect remains a potential area for future research.

7.3 Implications and Future work

In summary, this thesis provides a thorough examination of influenza transmission dynamics within a unique, semi-isolated island community—a setting that offers valuable insights into infectious disease studies. **Chapter 3** contributes crucial insights into circulating viral pathogens for two influenza seasons, emphasizing the generation of extensive influenza sequence data for Japan's influenza sequences database.

Chapters 4 and 5 reveal influenza transmission patterns within the islands, emphasizing the importance of initial importations, subsequent local transmissions, and various determinants influencing these dynamics. **Chapter 4** underscores the significant role of younger children in influenza outbreaks, highlighting the need for consistent vaccination

coverage, particularly in densely populated and busy districts. **Chapter 5**, utilizing genomic analysis, emphasizes the role of densely populated areas and working-age adults in initial outbreaks, emphasizing the importance of control measures, especially at ports, to limit influenza spread.

Chapter 6 focuses on simultaneous virus detections within hosts and their impact on within-host viral diversity. Notably, the study suggests that within-host viral diversity appears random, with age-related differences in viral diversity emerging as a new aspect for further investigation.

This study promotes a holistic approach to understanding and managing infectious disease outbreaks. The findings contribute to our understanding of the influenza virus and lay the groundwork for future research and evidence-based public health interventions.

In conclusion, this research makes a significant contribution to the field by offering nuanced insights into influenza transmission dynamics within a unique community context. The study's comprehensive nature provides a strong foundation for future research and underscores the importance of evidence-based public health interventions in managing infectious disease outbreaks.

Appendix

RNA extraction procedure

Reagents and consumable used;

- QIAamp Viral RNA Mini Kit (250) QIANGEN
- 99.5% Ethanol
- 1.5 ml microcentrifuge tube

Nasopharyngeal swab samples are thawed on the icetray, and spin down at **1800 rpm** for **2 min** (10 mins was suggested by Prof Lay)

For each kit, add 130 ml and **160 ml** of 99.5% ethanol to **AW1** and **AW2** respectively

- Add **310 µl** (*155 µl two times*) of **AVE elution buffer** (purple cap) into carrier RNA tube (red cap) and mix
- Add this 310 µl mixture to **AVL** bottle and mix
- Aliquot 560 µl of the mixture to microcentrifuge tube (keep at -20 °C if not used immediately)
- Follow the RNA extraction procedure as instructed in the manual

**Manual of “QIAmp Viral RNA Mini Handbook” as the main reference^[2]

Multiplex RT-PCR reaction

Reagents and consumable used;

- One-Step RT-PCR Kit (100). QIAGEN
- Primers (list in the appendix)

All the primer are added TE as instructed on the tube

(TE amount to be added to each primer)

- 8-well PCR tubes
- GoTaq® Flexi DNA Polymerase. Promega

**all the reagents are thawed on the icetray and all the procedures done on the icetray

4 panels of RT-PCR reaction to identify 13 respiratory viruses. Each panel has unique primers to detect viruses and reagents.

Appendix Table 1: Multiplex assay detecting Influenza A & B, RSV and hMPV

QIA One Step RT-PCR	25ul reaction 1x		final concentration	x 50
DW	7	ul		350
5xbuffer	5	ul	1x	250
5xQsolution	5	ul	1x	250
10mM dNTP	1	ul	0.4mM	50
InfA-YF	0.125	ul	0.5uM	6.25
InfA-YR1	0.125	ul	0.5uM	6.25
InfB-YF	0.125	ul	0.5uM	6.25
InfB-YR1	0.125	ul	0.5uM	6.25
hmpv-YF	0.125	ul	0.5uM	6.25
hmpv-YR1	0.125	ul	0.5uM	6.25
hRSVYF1	0.125	ul	0.5uM	6.25
hRSV-YR	0.125	ul	0.5uM	6.25
enzyme mix	1	ul	5u	50
subtotal	20	ul		1000
template RNA	5	ul		
Total	25	ul		

50(30'), 95(15') [94(30"), 57(30"), 72(45")] x 40cycles, 72(5'), 4(a)

Appendix Table 2: Multiplex assay detecting Parainfluenza I-IV

QIAGEN RT-PCR	25ul reaction 1x		final concentration	50 x
DW	7	ul		350
5xbuffer	5	ul	1x	250
5xQsolution	5	ul	1x	250
10mM dNTP	1	ul	0.4mM	50
PIV1-523OF	0.125	ul	0.5uM	6.25
PIV2-872OF	0.125	ul	0.5uM	6.25
PIV3-415OF	0.125	ul	0.5uM	6.25
PIV4-PP23F	0.125	ul	0.5uM	6.25
PIV1-823OR	0.125	ul	0.5uM	6.25
PIV2-1258OR	0.125	ul	0.5uM	6.25
PIV3-645OR	0.125	ul	0.5uM	6.25
PIV4-PP465R	0.125	ul	0.5uM	6.25
enzyme mix	1	ul	5u	50
subtotal	20	ul		1000
template RNA	5	ul		
Total	25	ul		

50(30'), 95(15') [94(30"), 55(30"), 72(45")] x 40cycles, 72(5'), 4(a)

