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A Retrospective, Matched Case-Control Analysis of Tick-Borne Encephalitis Vaccine Effectiveness by Booster Interval, Switzerland 2006-2020

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ABSTRACT

Objective: To estimate effectiveness of Tick-Borne Encephalitis (TBE) vaccination by time interval (<5, 5-10, and 10+ years) post-vaccination.

Design: A retrospective, matched case-control study.

Participants: Cases – all adult (age 18–79) TBE cases in Switzerland reported via the national mandatory disease reporting surveillance system from 2006–2020 (final n=1,868). Controls – community controls from a database of randomly selected adults (age 18–79) participating in a 2018 cross-sectional study of TBE vaccination in Switzerland (final n=4,625).

Primary outcome measures: For cases and controls, the number of TBE vaccine doses received and the time since last vaccination were determined. Individuals were classified as being "unvaccinated" (0 doses), "incomplete" (1–2 doses) or "complete" (3+ doses). Individuals with "complete" vaccination were further classified by time since the last dose was received (<5 years, 5–10 years, or 10+ years). A conditional logistic regression model was used to calculate Vaccine Effectiveness (VE: 100 x [1- odds ratio]) for each vaccination status category.

Results: VE for incomplete vaccination was 76.8% (95% CI 69.0–82.6). For complete vaccination, overall VE was 95.0% (93.5–96.1. When the most recent dose was received <5 years prior VE was 91.6% (88.4–94.0), 95.2% (92.4–97.0) when the most recent dose was received 5–10 years prior, and 98.5% (96.8–99.2) when the most recent dose was received 10+ years prior.

Conclusions: That VE does not decrease among completely vaccinated individuals over 10+ years since last vaccination supports the longevity of the protective response following complete TBE vaccination. Our findings support the effectiveness of 10-year TBE booster intervals currently used in Switzerland.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Switzerland has a complete national mandatory disease reporting surveillance system, and case data should be representative.
- The case-control design allows direct comparison of vaccination status among cases and individuals matched by sex, age, and area of residence.
- Despite a large number of cases (n=1,868), only a small number were vaccinated (n=151), preventing a more detailed analysis of factors which could affect VE within groups.
- Data on other factors which might impact the response to vaccination (chronic medical conditions, immunosuppression, age of first vaccination, whether individuals were vaccinated according to the recommended vaccination schedule) were not available.
- As cases and controls were matched by age, VE values between age groups cannot be directly compared.

BACKGROUND

Tick-Borne Encephalitis (TBE) is a serious viral infection of the central nervous system which can result in permanent neurological injury and death. TBE is caused by the Tick-Borne Encephalitis Virus (TBEV), which is transmitted by ticks of the *Ixodidae* family. Currently, TBEV is endemic throughout much of Europe [1, 2]. In Switzerland, mandatory reporting of TBE cases was initiated in 1988. Since then, both the incidence and geographic range of disease have continued to increase. In 2020, the country experienced its most severe disease season with an overall incidence of 5.16 cases/100,000 individuals, exceeding the World Health Organization's (WHO) definition of a "highly endemic" area [1, 2].

Vaccination is highly protective against TBE; producing virus-neutralizing antibodies which are associated with disease prevention, but are not universally considered the "correlate of protection". Two vaccines are currently licensed by the European Medicines Agency (EMA): Encepur® and FSME-Immun®. Both are recommended for individuals living, working or traveling within endemic areas [2]. Both are administered as a primary series of three doses given at day 0, 1-3 months, and 5-12 months with booster doses every 36-60 months (3-5 years) thereafter, depending on age and vaccine formulation [3, 4]. In 2006 the Swiss Federal Office of Public Health (FOPH) amended its official recommendation for TBE vaccination, extending the EMA-approved booster interval to 120 months (10 years) [5, 6].

