ORIGINAL ARTICLE

Tick-borne encephalitis (TBE) in Switzerland: does the prolongation of vaccine booster intervals result in an increased risk of breakthroughs?

Running title: TBE-vaccine breakthroughs in Switzerland (40 letters and spaces)

Axel J. Schmidt, M.D. MPH[1,2], Ekkehardt Altpeter, M.D. MPH MSc[1], Simone Graf, RN MSc[1], Robert Steffen, M.D.[3,4]

[1] Communicable Diseases Division, Swiss Federal Office of Public Health, 3003 Bern, Switzerland

[2] Department of Public Health, Environments and Society, London School of Hygiene and Tropical Medicine, London, U.K.

[3] Department of Public and Global Health, Division of Infectious Diseases, World Health Organization Collaborating Centre for Traveller's Health, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich / Switzerland,

[4] Division of Epidemiology, Human Genetics and Environmental Sciences, University of Texas School of Public Health, Houston, TX, U.S.A.

Correspondence: Axel.Schmidt@bag.admin.ch

Dr. med. Axel J. Schmidt, MPH
Bundesamt für Gesundheit
Schwarzenburgstrasse 157
CH-3003 Bern
Switzerland

The paper has been presented in part at the XIV[th] International Symposium on Ticks and Tick-Borne Diseases, Weimar (virtual) 24-26 March 2021.

AJS: No conflicts of interest / financial disclosure.

KEY WORDS

Tick-Borne Diseases; Vaccine-Preventable Diseases; Immunization; Immunization Programs; Immunosenescence; Serology; Memory

ABBREVIATIONS

FOPH	Federal Office of Public Health
IgG	Immune globulin G
TBE	Tick-borne encephalitis
Y	Years

ABSTRACT

Background: In 2006, the Swiss Federal Office of Public Health decided recommending a prolongation of vaccine booster intervals after the 3rd dose for the prevention of tick-borne encephalitis (TBE) from 3 to 10 years.

Methods: To ascertain whether this amendment resulted in an increased rate of vaccine breakthroughs we conducted a retrospective analysis of surveillance data collected 2000–2019 by mandatory reporting to the Swiss Federal Office of Public Health (FOPH). Fractions of breakthroughs (with 95% confidence intervals) — 0 to 3 years vs. >3 to 10 years after the 3rd vaccination dose — were compared across time periods and age groups.

Results: Among 3,205 notified TBE cases, known vaccination status was reported in 2,562 (79.9%), including 103 patients with ≥3 vaccine doses (4.0%). Among those, there were 39 patients who had received the last dose within 3 years and 48 patients in the >3 to 10 years group. Accordingly, the annual breakthrough rate was 7.7 cases during the first three years after the last dose, and 5.4 cases in following seven years. We observed no significant trend of TBE breakthroughs with increasing age. Increasing numbers of TBE and of vaccine breakthroughs over time have been associated with spreading endemicity and higher vaccination coverage in Switzerland.

Conclusions: there is no indication that extended booster intervals resulted in an increased rate of breakthroughs, but there was a marked public health benefit with respect to increased acceptability of TBE immunization in the general population.

240 words, MAX 300

Introduction

Despite increasing endemicity of tick-borne encephalitis (TBE), vaccination coverage in Switzerland is relatively low, particularly when compared with neighbouring Austria where TBE immunization is recommended already for infants.[1] According to a survey conducted 2005–07, only 8% of the 16-year-olds residing in Swiss cantons with endemicity were immunized with at least 3 doses of TBE vaccine.[2, 3] Even among individuals reporting tick bites to the Swiss Sentinella system 2008–19, vaccination coverage (without information on the number of doses) was only 16–18% (unpublished data, FOPH). Reluctance to accept TBE immunization was associated with the need of frequent boosters [4], all of which are not re-imbursed by the Swiss health care system. Serological evaluations conducted in the Swiss canton of Schaffhausen showed that TBE IgG persisted for many years in a majority of the vaccinated subjects [5, 6], and the authors concluded on long-lasting immunity.[4] In 2006 FOPH recommended extending TBE vaccine booster intervals from 3 to 10 years, which is also more cost-effective.[8] Finland is the only country which introduced a similar expansion of the booster interval in 2014.[9]