Appendix Table 3: Multiplex assay detecting human-corona viruses (229F and OC43) and Rhino virus

QIAGEN RT-PCR	25ul reaction 1x		final concentration	50 x
DW	7.25	ul		362.5
5xbuffer	5	ul	1x	250
5xQsolution	5	ul	1x	250
10mM dNTP	1	ul	0.4mM	50
rv298F	0.125	ul	0.5uM	6.25
rv552OR	0.125	ul	0.5uM	6.25
oc43OF	0.125	ul	0.5uM	6.25
oc43R	0.125	ul	0.5uM	6.25
229eF	0.125	ul	0.5uM	6.25
229OR	0.125	ul	0.5uM	6.25
enzyme mix	1	ul	5u	50
subtotal	20	ul		1000
template RNA	5	ul		
Total	25	ul		

50(30'), 95(15') [94(30"), 55(30"), 72(45")] x 40cycles, 72(5'), 4(a)

Appendix Table 4: Multiplex assay detecting DNA viruses: Adeno and Boca

QIAGEN RT-PCR	25ul reaction 1x		final concentration.	x 50
DW	11.5		\$	575
5× buffer	5	ul	1×	250
25mM MgCl ₂	2.5	ul	2.5mM	125
10mM dNTP	0.5	ul	0.2mM	25
adeno1831F	0.1	ul	0.4uM	5
adeno2024R	0.1	ul	0.4uM	5
boca188F	0.1	ul	0.4uM	5
boca542R	0.1	ul	0.4uM	5
Taq Polymerase	0.1	ul	0.05U/ul	5
	20	ul		200
template DNA	5	ul		
Total	25	ul		

94(5') [94(30"), 55(30"), 72(45")] x 40cycles, 72(5'), 4(a)

Hemi-nested RT-PCR

- 8-well PCR tubes
- GoTaq® Flexi DNA Polymerase. Promega
- RNase free water QIAGEN kit
- DNA template

1 µl or 2 µl (fainted band in RT-PCR) of DNA templates were used for hemi-nested RT-PCR

Appendix Table 5: Hemi-nested assay detecting Inf-A and RSV

	1x		100
DW	14.5	ul	1450
5× buffer	5	ul 1×	500
25mM MgCl ₂	2.5	ul 2.5mM	250
10mM dNTP	0.5	ul 0.2mM	50
InfA-YF	0.1	ul 0.4µM	10
InfA-YR2	0.1	ul 0.4µM	10
hRSV-524F	0.1	ul 0.4µM	10
hRSV-YR	0.1	ul 0.4µM	10
Taq Polymerase	0.1	ul 0.05U/ul	10
	23	ul	2300
1st PCR product	2	ul	
Total	25	ul	

94(5') [94(30"), 57(30"), 72(45")] x 40cycles, 72(5'), 4(a)

Appendix Table 6: Hemi-nested assay detecting Inf-B and hMPV.

	1x 25ul reaction		final concentration	50
DW	14.5	ul		725
5× buffer	5	ul	1×	250
25mM MgCl ₂	2.5	ul	2.5mM	125
10mM dNTP	0.5	ul	0.2mM	25
InfB-YF	0.1	ul	0.4µM	5
InfB-YR2	0.1	ul	0.4µM	5
hmpv-YF	0.1	ul	0.4µM	5
hmpv-YR2	0.1	ul	0.4µM	5
Taq Polymerase	0.1	ul	0.05U/ul	5
	23	ul		1150
1st PCR product	2	ul		
Total	25	ul		

94(5') [94(30"), 57(30"), 72(45")] x 40cycles, 72(5'), 4(a)

Appendix Table 7: Hemi-nested assay detecting PIV-1, PIV-2, PIV-3 and PIV-4

	1x 25ul reaction		final concentration	50
DW	14.1	ul		705
5× buffer	5	ul	1×	250
25mM MgCl ₂	2.5	ul	2.5mM	125
10mM dNTP	0.5	ul	0.2mM	25
PIV1-613IF (100pmol/ul)	0.1	ul	0.4uM	5
PIV1-823OR (100pmol/ul)	0.1	ul	0.4uM	5
PIV2-872OF (100pmol/ul)	0.1	ul	0.4uM	5
PIV2-1201IR (100pmol/ul)	0.1	ul	0.4uM	5
PIV3-415OF (100pmol/ul)	0.1	ul	0.4uM	5
PIV3-563IR (100pmol/ul)	0.1	ul	0.4uM	5
PIV4-PP23F (100pmol/ul)	0.1	ul	0.4uM	5
PIV4-PP314R (100pmol/ul)	0.1	ul	0.4uM	5
Taq Polymerase	0.1	ul	0.05U/ul	5
	23	ul		1150
template DNA	2	ul		
Total	25	ul		
94(5') [94(30"), 55(30"), 72(45")] x 40cycles, 72(5'), 4(a)				

Appendix Table 8: Hemi-nested assay detecting Rhinovirus and coronavirus.