Previous studies have demonstrated sustained levels of virus-specific and neutralizing antibodies up to and exceeding 10 years after TBE vaccination [7-9]. Whether this translates to sustained effectiveness, however, is not clear. Additionally, irregular TBE vaccination has been associated with reduced vaccine effectiveness (VE) [10, 11], indicating that deviations from the established vaccination schedule can influence lasting immunity. Whether the prolonged TBE booster intervals in Switzerland impact vaccine effectiveness is of great public health interest as reducing unnecessary vaccinations can improve cost-effectiveness and vaccine compliance. Here, we conducted a retrospective case-control study to evaluate TBE VE in Switzerland at <5, 5-10, and 10+ years post-vaccination.

METHODS

Study Design: We used a retrospective, matched case-control study design, comparing all TBE cases among adults 18-79 in Switzerland reported via the national mandatory disease reporting surveillance system in the 15-year period between 2006 and 2020, to community controls selected from a 2018 nationwide study of TBE vaccination coverage [12, 13].

Selection of Cases: TBE is a mandatory notifiable disease in Switzerland, with all confirmed TBE cases (based on serology and clinical picture [14]) reported via the national disease surveillance system [14, 15]. Age, sex, canton of residence and information on vaccination status, including number of doses received and date of last vaccination, are reported to the Swiss FOPH by the submitting physician. From the Swiss FOPH we obtained data for all TBE cases among residents of Switzerland aged 18-79 reported from 2006-2020. Among the 2,450 eligible cases, 6 were excluded as sex was unknown, 550 were excluded as vaccination status

was unknown, and another 26 were excluded due to missing information on the number of vaccine doses received (final n=1,868, Figure 1).

Selection of Controls: Community controls were selected from among a database of individuals participating in a 2018 cross-sectional study of TBE vaccination in Switzerland [12, 13]. In brief, adults with a Swiss mailing address in each of three age groups (18-39, 40-59, 60-79) were selected from each of the seven Swiss geographical regions (European NUTS-2 level) by disproportional stratified random sampling. Selected individuals (n=26,880; 1,280 from each age group and region) were requested by mail to submit a copy of their vaccination record. A total of 4,626 individuals submitted vaccination records. From these, date(s) of TBE immunization were recorded into a database. All participants in this database were eligible for inclusion into this study. One case was excluded due to missing information on vaccine dose number (final n=4,625, Figure 1).

Matching: Cases and controls were matched on sex, age (within 5-year intervals) and canton of residence (half-cantons - Basel City and Basel Land, Appenzell Ausserrhoden and Appenzell Innerrhoden, Nidwalden and Obwalden - were combined). All possible matches for each case were considered. Matching was performed using nearest neighbor matching with the *matchit* function in R v 4.0.3 [16], R Foundation for Statistical Computing, Vienna, Austria).

Analysis: For cases and controls, the total number of TBE vaccine doses received and the time since the most recent vaccination were determined. Individuals were classified as being "unvaccinated" (0 doses), "incomplete" (1-2 doses) or "complete" (3+ doses). Among those with "complete" vaccination, individuals were further classified by the time since the last dose was received (<5 years, 5-10 years, or 10+ years). Based on these criteria, a conditional logistic regression model was used to calculate Vaccine Effectiveness (VE: 100 x [1- odds ratio]) for each of the defined vaccination status categories. Statistical analyses were performed using Stata v.17.0 (StataCorp, LLC, College Station, TX, USA) and GraphPad Prism v.8.0 (GraphPad Software, Inc., San Diego, CA, USA); p values <0.05 were considered statistically significant.

Ethics Statement: Mandatory reporting data for TBE cases were provided to us by the Swiss FOPH, which maintains the national disease surveillance system. Data were provided to us in an anonymized form and were treated confidentially throughout the analysis, therefore, ethical approval was not necessary. For the cross-sectional TBE vaccination coverage database used to select controls, potential participants were sent a letter explaining the study's purpose and stating that, by submitting vaccination records, they were voluntarily consenting to participation [12, 13]. All data were anonymized and treated confidentially throughout the analysis. The procedure and method of consent for the cross-sectional study were approved by the Department of Data Protection of the University of Zurich and the Ethics Committee of the Canton of Zurich (approval number 2017-02-027).

Patient and Public Involvement: There was no patient and/or public involvement in the design, conduct, or dissemination plans of this research study.