In addition to the prolonged booster interval, FOPH recommended TBE immunization to all adults and children (above the age of 6 years) who temporarily or permanently live in an endemic region. Primary vaccination always consisted of three doses at 0, 1–3, and 9–12 (Encepur®) or 5–12 (FSME-Immun®) months. Subsequent to rapid immunization with Encepur® on days 0, 7, 21 a fourth dose at 12–18 months became necessary. While the minimal intervals are essential, there is no evidence for the necessity to completely re-start of basic immunization if the recommended interval has been missed.[10] Since that the 2006 amendment the recommendations were modified twice: In 2016, experts and the FOPH encouraged the population and the medical

community to start immunizations already in winter in order to provide protection from TBE in the next tick season, but primary series could still be started anytime. In 2019, vaccination recommendations were geographically extended to the entire country except the cantons of Geneva and Ticino. The second vaccine dose now more precisely was recommended to be scheduled after 1 month, but otherwise the recommendations remained unchanged.[11]

As a result of the 2006 recommendations the annual TBE vaccine sales increased from <140'000 in and before 2005 to more than 600,000 in the 2006–08 period.[7] By 2018, based on a large national survey linked with medical vaccination records, coverage of TBE vaccination had increased to 42% overall and ranged from 14% in the Ticino region (no vaccination recommendation) to 60% for ≥1 dose.[12] However, no regular assessment of TBE vaccination coverage has been performed which would allow determining rates of vaccine breakthroughs with reliable denominator data.

As a result of the lockdown in spring 2020 Switzerland has experienced a decrease in all notifiable diseases with a single exception: TBE increased by 87.5% as compared to the mean of the same periods 2016–2019[13], or by 70% when taking into account trend and seasonality.[14] Overall, 2020 became an all-time TBE record year with 457 cases.[14] In view of persisting 'pandemic travel patterns' with limited border crossings, but with more in-country excursions, vacations, camping, *etc*. there is continued concern about neglecting TBE prevention while everybody focuses on COVID-19 vaccination.

The objective of this public health report is to evaluate the available data on the impact of the described change in strategy, based entirely on notification data to ascertain whether it has been associated with an increased rate of vaccine breakthroughs or not, with special attention to older age groups.

Methods and definitions

This is a retrospective analysis of surveillance data based upon mandatory reporting of TBE in Switzerland, which was introduced in 1984. As previously described in detail, initial laboratory reports are linked to subsequent clinical information, including immunization status.[2, 15] This means that all information presented here is based on information provided by clinicians who completed notification forms upon receipt of laboratory report confirming a case of TBE. Essentially this reporting system remained unchanged during the study period. The accuracy of the information provided, *e.g.* the number, date, or brand of vaccinations cannot be verified by the FOPH.

As the case definition was different prior to 1999, we included only cases from 2000 onwards. The Swiss case definition of TBE differs from the one recommended by the European Centre of Disease Prevention and Control (ECDC) by not only including probable and confirmed cases, but also possible cases.[16] Both case definitions exclude patients who do not meet the clinical criteria.

In this study, we define vaccine breakthrough as TBE notification meeting the Swiss case criteria in patients with a history of three or more TBE vaccine doses overall. Neither for vaccine breakthrough nor failure there is a consistent definition.[17, 18]

Results

Overall, there was a trend to an increasing TBE incidence over time (Figure 1) mainly due to unvaccinated patients. This most likely is associated with the expansion of the endemic areas during the study period. Table 1 contains the TBE cases notified to the Swiss FOPH in the 5-year period prior to the revised recommendations (2000–04), a

transition period (2005–09) and two 5-year periods during which the prolonged booster intervals were broadly implemented (2010–19).

Data completeness regarding vaccination status showed no clear trend and varied between 75.2% (95% confidence interval: 71.5–78.6) for the period 2005–09 and 85.3% (82.1–88.0) for the period 2010–14 (Table 1). Among the 193 TBE patients who had ever received at least one TBE vaccine dose, 103 (53.4%) reported a complete basic immunization with three or more doses, and 15 (14.6% of those assumed completely immunized) more than three doses. In 100 of 133 individuals who obtained at least one TBE vaccine dose 2000–2019, the brand of the last dose was FSME-Immun® in 72%, and Encepur® in 28%, broadly reflecting the respective market shares in Switzerland; for the remaining 33 individuals the brand was not reported.