	1x 25ul reaction		final concentration	50
DW	14.3	ul		715
5× buffer	5	ul	v	250
25mM MgCl ₂	2.5	ul	2.5mM	125
10mM dNTP	0.5	ul	0.2mM	25
rv-298f (100pmol/ul)	0.1	ul	0.4uM	5
rv-473ir(100pmol/ul)	0.1	ul	0.4uM	5
229eF(100pmol/ul)	0.1	ul	0.4uM	5
hCoV 229E(100pmol/ul)	0.1	ul	0.4uM	5
hCoVOC43(100pmol/ul)	0.1	ul	0.4uM	5
oc43R(100pmol/ul)	0.1	ul	0.4uM	5
Taq Polymerase	0.1	ul	0.05U/ul	5
	23	ul		1150
1st PCR product	2	ul		
Total	25	ul		
94(5') [94(30"), 55(30"), 72(45")] x 40cycles, 72(5'), 4(a)				

Appendix Table 9: Hemi-nested assay detecting adenovirus and bocavirus

	1x 25ul reaction		final concentration	50
DW	14.5	ul		725
5× buffer	5	ul	1×	250
25mM MgCl ₂	2.5	ul	2.5mM	125
10mM dNTP	0.5	ul	0.2mM	25
AdenoF1831 (100pmol/ul)	0.1	ul	0.4uM	5
AdenoR1983 (100pmol/ul)	0.1	ul	0.4uM	5
boca188F (100pmol/ul)	0.1	ul	0.4uM	5
boca303IR (100pmol/ul)	0.1	ul	0.4uM	5
Taq Polymerase	0.1	ul	0.05U/ul	5
	23	ul		1150
template DNA	2	ul		
Total	25	ul		

94(5') [94(30"), 55(30"), 72(45")] x 40cycles, 72(5'), 4(a)

Gel electrophoresis procedure

Reagents and consumables used;

- 1XTAE (50 μ l)
- Nusieve Agarose
- Seakem Le Agarose
- Ethium bromide
- XL-DNA Ladder 100 plus intégrale (KE-2410)
- Loading buffer
- Gel tray

Procedures

- **1960 ml of milliQ** mix with **40 ml of 50x TAE** (this gives 1x TAE)
- for each gel, mix 50 μ l of 1xTAE, 0.5g each of Nusieve and seakem le Agaoose
- The mix is put in the microwave and boil
- 2.5 μ l of Ethium bromide is added to the boiled mixture
- Put the mixture into the gel tray (quickly before the gel getting hard)
- Wait for 20-30 minutes (or put it in the 4°C refrigerator for 10 mins)
- For each DNA template, mix 10 μ g of DNA template and 1 μ g of loading buffer
- Add 7 μ g of DNA ladder (for marker)
- 100 voltage is used (run time is about 35 mins)

The DNA bands are then visualized under Blue/Green LED Transilluminator.

Appendix Table 10: Primers for multiplex RT-PCR for Influenza virus

Primer Type	Primer name	Sequence 5'- 3'
Influenza A virus		
Fw	Uni12/Inf-1	GGGGGGAGCAAAAGCAGG
Fw	Uni12/Inf-3	GGGGGGAGCGAAAGCAGG
Rv	Uni13/Inf-1	CGGGTTATTAGTAGAAACAAGG

Appendix Table 11: RT-PCR reaction protocol for influenza A (Zhou, B., et al)^[3]

RT-PCR (Influenza A)	
ddH ₂ O	10 ul
2× buffer	25 ul
Uni12/Inf1 10 uM	0.8 ul
Uni12/Inf3 10 uM	1.2 ul
Uni13/Inf1 10 uM	2 ul
SSIII/Platinum Taq Enzyme Mix	1 ul
	40 ul
template RNA	10 ul
Total	50 ul

42 (60') 94 (2') [94(30'') 44(30'') 68 (3')]x5 cycles [94(30'') 57(30'') 68(3'')]x35 cycles 68(5') 4(a)

Laboratory procedure for Miseq Illumina sequencing

Written by Su Myat Han (pearl.june@gmail.com)

Whole genome RT-PCR

Applied consumables and reagents;

- SuperScript™ III One-Step RT-PCR System with Platinum™ Taq High Fidelity DNA Polymerase
- 2X Reaction Mix (MgSo₄, dNTPs) [included in superscript™]
- RNase free water (QIAGEN)
- 8 well PCR tubes
- PCR Thermocycler (AB Applied Biosystems, Veriti)

	50ul reaction 1x		Final concentration	40 x
ddH2O	10 ul		400	
2xRT-PCR buffer	25 ul	1x	800	25.
Uni 12/Inf1 10 uM	0.8 ul	1x	6	38.
Uni 12/Inf3 10 uM	1.2 ul	0.4mM	4	
Uni 13/Inf1 10 uM	2 ul	0.5uM	64	
SSIII/Platinum Taq HiFi Enzyme mix	1 ul	0.5uM	32	160
subtotal	40 ul		0	
template RNA	10 ul			
Total	50 ul			

42(60'), 94(2') [94(30"), 44(30"), 68(3')] x 5 cycles [94(30"), 57(30"), 68(3')]x35 cycles, 68(5'), 4(a)

The quality of the RT-PCR products is checked using an agarose gel

Clean-up of the PCR products for the library preparation

Consumable and reagents used;