RESULTS

In total, 1,828 cases and 3,667 controls were matched for our study (Figure 1, Table 1). Among cases, 8.3% (n=151) had received at least 1 TBE vaccine dose, compared to 45.2% (n=1,656) of controls (p<0.0001 Chi-squared test). Of vaccinated cases, 49.7% were "incomplete" (1-2 doses) and 50.3% were "complete" (3+ doses). Of vaccinated controls, 16.8% were "incomplete" and 83.2 were "complete" (p<0.0001 Chi-squared test).

VE for incomplete vaccination was 76.8% (95% CI 69.0-82.6, Table 1). For complete vaccination, overall VE was 95.0% (93.5-96.1, Table 1). When the most recent dose was received <5 years prior VE was 91.6% (88.4-94.0), 95.2% (92.4-97.0) when the most recent dose was received 5-10 years prior, and 98.5% (96.8-99.2) when the most recent dose was received 10+ years prior (Table 1). Compared to <5 years prior, VE 10+ years prior was significantly higher (p<0.0001 conditional logistic regression). These values were also comparable between those aged 18-39, 40-59, and 60-79 (Figure 2).

Among incompletely vaccinated TBE cases, the median time since last vaccination was 1.3 years (15.5 months), compared to 6.7 years (79.8 months) for incompletely vaccinated controls (p<0.0001 Mantel-Cox Log-rank test) (Figure 3a). 37.5% of incompletely vaccinated cases occurred within 2 months of last vaccination. For completely vaccinated TBE cases, median time since last vaccination was 3.8 years (46.0 months) compared to 7.8 years (93.3 months) for controls (p<0.0001 Mantel-Cox Log-rank test, Figure 3b). Comparing timing of last vaccination to the recommended booster vaccination scheme, 63.2% of cases had been last vaccinated within the preceding 5 years, 26.3% within the preceding 5-10 years and 10.5% had been last vaccinated more than 10 years prior. For controls, 38.0%, 28.8% and 33.3% of individuals had received a last vaccination <5, 5-10, or 10+ years prior, respectively (p<0.0001 Chi-squared test).

Table 1. Demographic Breakdown of Cases and Controls and Vaccine Effectiveness by Vaccination Status

	Controls (n = 3,667)	Cases (n = 1,828)	% Vaccine Effectiveness (1-OR)*100	95% CI Lower	95% CI Upper	p Value
Male	1,925 (52.5%)	1,159 (63.4%)	-	-	-	-
Female	1,742 (47.5%)	669 (36.6%)	-	-	-	-
18-39	1,060 (28.9%)	463 (25.3%)	-	-	-	-
40-59	1,257 (34.3%)	800 (43.8%)	-	-	-	-
60-79	1,350 (36.8%)	565 (30.9%)	-	-	-	-
Unvaccinated	2,011 (54.8%)	1,677 (91.7%)	Ref.	-	-	-

1-2 Doses (Incomplete)	279 (7.6%)	75 (4.1%)	76.8	69.0	82.6	<0.001
3+ Doses (Complete) <5 years	522 (14.2%)	48 (2.6%)	91.6	88.4	94.0	<0.001
3+ Doses Complete 5-10 years	397 (10.8%)	20 (1.1%)	95.2	92.4	97.0	<0.001
3+ Doses Complete >10 years	458 (12.5%)	8 (0.4%)	98.5	96.8	99.2	<0.001
3+ Doses (Complete) Any time	1,377 (37.6%)	76 (4.2%)	95.0	93.5	96.1	<0.001

DISCUSSION

Here we used a retrospective, matched case-control study design to investigate TBE VE in Switzerland considering both incomplete and complete vaccination, and, among completely vaccinated individuals, different time intervals since last vaccination. Of the 8.3% of cases that had received at least one vaccine dose, 50.3% were completely vaccinated (3+ doses). Based on this definition, we estimate a failure rate of 4.2%, which is in line with TBE vaccine failure rates estimated in other studies [10, 17-20], including two previous studies also using Swiss mandatory reporting data from the national database which we draw from here [21, 22].