The 103 TBE patients with reportedly three or more vaccine doses met our definition of vaccine breakthrough. As shown in Table 1, the proportion of breakthroughs over the 5-year periods showed no clear trend—it varied between 1.3% in 2000–04, 4.7% in 2005–09, 7.4% in 2010–14, and finally 2.0% in 2015–19. While the proportion for the period 2005–09 was significantly higher than for the other three 5-year periods, the other three 95% confidence intervals overlapped.

Regarding the timing of the last dose among fully vaccinated cases, during the 2010–19 period in which the 10-year booster strategy was implemented, 23 persons developed TBE within the initial three years after the last dose and 38 in the following seven years. Accordingly, the annual breakthrough rate was 7.7 cases per year (23 cases divided by 3 years; 95% C.I.: 5.0–11.7) during the first three years after the last dose, and 5.4 cases per year in the following seven years (33 cases divided by 7 years; 95% C.I.: 3.9–7.5). In the entire 2000–19 period there was no gradual increase in vaccine breakthroughs (data not shown).

Swiss notification data 2010–19 yielded no evidence for the older population to be at an increased risk if not boostered after 3 years: among those aged <60 years, the breakthrough rate during the initial three years after having obtained the last vaccine dose was 3.7 (1.9–6.7) per year *vs*. 3.7 (2.5–5.5) per year during the subsequent seven years; and among those aged 60 years or older, the respective breakthrough rates were 4.0 (2.2–7.1) per year *vs*. 1.7 (1.2–2.5) per year. Similarly, and these data are shown at the bottom of the table, the annual breakthrough rate among those aged ≥50 years was 6.0 (3.7–9.6) in the first three years *vs.* 2.9 (1.8–4.5) in the subsequent 7 years.

Discussion

Swiss notification data shows that over the past 20 years, 4.0% of tick-borne encephalitis occurred despite a history of full vaccination coverage, independent of age, gender, and without a significant trend over time. The increasing total number of TBE cases over time is associated with increased transmission and a gradual extension of endemicity in Switzerland; the same has been observed in neighbouring countries, such as *e.g.* Germany [19] and Italy.[11, 20] Also the proportion of breakthroughs will increase parallel to vaccination coverage; in a hypothetical population in which all are immunized 100% of the cases will be breakthroughs. The incidence of breakthroughs may be slightly higher as compared to other countries since 'possible' cases were included. Similarly to an earlier Swiss assessment, the male to female ratio was approximately 2:1 [15], while overall European data showed a ratio of 3:2.[21] In the total TBE population, 27.6% were 60 years or older like the respective proportion presented by the ECDC.

Compliance with the completion of the primary TBE immunization series appears to be

unsatisfying, as almost half of TBE patients who reported any TBE vaccination did not receive at least three doses. Those in the latter group were insufficiently protected. This is implicitly demonstrated by the fact that according to a recent assessment on TBE vaccination coverage in Switzerland 41.7% had received at least 1 dose, 32.9% at least 3 doses — leaving a substantial proportion with incomplete primary series.[12] The same problem with suboptimal rates of completed vaccination has been noted elsewhere.[22, 23]

Similarly to the data presented here, an earlier Swiss report on the 2005–11 period rated 33 of 1,055 TBE cases (3.1%) as possible vaccine failures, the patients having received the last TBE vaccine dose within the past five years before disease onset.[15] Overall, 38 (4.6%) had received a complete primary series with at least three doses and 65 (7.9%) had a history of at least one dose.[15] The variation in breakthrough rates across the four 5-year-periods in the current assessment showed no clear trend over time.

If there was a massive problem with the Swiss decision to prolong the booster interval from three to ten years, the annual number of breakthroughs would be low during the first three years after the last dose, and then rise during the subsequent seven years. As shown, annual incidence of breakthroughs were marginally higher (no significant difference) in the first three years after vaccination as compared to the subsequent seven years. Thus, our data provide no evidence that the rate of breakthroughs increases with time as would be expected because of continuously decreasing antibodies. Previous publications and, most recently, a carefully compiled systemic review mainly focused on immunogenicity and protective antibody levels, but the importance of effectiveness was also highlighted.[24]. The data presented here suggest that protection may not only depend of sero-persistence of antibodies, but that immune

memory and ‘boostability’ by natural infection must be additional decisive factors resulting in field effectiveness persisting over a prolonged period.[7]