- Magnetic stand (Ambion)

- 10 mM Tris pH 8.0 (Manually prepared from lab procedure)
- 80% Ethanol

(to prepare the fresh one every time: 10 ml 100% Ethanol + 40 ml of milliQ)

- Midi Deepwell plate (thermo scientific)
- Agencourt AMPure XP beads (Beckman Coulter)
- 8-channel pipette
- RNase free water (QIAGEN)

Procedure

- Prepare the fresh 80% Ethanol solution
- Take out the Agencourt AMPure XP beads 10- 15 minutes before the procedure begins (vortex the bottle to ensure the beads mix well)
- **45 µl** of Agencourt is aliquoted to each well of the Midi Deepwell plate
- **30 µl** of RNase free water is added to each of those wells
- Then, **10 µl** of PCR product is added by **mixing** with pipette for **10 times**
- Incubate the solution at room temperature for **5 minutes**
- Put the Midi plate on the Magnetic stand and incubate for another **2 minutes**
- **From this step, the midi plate is to be kept on the magnetic stand**
- Using the 8-channel pipette, remove **80 µl** clear supernatant of each without touching the beads
- Wash with ethanol for two times (following steps)
 - o add **200 µl** of 80% ethanol to each well with 8-channel pipette
 - o incubate at room temperature for **30 seconds**
 - o remove and discard ethanol of each well with 8-channel pipette (not touching the beads)
- Air-dry on the magnetic stand for 5 minutes
- Then, remove the Midi Deepwell from the magnetic stand
- Add **25 µl** of 10mM Trips pH 8.0 to each well and mix 10 times
- Put the midi plate on the magnetic stand back
- Incubate at room temperature for **2 minutes**

- Keep midi plate on the magnetic stand, transfer **23 µl** of supernatant to the new 96 PCR plate.
- DNA concentration of these samples are quantified by using Qubit fluorometer

Preparation to get 1ng DNA (5 µl)

- Qubit dsDNA HS Assay Kit (Life Technologies)
- 0.5mL PCR tube.

Procedure

- On Qubit fluorometer, choose DNA, then dsDNA (high sensitivity)
- Standard solution is prepared: 199 µl Qubit buffer + 1 µl Qubit reagent (ds DNA) for each sample
- For each sample, add 199 µl of standard solution and 1 µl of PCR product in the Qubit tube
- Vortex the tubes for 2-3 seconds
- Incubate at room temperature for 2 minutes
- Standards 1 and 2 were read by the fluorometer before reading for the samples
- Then, put the tube on the Qubit and take the readings (ng/µl for 1 µl sample used)
- Then dilute the samples to get **5 µl of 1 ng DNA** for library preparation
- I used the C1V1= C2V2 formula

ng/µl (C1)	V1 (samples volume to add)	RSB/RNase freewater (to add)
Readings from Qubit	= (1*10)/ ng/µl	= 10- V1

*** I prepare 10 µl solution though I need only 5 µl, in order to avoid pipetting error when I have to use only 1 µl of original sample to dilute

Library preparation for Nextra XT V2

- The maximum sample (cDNA template) to use per sequencing is 30.
- Normally, I do whole-genome RT-PCR for 30 samples

- Those with good visualization of the bands are taken for library preparation to do sequencing

Tagmentation of genomic DNA

Reagents and consumable used

Nextra XT library preparation kits (***Thaw on Ice before and during the procedure***)

- Amplicon tagment mix (ATM)
- Tagment DNA buffer (TD)
- Neutralization buffer (NT). Room temperature (vortex if precipitates are found)
(Invert all reagents 3-5 times, followed by pulse spin)
- 96-well PCR plate
- Micro adhesive seal B

Procedure:

- Firstly, I set up and get ready to run the thermocycler for TAG program with the following setting: (preheat lid option set to 100C)
 - o **55C for 5 mins**
 - o **hold at 10C**
- I first add the 10 μ l of TD to each well of 96-well PCR plate by pipetting for 10 times for each DNA sample
- Then **5 μ l of DNA** (1 ng/ μ l) are added to each well
- **5 μ l of ATM** is added to each well, pipetting up and down to mix
- Seal the plate and centrifuge at **280g at 20C for 1 min**
- Put plate in thermocycler and run the ATM program
- After removal of the seal, add **5 ul of NT** to each well, pipetting up and down to mix
- Seal the plate and then centrifuge at **280g at 20C for 1 min**
- Incubate at **room temperature for 5 mins**

Amplification of PCR samples

Reagents and consumable used

- nextera PCR mastermix (NPM)
- index primers (I use tubes type)

(All the reagents are inverted for 3-5 times, followed by pulse spin)

- Arrange index primers in the following order

Procedures:

- Prepare the index manual sheets for documentation of index attachment with the sample
- Prepare the thermocycler for PCR amplification setting

72C – 3 mins	1 cycle
95C – 30 secs	1 cycle
95C – 10 secs	
55C – 30 secs	12 cycles
72C – 30 secs	
72C – 5 mins	1 cycle
Hol at 10C	