Importantly, nearly half of vaccinated cases were among recipients of only 1-2 doses. Here, we calculated VE for incomplete vaccination at 76.8%, which was substantially and significantly less than that for complete vaccination (95.0%). Furthermore, we found that nearly 40% of the cases among incompletely vaccinated individuals occurred within 2 months of their last dose, suggesting they were exposed before they had developed a protective immune response to vaccination. As TBE is a strongly seasonal disease (peaking from April to October), and because primary vaccination for TBE according to the "conventional" schedule takes a minimum of 5-9 months, vaccination should ideally begin in the fall or winter of the year prior to planned exposure. Alternatively, a rapid immunization scheme, such as that used for Encepur® (0, 7 and 21 days plus a fourth dose after 12-18 months), could possibly provide an option to limit a period of reduced protection. Previous studies have not found substantial differences in serological response to TBE vaccination based on use of the "rapid" or "conventional" schedules [8, 23, 24]. While our dataset did not include complete timing of TBE vaccination history, which could allow us to investigate VE by vaccination schedule, such an analysis could be informative.

Among completely vaccinated individuals, overall TBE VE was 95.0%. Interestingly, we did not observe a decrease in VE with increasing time since the last vaccine dose was received, consistent with the findings of a recent study evaluating TBE cases in vaccinated individuals using a different methodology [21]. If anything, VE was lower in the first 5 years following last vaccination compared to last vaccination 10+ years prior. We further observed the median time to vaccine failure among completely vaccinated cases was 3.8 years (46.0 months). While

not completely clear, this observation could potentially be explained by a fraction of individuals which remained insufficiently protected by vaccination. The median time to vaccine failure did not, however, differ between cases having received 3 doses or those having received 4+ doses (not shown), suggesting no impact of adding an additional dose. It should also be noted that we did not observe appreciable differences in overall VE or VE over time between age groups (in agreement with findings summarized in a recent systematic review of TBE vaccine booster intervals [25]).

An important limitation of our study is the relatively small number of vaccinated cases (n=151). Furthermore, we do not have data on other factors which might impact the response to vaccination such that we could control for them in our analysis. Whether individuals have a chronic medical condition or immunosuppression [26-29], the age at which the person was first vaccinated, [17, 20, 30, 31] or whether they were regularly vaccinated in their primary series [10, 11] and possibly whether they received a "conventional" or "rapid" schedule, could potentially have an impact on our assessment of VE. An additional limitation is that, while we found that TBE VE appeared similar between age groups, as we matched cases and controls by age we were unable to directly compare VE values. Several studies have demonstrated, though, reduced serological responses to TBE vaccination among older individuals, and, that vaccine failures may be increased among older individuals, though this is not completely clear [17, 20, 30, 31]. Whether TBE VE differs by age, however, remains an important question warranting further study.

Taken together, and despite our study limitations, these results do not indicate a consistent decrease in TBE VE over time among fully-vaccinated individuals, as might be predicted by antibody decay kinetics. These findings also highlight that antibody responses may not necessarily always be a suitable surrogate for VE estimates, which have been shown to decline with time in several publications [7, 9, 32, 33].

CONCLUSIONS

Despite that a substantial portion of the Swiss population has been vaccinated for TBE—42% coverage for 1 dose and 34% for 3 doses [12] —disease incidence continues to increase, indicating that current vaccination coverage is insufficient. To better address this, additional information related to vaccination uptake, schedule compliance, and effectiveness is needed. Our findings highlight the increased effectiveness of complete (3+ dose) versus incomplete (1-2 dose) TBE vaccination. That 40% of breakthroughs among incompletely vaccinated individuals occur within 1-2 months of vaccination suggests that individuals are being exposed before they have had time to develop a protective immune response to vaccination. That VE does not appreciably change or decrease among completely vaccinated individuals over 10+ years since last vaccination supports the longevity of the protective response following complete TBE vaccination; also among both younger and older age groups. In total, our findings support the effectiveness of 10-year TBE booster intervals currently used in Switzerland.

COMPETING INTERESTS STATEMENT

The authors declare no competing interests.

FUNDING STATEMENT

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DATA AVAILABILITY STATEMENT

To ensure participant privacy, the datasets analyzed for this study are not publicly available. They are, however, available upon request, without undue reservation, by contacting the study authors (phung.lang@uzh.ch).