On the other hand, we observed only 15 cases of TBE among those who had received more than three doses of TBE vaccine (14.6%). We can compare this proportion to 9.5% (95% C.I.: 8.5–10.6) of individuals in the Swiss population who received 4 or more doses.[12] While the methods of assessment differ and the numbers are small, this might indicate that a fourth dose of TBE vaccine is relevant as a booster, as it has been recently suggested in relation to both brands of TBE vaccines used in Western countries.[17, 25, 26] In contrast, in an ECDC assessment, there were 24 TBE vaccine failure patients who had received four vaccine doses as compared to 36 with three shots; the difference is less impressive. This larger survey did not contain details on vaccination status, gender and age.[27]

Although the immune response in younger subjects is better, our results do not suggest that older people are at increased risk of vaccine breakthroughs. Some studies have come to the same conclusion [18, 28, 29], while mainly Swedish groups have claimed that this risk was increasing with age.[17, 30]

There are several limitations inherent to our data. Most importantly, the basis for this analysis is notification data only without information on the underlying number of vaccinated individuals, precluding the calculation of actual vaccine failure rates. There is a lack of denominator data on the proportion of the vaccinated population preventing to estimate vaccine effectiveness, particularly we ignore whether the number of subjects immunized 1, 2 or 3 years prior to the breakthrough significantly differed from the number of those who got their last vaccine dose 4, 5, …,10 years ago. Although residents can still request a TBE booster dose every 3 or 5 years, anecdotal evidence from travel and vaccination clinics suggests that hardly anybody in Switzerland gets a

TBE booster earlier than 9 or 10 years, rather there is concern that some miss the recommended booster date at 10 years. Thus, we assume that the denominators for the individual years do not greatly vary. The number of TBE virus exposure remains elusive, and even the data on the number of tick bites would not be a valid surrogate. Further, although all notified cases were included, and laboratories capable of determining TBE serological assessments are reliable in submitting their reports, we cannot exclude that some cases have been missed for lack of serological assessment. In contrast to an earlier survey, we did not differentiate between confirmed, probable, and possible cases[15], so some of the cases of encephalitis assumed to be caused by the TBE virus might result from a different aetiology.

The Swiss FOPH will continue to monitor TBE breakthroughs. Further studies are needed to determine for how many years after the last TBE vaccine dose the risk of vaccine breakthroughs does not increase. Additional data on the need and ideal timing of a fourth and possibly further vaccine doses are also needed. Overall, we must refine our immunological knowledge relating to the interplay between humoral and cellular immune response *e.g.* with a prospective long-term study.

Conclusions

Back in 2006 when the booster intervals for TBE vaccination were officially extended to 10 years, several experts considered that this was going to be an interesting, potentially risky, 'public health experiment'. Our data shows no evidence that the new strategy has resulted in an increased rate of vaccine breakthroughs in any age group. As shown elsewhere[7] it has resulted in a marked increase in the number of people accepting TBE vaccination—a substantial benefit for public health. Thus, there is no reason to change this 10-year TBE booster strategy in Switzerland. However, in these

times of mainly intercontinental travel restrictions and potentially increased exposure to TBE risk associated with intra-national or regional travel, documentation of COVID-19 vaccination often offers an opportunity to review the vaccination certificates and to remind the individuals whenever boosters (or primary vaccination) against TBE, diphtheria/tetanus/pertussis, *etc.*, are indicated. As soon as post-COVID-19 global travel will resume, visitors to endemic areas of Switzerland and elsewhere should be recommended TBE vaccination. TBE is not just a problem for the local population, but occurs in travellers.[31] According to the latest ECDC report, 1.8% of TBE cases were associated with international travel.[32]

2520 words, MAX 3000

References

1 Federal Ministry of Social Affairs (Austria). [Vaccination plan Austria]. Vienna: Österreichisches Bundesministerium Soziales, Gesundheit, Pflege und Konsumentenschutz 2021. https://www.sozialministerium.at/Themen/Gesundheit/Impfen/Impfplan-Österreich.html

2 E Altpeter, H Zimmermann, J Oberreich, et al. Tick related diseases in Switzerland, 2008 to 2011. Swiss Med Wkly 2013; 143:w13725.