- Add **15 ul of NPM** to each well
- Add **5 ul of index 2 primers (white caps)** to each column and pipette up and down to mix
- Add **5 ul of index 1 primers (orange caps)** to each row and pipette up and down to mix
- Seal the plate and centrifuge at **280g at 20C for 1 min**
- perform PCR
- then centrifuge at **280g at 20C for 1 min**

I usually continue to the next steps, but accordingly to the illumine guidebook the sample can be saved in the fridge for up to 2 days before doing the sequencing procedures

PCR Cleanup

Reagents and consumables used:

- Agencourt AMPure XP beads
- 80% ethanol (I prepare the freshly new every time)
- Resuspension Buffer (RSB)
- 96-well deepwell midi plate
- 96-well PCR plate
- Microadhesive seal
- Nuclease-free water
- 8-channel pipette

Preparation

- Bring out agencour AMPure beads to room temperature 15 mins before the procedure
- Vortex well to ensure the even distribution of the beads
- Centrifuge at **280g at 20C for 1 min** (if the samples were kept for this step)
- Transfer **50 µl supernatant** to new PCR plate, and pipette up and down to mix
- Add **30 µl of ampure XP beads** to each well (to do slowly due to its viscosity)
- Seal the plate and put on the shaker (1800 rpm) for **2 min**
- incubate at **room temp for 5 mins**
- Then put the plate on the **magnet and wait for 5 mins** (or more) till the liquid becomes clear, (keep the plate on the magnet for next steps)
- Remove and discard all the supernatant (without touching the beads)
- Then wash for two times (I use the 8-channel pipette here)
 - o add **200 ul of 80% Ethanol** to each well
 - o **wait 30 secs**
 - o Remove and discard all the supernatant (without touching the beads)
- Check wells whether no liquid left, if left remove and discard
- Airdry for ~ 15mins, or until no EtOH can be detected (I place the plate, magnet attached on the clean bench with fan opened)
- Then remove plate from magnet
- Add **52.5 ul resuspension buffer** to each well, and pipette up and down to mix
- Seal the plate and put on the shaker (1800 rpm) for **2 min**

- incubate at **room temperature for 5 mins**
- put the plate on **magnet for 5 mins** (or until supernatant has cleared)
- then transfer **50 ul** supernatant to new 96-well PCR plate

I normally continue the next step, but if we want to stop here, the samples can be kept in the freezer up to 7 days before the sequencing

Library Normalisation and Pooling

A reagent cartridge was removed from storage at -20 °C and placed in a water bath at room temperature for 60 min. The cartridge was inverted several times to ensure adequate mixing of reagents and to check for any precipitation which would indicate that the cartridge was not usable.

- The concentration of each sample was measured with Qubit
- The DNA amount per sample is then calculated ($\text{ng}/\mu\text{l} \times \text{volume} = \text{total ng}$)
- For first batches of the sequencing, I calculated the average library size as 600 bp. For later batches, High Sensitivity D1000 ScreenTape System (Agilent). A 2 μl aliquot of the prepared library was transferred to a fresh 0.2 ml tube, to which 2 μl of High Sensitivity D1000 Sample Buffer was added. For each set of samples 1 lane contained High Sensitivity D1000 Ladder in place of a library to allow fragment size quantification. The tubes were loaded into the 2200 Tapestation and sample names entered into the controller software before commencing the run.
- Library concentration is then calculated by

$$\frac{\text{ng}/\mu\text{l}}{\text{average bp size}} \times 452 = \text{Concentration} \left(\frac{\text{ng}}{\mu\text{l}} \right)$$

$$\frac{\text{Concentration} \left(\frac{\text{ng}}{\mu\text{l}} \right)}{\text{Molecular weight dsDNS (660)} \times \text{bp size}} \times 10^6 = \text{Molar concentration (nM)}$$

- Adjust the concentration of the pooled DNA to **4 nM** using C1V1=C2V2 formula

$\text{ng}/\mu\text{l} (\text{C1})$	V1 (samples volume to add)	RSB/RNase free water (to add)
Readings from Qubit	= $(1 \times 10)/\text{ng}/\mu\text{l}$	= $10 - V1$

- **5 ul** aliquot of each diluted library was then pooled in one single tube.
- Mix **(800 ul)** of laboratory-grade water and **(200 ul)** of 1.0 N NaOH to get 0.2 N NaOH concentration

- **5 ul** of 4nM library and **5 ul** of 0.2 N NaOH were added to new microcentrifuge tube
- Briefly vortex and then centrifuge at **280g at 20C for 1 min**
- Incubate at room temperature for 5 mins
- **990 ul** of prechilled HT1 is added (~ to 1 ml of 20 pM denatured library)
- Transfer **360 ul** of 20 pM libraries to new microcentrifuge tube
- Add **240 ul** of prechilled HT1 to the tube (this gets 12pM library)
- Invert to mix and then pulse centrifuge.

This is ready for sequencing

Appendix Table 12. Sample accession numbers. Sequences are available from GISAID.