AUTHOR CONTRIBUTIONS

KDZ and PL conceived the study. KDZ, SRH and PL designed the study, KDZ and PL acquired study funding. AJS and EA provided case data. KDZ and SRH organized the database and analyzed the data, KDZ wrote the first draft of the manuscript. KDZ, SRH, AJS, EA, JSF, and PL critically reviewed the manuscript and approved the submitted version.

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FIGURE LEGENDS

Figure 1. Study Flow Diagram.

Figure 2. Vaccine Effectiveness by Age. For each age group (18-39, 40-59, and 60-79), individuals were categorized as unvaccinated, incompletely vaccinated (1-2 doses), completely vaccinated (3+ doses) <5 years prior, 5-10 years prior, or 10+ years prior and VE was calculated using the formula (VE=100*1-Odds Ratio), with unvaccinated as the reference.

Figure 3. Time Since Last Vaccination Among Vaccinated Cases and Controls. (A) Among incompletely vaccinated cases (n=75) or controls (n=279), the percentage of individuals (with 95% Confidence Intervals) that received their last vaccine dose by indicated times. **(B)** Among completely vaccinated cases (n=76) or controls (n=1,377), the percentage of individuals (with 95% Confidence Intervals) that received their last vaccine dose by indicated times.

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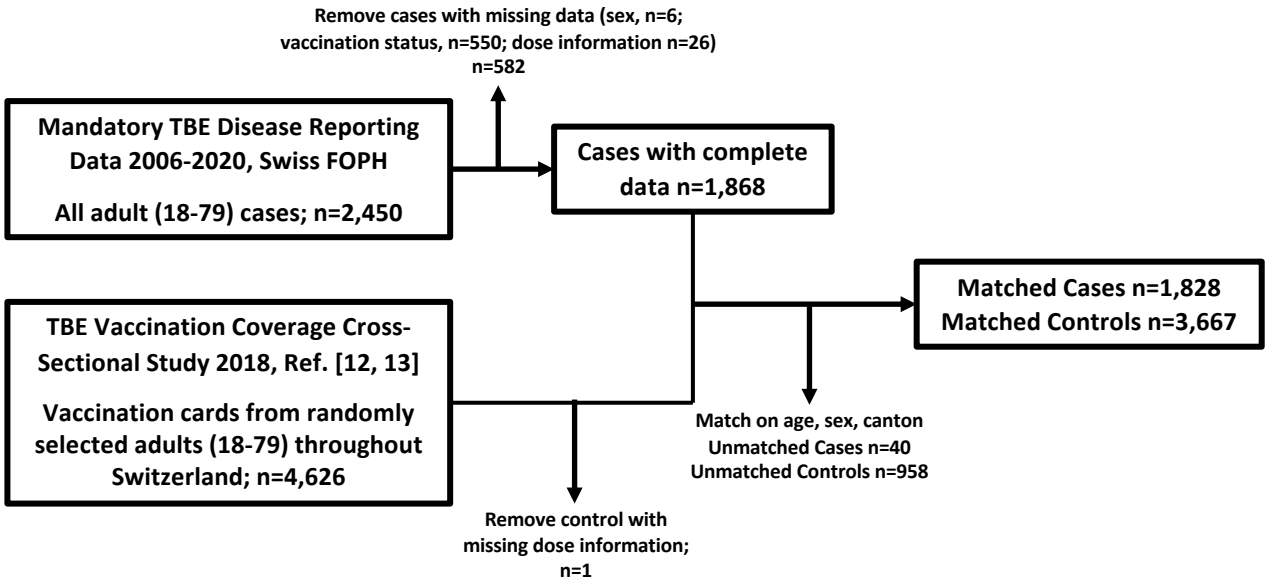