3 P Lang, H Zimmermann, U Piller, et al. The Swiss National Vaccination Coverage Survey, 2005-2007. Public Health Rep 2011; 126 Suppl 2:97-108.

4 A Kind, P Ritzmann, F Marty, H Zimmermann. Der Impfschutz gegen die Zeckenenzephalitis hält viel länger als bisher angenommen. Tick-borne encephalitis (TBE) — Antibody titers and long-term immunity. Z Allg Med 2008; 84( ):153-156.

5 A Kind. Wie viele Auffrischimpfungen sind notwendig gegen die Zeckenenzephalitis FSME. Schweizerische Ärztezeitung 2004; 85:844-848.

6 A Kind. Erfahrungen mit Titermessungen zur Impfschutzkontrolle bei der Zeckenenzephalitis FSME. Primary Care 2005; 5:231-235.

7 R Steffen, W Erber, HJ Schmitt. Can the booster interval for the tick-borne encephalitis (TBE) vaccine 'FSME-IMMUN' be prolonged? — A systematic review. Vaccine 2021; 12(5):101779.

8 Federal Office of Public Health FOPH. [Recommendations for TBE vaccination]. Bulletin 2006; 13:225-231 [Article in French & German].

9 Finnish Institute for health and welfare. Infectious Diseases and vaccinations: TBE, or 'tick vaccine'. Helsinki: Terveyden ja hyvinvoinnin laitos, 2014. https://thl.fi/fi/web/infektiotaudit-ja-rokotukset/rokotteet-a-o/tbe-rokote-eli-punkkirokote#annostus

10 R Schosser, A Reichert, U Mansmann, et al. Irregular tick-borne encephalitis vaccination schedules: the effect of a single catch-up vaccination with FSME-IMMUN. A prospective non-interventional study. Vaccine 2014; 32(20):2375-81.

11 Federal Office of Public Health FOPH. [TBE — expansion of regions at risk]. Bulletin 2019; 6:12-14 [Article in French & German].

12 V Baroutsou, KD Zens, P Sinniger, et al. Analysis of Tick-borne Encephalitis vaccination coverage and compliance in adults in Switzerland, 2018. Vaccine 2020; 38(49):7825-7833.

13 R Steffen, S Lautenschlager, L Fehr. Travel restrictions and lockdown during the COVID-19 pandemic-impact on notified infectious diseases in Switzerland. J Travel Med 2020; 27(8):taaa180.

14 Federal Office of Public Health FOPH. [Impact of COVID on notifiable diseaes]. Bulletin 2021; 30:[Article in French and German].

15 M Schuler, H Zimmermann, E Altpeter, U Heininger. Epidemiology of tick-borne encephalitis in Switzerland, 2005 to 2011. Euro Surveill 2014; 19(13):20756.

16 H Zimmermann, D Koch. [Epidemiology of tick-borne encephalitis (TBE) in Switzerland 1984 to 2004]. Ther Umsch 2005; 62(11):719-25.

17 KE Hansson, A Rosdahl, M Insulander, et al. Tick-borne Encephalitis Vaccine Failures: A 10-year Retrospective Study Supporting the Rationale for Adding an Extra Priming Dose in Individuals Starting at Age 50 Years. Clin Infect Dis 2020; 70(2):245-251.

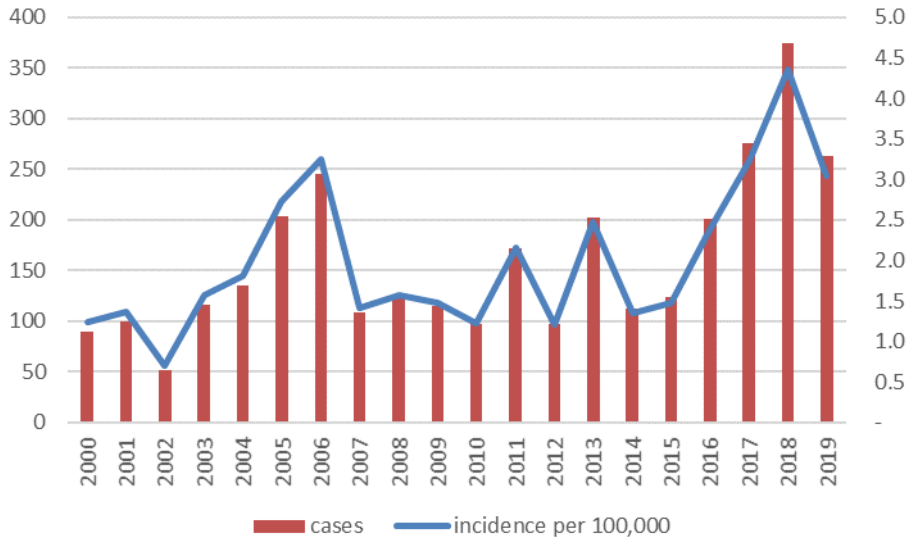
18 G Dobler, K Kaier, P Hehn, et al. Tick-borne encephalitis virus vaccination breakthrough infections in Germany: a retrospective analysis from 2001 to 2018. Clin Microbiol Infect 2020; 26(8):1090e7-1090e13.