Isolate Name	Isolate ID
A/Kamigoto/728/2012 (A/H3N2)	EPI_ISL_17103063
A/Kamigoto/199/2013 (A/H3N2)	EPI_ISL_17092317
A/Kamigoto/1447/2013 (A/H3N2)	EPI_ISL_18002728
A/Kamigoto/1454/2013 (A/H3N2)	EPI_ISL_18002450
A/Kamigoto/1461/2013 (A/H3N2)	EPI_ISL_18002449
A/Kamigoto/1444/2013 (A/H3N2)	EPI_ISL_18002434
A/Kamigoto/1467/2013 (A/H3N2)	EPI_ISL_18002433
A/Kamigoto/1442/2013 (A/H3N2)	EPI_ISL_18002432
A/Kamigoto/1476/2013 (A/H3N2)	EPI_ISL_18001909
A/Kamigoto/1480/2013 (A/H3N2)	EPI_ISL_18001908
A/Kamigoto/1437/2013 (A/H3N2)	EPI_ISL_18001895
A/Kamigoto/1433/2013 (A/H3N2)	EPI_ISL_18001894
A/Kamigoto/1432/2013 (A/H3N2)	EPI_ISL_18001808
A/Kamigoto/1431/2013 (A/H3N2)	EPI_ISL_18001804
A/Kamigoto/1420/2013 (A/H3N2)	EPI_ISL_18001803
A/Kamigoto/1482/2013 (A/H3N2)	EPI_ISL_18001802
A/Kamigoto/1491/2013 (A/H3N2)	EPI_ISL_18001801
A/Kamigoto/1494/2013 (A/H3N2)	EPI_ISL_18001747
A/Kamigoto/1498/2013 (A/H3N2)	EPI_ISL_18001746
A/Kamigoto/1502/2013 (A/H3N2)	EPI_ISL_18001715
A/Kamigoto/1512/2013 (A/H3N2)	EPI_ISL_18001714
A/Kamigoto/1542/2013 (A/H3N2)	EPI_ISL_18001713
A/Kamigoto/1544/2013 (A/H3N2)	EPI_ISL_18001707
A/Kamigoto/1547/2013 (A/H3N2)	EPI_ISL_18001706
A/Kamigoto/1553/2013 (A/H3N2)	EPI_ISL_18001705
A/Kamigoto/1588/2013 (A/H3N2)	EPI_ISL_18001704
A/Kamigoto/1592/2013 (A/H3N2)	EPI_ISL_18001703
A/Kamigoto/1596/2013 (A/H3N2)	EPI_ISL_18001702
A/Kamigoto/1598/2013 (A/H3N2)	EPI_ISL_18001701
A/Kamigoto/1601/2013 (A/H3N2)	EPI_ISL_18001686
A/Kamigoto/1603/2013 (A/H3N2)	EPI_ISL_18001652
A/Kamigoto/1607/2013 (A/H3N2)	EPI_ISL_18001626
A/Kamigoto/1610/2013 (A/H3N2)	EPI_ISL_18001610
A/Kamigoto/1778/2013 (A/H3N2)	EPI_ISL_18001609
A/Kamigoto/1803/2013 (A/H3N2)	EPI_ISL_18001608
A/Kamigoto/1804/2013 (A/H3N2)	EPI_ISL_18001607
A/Kamigoto/1816/2013 (A/H3N2)	EPI_ISL_18001606

A/Kamigoto/1821/2013 (A/H3N2)	EPI_ISL_18001522
A/Kamigoto/1849/2013 (A/H3N2)	EPI_ISL_18001521
A/Kamigoto/1856/2013 (A/H3N2)	EPI_ISL_18001520
A/Kamigoto/1876/2013 (A/H3N2)	EPI_ISL_18001519
A/Kamigoto/1877/2013 (A/H3N2)	EPI_ISL_18001518
A/Kamigoto/1881/2013 (A/H3N2)	EPI_ISL_18001517
A/Kamigoto/1884/2013 (A/H3N2)	EPI_ISL_18001516
A/Kamigoto/1896/2013 (A/H3N2)	EPI_ISL_18001514
A/Kamigoto/1903/2013 (A/H3N2)	EPI_ISL_18001513
A/Kamigoto/1913/2013 (A/H3N2)	EPI_ISL_18001512
A/Kamigoto/1938/2013 (A/H3N2)	EPI_ISL_18001511
A/Kamigoto/2014/2013 (A/H3N2)	EPI_ISL_18001510
A/Kamigoto/2134/2013 (A/H3N2)	EPI_ISL_18001486
A/Kamigoto/2146/2013 (A/H3N2)	EPI_ISL_18000339
A/Kamigoto/2164/2013 (A/H3N2)	EPI_ISL_18000338
A/Kamigoto/2166/2013 (A/H3N2)	EPI_ISL_18000336
A/Kamigoto/1419/2013 (A/H3N2)	EPI_ISL_17786021
A/Kamigoto/1409/2013 (A/H3N2)	EPI_ISL_17785996
A/Kamigoto/1407/2013 (A/H3N2)	EPI_ISL_17785995
A/Kamigoto/1399/2013 (A/H3N2)	EPI_ISL_17785743
A/Kamigoto/1397/2013 (A/H3N2)	EPI_ISL_17785739
A/Kamigoto/1396/2013 (A/H3N2)	EPI_ISL_17785738
A/Kamigoto/1389/2013 (A/H3N2)	EPI_ISL_17785724
A/Kamigoto/1386/2013 (A/H3N2)	EPI_ISL_17785723
A/Kamigoto/1385/2013 (A/H3N2)	EPI_ISL_17785722
A/Kamigoto/1382/2013 (A/H3N2)	EPI_ISL_17785719
A/Kamigoto/1381/2013 (A/H3N2)	EPI_ISL_17785716
A/Kamigoto/1378/2013 (A/H3N2)	EPI_ISL_17785715
A/Kamigoto/1376/2013 (A/H3N2)	EPI_ISL_17785627
A/Kamigoto/1375/2013 (A/H3N2)	EPI_ISL_17785624
A/Kamigoto/1373/2013 (A/H3N2)	EPI_ISL_17785619
A/Kamigoto/1370/2013 (A/H3N2)	EPI_ISL_17785617
A/Kamigoto/1369/2013 (A/H3N2)	EPI_ISL_17785616
A/Kamigoto/1368/2013 (A/H3N2)	EPI_ISL_17785615
A/Kamigoto/1367/2013 (A/H3N2)	EPI_ISL_17785614
A/Kamigoto/1360/2013 (A/H3N2)	EPI_ISL_17785613
A/Kamigoto/1356/2013 (A/H3N2)	EPI_ISL_17761517
A/Kamigoto/1317/2013 (A/H3N2)	EPI_ISL_17761516
A/Kamigoto/1301/2013 (A/H3N2)	EPI_ISL_17739156