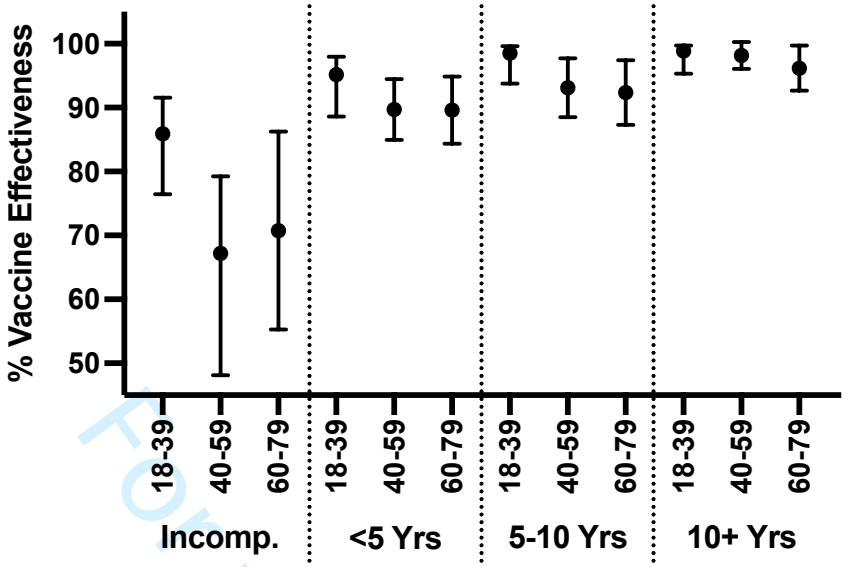

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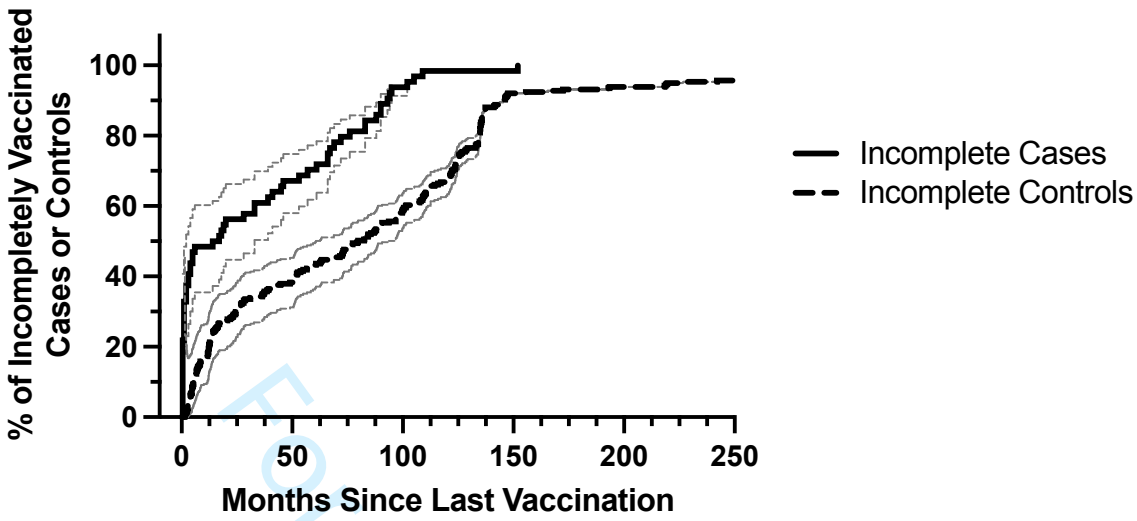