19 W Hellenbrand, T Kreusch, MM Bohmer, et al. Epidemiology of Tick-Borne Encephalitis (TBE) in Germany, 2001–2018. Pathogens 2019; 8(2):42.

20 N Alfano, V Tagliapietra, F Rosso, et al. Tick-borne encephalitis foci in northeast Italy revealed by combined virus detection in ticks, serosurvey on goats and human cases. Emerg Microbes Infect 2020; 9(1):474-484.

21 European Centre for Disease Prevention and Control. Tick-borne encephalitis. In: ECDC. Annual epidemiological report for 2018. Stockholm: ECDC, 2019.
22 L Jacob, K Kostev. Compliance with vaccination against tick-borne encephalitis virus in Germany. Clin Microbiol Infect 2017; 23(7):460-463.
23 W Erber, HJ Schmitt. Self-reported tick-borne encephalitis (TBE) vaccination coverage in Europe: Results from a cross-sectional study. Ticks Tick Borne Dis 2018; 9(4):768-777.
24 JE Rampa, HH Askling, P Lang, et al. Immunogenicity and safety of the tick-borne encephalitis vaccination (2009-2019): A systematic review. Travel Med Infect Dis 2020; 37:101876.
25 J Beran, M Lattanzi, F Xie, et al. Second five-year follow-up after a booster vaccination against tick-borne encephalitis following different primary vaccination schedules demonstrates at least 10years antibody persistence. Vaccine 2019; 37(32):4623-4629.
26 R Konior, J Brzostek, EM Poellabauer, et al. Seropersistence of TBE virus antibodies 10 years after first booster vaccination and response to a second booster vaccination with FSME-IMMUN 0.5mL in adults. Vaccine 2017; 35(28):3607-3613.
27 J Beaute, G Spiteri, E Warns-Petit, H Zeller. Tick-borne encephalitis in Europe, 2012 to 2016. Euro Surveill 2018; 23(45):1800201.
28 B Kohlmaier, NA Schweintzger, MG Sagmeister, et al. Clinical Characteristics of Patients with Tick-Borne Encephalitis (TBE): A European Multicentre Study from 2010 to 2017. Microorganisms 2021; 9(7):1420.
29 HJ Schmitt, G Dobler, D Zavadska, et al. TBE Vaccination Breakthrough Cases-Does Age Matter? Vaccines (Basel) 2021; 9(8):932.
30 CR Andersson, S Vene, M Insulander, et al. Vaccine failures after active immunisation against tick-borne encephalitis. Vaccine 2010; 28(16):2827-2831.
31 R Steffen. Epidemiology of tick-borne encephalitis (TBE) in international travellers to Western/Central Europe and conclusions on vaccination recommendations. J Travel Med 2016; 23(4):taw018.
32 European Centre for Disease Prevention and Control. Tick-borne encephalitis. In: ECDC. Annual epidemiological report for 2019. Stockholm: ECDC, 2021.