A/Kamigoto/1262/2013 (A/H3N2)	EPI_ISL_17738971
A/Kamigoto/1248/2013 (A/H3N2)	EPI_ISL_17738944
A/Kamigoto/1247/2013 (A/H3N2)	EPI_ISL_17730095
A/Kamigoto/1244/2013 (A/H3N2)	EPI_ISL_17730092
A/Kamigoto/1240/2013 (A/H3N2)	EPI_ISL_17730088
A/Kamigoto/1239/2013 (A/H3N2)	EPI_ISL_17730086
A/Kamigoto/1236/2013 (A/H3N2)	EPI_ISL_17730085
A/Kamigoto/1215/2013 (A/H3N2)	EPI_ISL_17730082
A/Kamigoto/1210/2013 (A/H3N2)	EPI_ISL_17730079
A/Kamigoto/1182/2013 (A/H3N2)	EPI_ISL_17730075
A/Kamigoto/1180/2013 (A/H3N2)	EPI_ISL_17730072
A/Kamigoto/1177/2013 (A/H3N2)	EPI_ISL_17730069
A/Kamigoto/1172/2013 (A/H3N2)	EPI_ISL_17730068
A/Kamigoto/1169/2013 (A/H3N2)	EPI_ISL_17730067
A/Kamigoto/1164/2013 (A/H3N2)	EPI_ISL_17730066
A/Kamigoto/1162/2013 (A/H3N2)	EPI_ISL_17730065
A/Kamigoto/1161/2013 (A/H3N2)	EPI_ISL_17730047
A/Kamigoto/1159/2013 (A/H3N2)	EPI_ISL_17730041
A/Kamigoto/1156/2013 (A/H3N2)	EPI_ISL_17726035
A/Kamigoto/1155/2013 (A/H3N2)	EPI_ISL_17692316
A/Kamigoto/1154/2013 (A/H3N2)	EPI_ISL_17692307
A/Kamigoto/1149/2013 (A/H3N2)	EPI_ISL_17692279
A/Kamigoto/1144/2013 (A/H3N2)	EPI_ISL_17692278
A/Kamigoto/1132/2013 (A/H3N2)	EPI_ISL_17692276
A/Kamigoto/1122/2013 (A/H3N2)	EPI_ISL_17692275
A/Kamigoto/1108/2013 (A/H3N2)	EPI_ISL_17692274
A/Kamigoto/1106/2013 (A/H3N2)	EPI_ISL_17692272
A/Kamigoto/1097/2013 (A/H3N2)	EPI_ISL_17692271
A/Kamigoto/1095/2013 (A/H3N2)	EPI_ISL_17692267
A/Kamigoto/1092/2013 (A/H3N2)	EPI_ISL_17692266
A/Kamigoto/1081/2013 (A/H3N2)	EPI_ISL_17692265
A/Kamigoto/1068/2013 (A/H3N2)	EPI_ISL_17692264
A/Kamigoto/1067/2013 (A/H3N2)	EPI_ISL_17692257
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A/Kamigoto/1060/2013 (A/H3N2)	EPI_ISL_17692112
A/Kamigoto/1052/2013 (A/H3N2)	EPI_ISL_17692053
A/Kamigoto/1050/2013 (A/H3N2)	EPI_ISL_17692052
A/Kamigoto/1038/2013 (A/H3N2)	EPI_ISL_17692051
A/Kamigoto/1036/2013 (A/H3N2)	EPI_ISL_17692004