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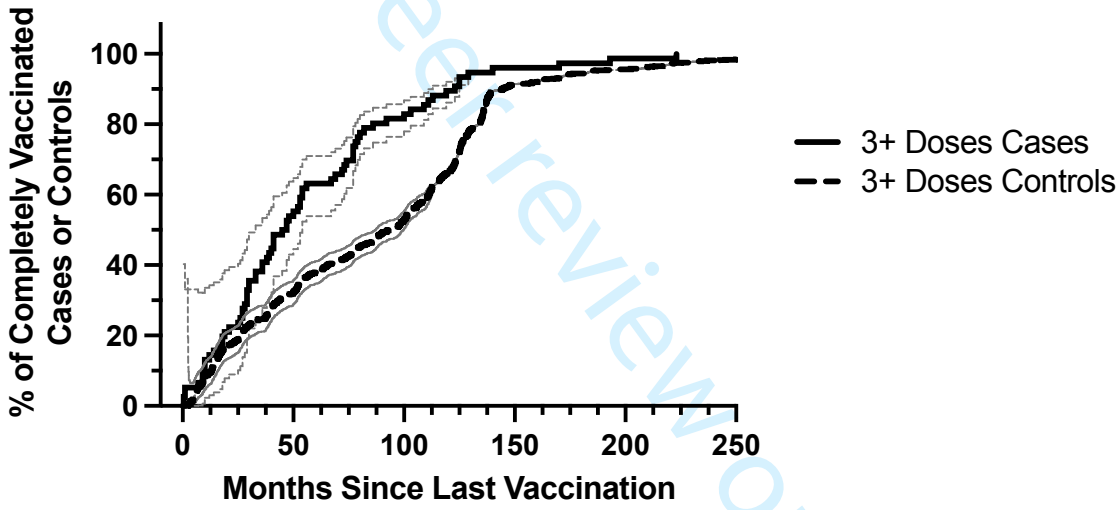

Reporting checklist for case-control study.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	2, 3
Objectives	#3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	#4	Present key elements of study design early in the paper	3
Setting	#5	Describe the setting, locations, and relevant dates, including periods	3

		of recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	3
Eligibility criteria	#6b	For matched studies, give matching criteria and the number of controls per case	3
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for cases and controls.	3, 4
Bias	#9	Describe any efforts to address potential sources of bias	NA
Study size	#10	Explain how the study size was arrived at	3
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	3, 4
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	4
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	4
Statistical methods	#12c	Explain how missing data were addressed	3, 4
Statistical methods	#12d	If applicable, explain how matching of cases and controls was addressed	3, 4
Statistical methods	#12e	Describe any sensitivity analyses	NA
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give	3, Figure 1, Table 1

		information separately for cases and controls.	
Participants	#13b	Give reasons for non-participation at each stage	3, Figure 1
Participants	#13c	Consider use of a flow diagram	Figure 1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	Table 1
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	3, Figure 1, Table 1
Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	Table 1
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	4, Table 1
Main results	#16b	Report category boundaries when continuous variables were categorized	4, Table 1
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	4, Figure 2, Figure 3
Discussion			
Key results	#18	Summarise key results with reference to study objectives	5, 6
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	6
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	6, 7
Generalisability	#21	Discuss the generalisability (external validity) of the study results	7
Other Information			

Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	7

Notes:

- 13a: 3, Figure 1, Table 1
- 13b: 3, Figure 1
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A Retrospective, Matched Case-Control Analysis of Tick-Borne Encephalitis Vaccine Effectiveness by Booster Interval, Switzerland 2006-2020

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A Retrospective, Matched Case-Control Analysis of Tick-Borne Encephalitis Vaccine Effectiveness by Booster Interval, Switzerland 2006-2020

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ABSTRACT

Objective: To estimate effectiveness of Tick-Borne Encephalitis (TBE) vaccination by time interval (<5, 5-10, and 10+ years) post-vaccination.

Design: A retrospective, matched case-control study.

Participants: Cases – all adult (age 18–79) TBE cases in Switzerland reported via the national mandatory disease reporting surveillance system from 2006–2020 (final n=1,868). Controls – community controls from a database of randomly selected adults (age 18–79) participating in a 2018 cross-sectional study of TBE vaccination in Switzerland (final n=4,625).

Primary outcome measures: For cases and controls, the number of TBE vaccine doses received and the time since last vaccination were determined. Individuals were classified as being "unvaccinated" (0 doses), "incomplete" (1–2 doses) or "complete" (3+ doses). Individuals with "complete" vaccination were further classified by time since the last dose was received (<5 years, 5–10 years, or 10+ years). A conditional logistic regression model was used to calculate Vaccine Effectiveness (VE: 100 x [1- odds ratio]) for each vaccination status category.

Results: VE for incomplete vaccination was 76.8% (95% CI 69.0–82.6). For complete vaccination, overall VE was 95.0% (93.5–96.1). When the most recent dose was received <5 years prior VE was 91.6% (88.4–94.0), 95.2% (92.4–97.0) when the most recent dose was received 5–10 years prior, and 98.5% (96.8–99.2) when the most recent dose was received 10+ years prior.