353 Figure 1: TBE notifications in Switzerland, 2000–2019



354

Table 1: Swiss TBE notification data (vaccination status, vaccine doses and time since last dose) across time period (2000–2019), gender, and age group

	TBE cases	Known vaccination status		Vaccinated ≥1 dose		Vaccinated ≥3 doses		Last dose ≤3 y*		Last dose >3–10 y*		Last dose >10 y*		Last dose unknown*	
Period	**N**	**n**	**% (95%-CI)**	**n**	**% (95%-CI)**	**n**	**% (95%-CI)**	**n**	**% (95%-CI)**	**n**	**% (95%-CI)**	**n**	**% (95%-CI)**	**n**	**% (95%-CI)**
2000–04	493	395	80.1 (75.8–83.9)	15	3.8 (2.2–6.3)	5	1.3 (0.5–3.1)	1	0.3 (0.0–1.6)	4	1.0 (0.3–2.8)	0	0.0 (0-0–1.2)	0	0.0 (0.0–1.2)
2005–09	794	597	75.2 (71.5–78.6)	45	7.5 (5.6–10.0)	22	3.7 (2.4–5.6)	15	2.5 (1.5–4.2)	6	1.0 (0.4–2.3)	1	0.2 (0.0–1.1)	0	0.0 (0.0–0.8)
2010–14	680	580	85.3 (82.1–88.0)	64	11.0 (8.7–13.9)	43	7.4 (5.5–9.9)	18	3.1 (1.9–5.0)	23	4.0 (2.6–6.0)	1	0.2 (0.0–1.1)	1	0.2 (0.0–1.1)
2015–19	1238	990	80.0 (77.3–82.5)	69	7.0 (5.5–8.8)	33	3.3 (2.3–4.7)	5	0.5 (0.2–1.2)	15	1.5 (0.9–2.5)	6	0.6 (0.2–1.4)	7	0.7 (0.3–1.5)
Gender															
Male	2063	1653	80.1 (78.1–82.0)	133	8.0 (6.8–9.5)	76	4.6 (3.7–5.8)	33	2.0 (1.4–2.8)	32	1.9 (1.1–2.9)	6	0.4 (0.1–0.8)	5	0.3 (0.1–0.7)
Female	1127	901	79.9 (77.1–82.5)	59	6.5 (5.1–8.4)	27	3.0 (2.0–4.4)	6	0.7 (0.3–1.5)	16	1.8 (1.2–2.7)	2	0.2 (0.0–0.9)	3	0.3 (0.1–1.1)
Missing gender	15	8		1		0		0		0		0		0	
Age group															
<20 years	503	424	84.3 (80.4–87.6)	38	9.0 (6.5–12.2)	17	4.0 (2.4–6.5)	7	1.7 (0.7–3.5)	9	2.1 (1.0–4.1)	0	0.0 (0.0–1.1)	1	0.2 (0.0–1.5)
20-39 years	672	523	77.8 (74.0–81.3)	37	7.1 (5.1–9.7)	14	2.7 (1.5–4.6)	2	0.4 (0.1–1.5)	10	1.9 (1.0–3.6)	2	0.4 (0.1–1.5)	0	0.0 (0.0–0.9)
40-59 years	1147	933	81.3 (78.7–83.8)	63	6.8 (5.3–8.6)	35	3.8 (2.7–5.2)	14	1.5 (0.9–2.6)	16	1.7 (1.0–2.8)	2	0.2 (0.0–0.9)	3	0.3 (0.1–1.0)
60+ years	883	682	77.2 (73.9–80.3)	55	8.1 (6.2–10.4)	37	5.4 (3.9–7.5)	16	2.3 (1.4–3.9)	13	1.9 (1.1–3.3)	4	0.6 (0.2–1.6)	4	0.6 (0.2–1.6)
Total	**3205**	**2562**	**79.9 (78.3–81.5)**	**193**	**7.5 (6.6–8.6)**	**103**	**4.0 (3.3–4.9)**	**39**	**1.5 (1.1–2.1)**	**48**	**1.9 (1.4–2.5)**	**8**	**0.3 (0.1–0.6)**	**8**	**0.3 (0.1–0.6)**
Age group for the period 2010–19															
<50 years	968	801	82.7 (79.9–85.3)	67	8.4 (6.6–10.6)	28	3.5 (2.4–5.1)	5	0.6 (0.2–1.5)	18	2.2 (1.4–3.6)	3	0.4 (0.1–1.2)	2	0.2 (0.0–1.0)
50+ years	950	769	80.9 (78.0–83.6)	66	8.6 (6.7–10.8)	48	6.2 (4.7–8.3)	18	2.3 (1.4–3.7)	20	2.6 (1.6–4.1)	4	0.5 (0.2–1.4)	6	0.8 (0.3–1.8)

*among cases with ≥3 doses