A/Kamigoto/1035/2013 (A/H3N2)	EPI_ISL_17691998
A/Kamigoto/1026/2013 (A/H3N2)	EPI_ISL_17691980
A/Kamigoto/1020/2013 (A/H3N2)	EPI_ISL_17691968
A/Kamigoto/1006/2013 (A/H3N2)	EPI_ISL_17691966
A/Kamigoto/994/2013 (A/H3N2)	EPI_ISL_17691965
A/Kamigoto/992/2013 (A/H3N2)	EPI_ISL_17689263
A/Kamigoto/920/2013 (A/H3N2)	EPI_ISL_17684817
A/Kamigoto/878/2013 (A/H3N2)	EPI_ISL_17684804
A/Kamigoto/817/2013 (A/H3N2)	EPI_ISL_17684803
A/Kamigoto/805/2013 (A/H3N2)	EPI_ISL_17684787
A/Kamigoto/722/2013 (A/H3N2)	EPI_ISL_17684786
A/Kamigoto/707/2013 (A/H3N2)	EPI_ISL_17684785
A/Kamigoto/667/2013 (A/H3N2)	EPI_ISL_17684676
A/Kamigoto/666/2013 (A/H3N2)	EPI_ISL_17684609
A/Kamigoto/665/2013 (A/H3N2)	EPI_ISL_17684607
A/Kamigoto/635/2013 (A/H3N2)	EPI_ISL_17684606
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A/Kamigoto/616/2013 (A/H3N2)	EPI_ISL_17683953
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A/Kamigoto/603/2013 (A/H3N2)	EPI_ISL_17683790
A/Kamigoto/600/2013 (A/H3N2)	EPI_ISL_17683728
A/Kamigoto/590/2013 (A/H3N2)	EPI_ISL_17683727
A/Kamigoto/561/2013 (A/H3N2)	EPI_ISL_17683726
A/Kamigoto/480/2013 (A/H3N2)	EPI_ISL_17683724
A/Kamigoto/475/2013 (A/H3N2)	EPI_ISL_17683723
A/Kamigoto/375/2013 (A/H3N2)	EPI_ISL_17683722
A/Kamigoto/369/2013 (A/H3N2)	EPI_ISL_17683294
A/Kamigoto/310/2013 (A/H3N2)	EPI_ISL_17683293
A/Kamigoto/296/2013 (A/H3N2)	EPI_ISL_17683292
A/Kamigoto/274/2013 (A/H3N2)	EPI_ISL_17683291
A/Kamigoto/273/2013 (A/H3N2)	EPI_ISL_17683048
A/Kamigoto/220/2013 (A/H3N2)	EPI_ISL_17683047
A/Kamigoto/216/2013 (A/H3N2)	EPI_ISL_17683046
A/Kamigoto/208/2013 (A/H3N2)	EPI_ISL_17683045
A/Kamigoto/1137/2012 (A/H3N2)	EPI_ISL_17296154

A/Kamigoto/1209/2012 (A/H3N2)	EPI_ISL_17296116
A/Kamigoto/1378/2012 (A/H3N2)	EPI_ISL_17296115
A/Kamigoto/1430/2012 (A/H3N2)	EPI_ISL_17296114
A/Kamigoto/1437/2012 (A/H3N2)	EPI_ISL_17296113
A/Kamigoto/1439/2012 (A/H3N2)	EPI_ISL_17296112
A/Kamigoto/1483/2012 (A/H3N2)	EPI_ISL_17296108
A/Kamigoto/1490/2012 (A/H3N2)	EPI_ISL_17296105
A/Kamigoto/1514/2012 (A/H3N2)	EPI_ISL_17296097
A/Kamigoto/1530/2012 (A/H3N2)	EPI_ISL_17296096
A/Kamigoto/894/2012 (A/H3N2)	EPI_ISL_17296073
A/Kamigoto/887/2012 (A/H3N2)	EPI_ISL_17296061
A/Kamigoto/886/2012 (A/H3N2)	EPI_ISL_17296025
A/Kamigoto/871/2012 (A/H3N2)	EPI_ISL_17295949
A/Kamigoto/805/2012 (A/H3N2)	EPI_ISL_17295903
A/Kamigoto/796/2012 (A/H3N2)	EPI_ISL_17295902
A/Kamigoto/784/2012 (A/H3N2)	EPI_ISL_17295671
A/Kamigoto/772/2012 (A/H3N2)	EPI_ISL_17104742
A/Kamigoto/771/2012 (A/H3N2)	EPI_ISL_17104741
A/Kamigoto/765/2012 (A/H3N2)	EPI_ISL_17104740
A/Kamigoto/763/2012 (A/H3N2)	EPI_ISL_17104739
A/Kamigoto/762/2012 (A/H3N2)	EPI_ISL_17104738
A/Kamigoto/757/2012 (A/H3N2)	EPI_ISL_17104737
A/Kamigoto/752/2012 (A/H3N2)	EPI_ISL_17104735
A/Kamigoto/1460/2012 (A/H3N2)	EPI_ISL_17103548
A/Kamigoto/749/2012 (A/H3N2)	EPI_ISL_17103148
A/Kamigoto/729/1012 (A/H3N2)	EPI_ISL_17103065
A/Kamigoto/175/2013 (A/H3N2)	EPI_ISL_17092239
A/Kamigoto/1075/2012 (A/H3N2)	EPI_ISL_17103062