Conclusions: That VE does not decrease among completely vaccinated individuals over 10+ years since last vaccination supports the longevity of the protective response following complete TBE vaccination. Our findings support the effectiveness of 10-year TBE booster intervals currently used in Switzerland.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Switzerland has a nearly complete national mandatory disease reporting surveillance system, and case data should be representative.
- The case-control design allows direct comparison of vaccination status among cases and individuals matched by sex, age, and area of residence.
- Despite a large number of TBE cases (n=1,868), only a small number were vaccinated (n=151), preventing a more detailed analysis of factors which could affect VE within groups.
- Data on other factors which might impact the response to vaccination (chronic medical conditions, immunosuppression, age of first vaccination, whether individuals were vaccinated according to the recommended vaccination schedule) were not available.

- As cases and controls were matched by age, VE values between age groups cannot be directly compared.

BACKGROUND

Tick-Borne Encephalitis (TBE) is a serious viral infection of the central nervous system which can result in permanent neurological injury and death. TBE is caused by the Tick-Borne Encephalitis Virus (TBEV), which is transmitted by ticks of the *Ixodidae* family. Currently, TBEV is endemic throughout much of Europe [1, 2]. In Switzerland, mandatory reporting of TBE cases was initiated in 1988. Since then, both the incidence and geographic range of disease have continued to increase. In 2020, the country experienced its most severe disease season with an overall incidence of 5.16 cases/100,000 individuals, exceeding the World Health Organization's (WHO) definition of a "highly endemic" area [1, 2].

Vaccination is highly protective against TBE; producing virus-neutralizing antibodies which are associated with disease prevention, but are not universally considered the "correlate of protection". Two vaccines are currently licensed by the European Medicines Agency (EMA): Encepur® and FSME-Immun®. Both are recommended for individuals living, working or traveling within endemic areas [2]. Both are administered as a primary series of three doses given at day 0, 1-3 months, and 5-12 months with booster doses every 36-60 months (3-5 years) thereafter, depending on age and vaccine formulation [3, 4]. In 2006 the Swiss Federal Office of Public Health (FOPH) amended its official recommendation for TBE vaccination, extending the Swissmedic and EMA-approved booster interval to 120 months (10 years) [5, 6].

Previous studies have demonstrated sustained levels of virus-specific and neutralizing antibodies up to and exceeding 10 years after TBE vaccination [7-9]. Whether this translates to sustained effectiveness, however, is not clear. Additionally, irregular TBE vaccination has been associated with reduced vaccine effectiveness (VE) [10, 11], indicating that deviations from the established vaccination schedule can influence lasting immunity. Whether the prolonged TBE booster intervals in Switzerland impact vaccine effectiveness is of great public health interest as reducing unnecessary vaccinations can improve cost-effectiveness and vaccine compliance. Here, we conducted a retrospective case-control study to evaluate TBE VE in Switzerland at <5, 5-10, and 10+ years post-vaccination.

METHODS

Study Design: We used a retrospective, matched case-control study design, comparing all TBE cases among adults 18-79 in Switzerland reported via the national mandatory disease reporting surveillance system in the 15-year period between 2006 and 2020, to community controls selected from a 2018 nationwide study of TBE vaccination coverage [12, 13].

Selection of Cases: TBE is a mandatory notifiable disease in Switzerland, with all confirmed TBE cases (based on serology and clinical picture [14]) reported by laboratories to the national disease surveillance system [14, 15]. Age, sex, canton of residence and information on vaccination status, including number of doses received and date of last vaccination, are reported to the Swiss FOPH by the submitting physician. From the Swiss FOPH we obtained

data for all TBE cases among residents of Switzerland aged 18-79 reported from 2006-2020. Among the 2,450 eligible cases, 6 were excluded as sex was unknown, 550 were excluded as vaccination status was unknown, and another 26 were excluded due to missing information on the number of vaccine doses received (final n=1,868, Figure 1).

Selection of Controls: Community controls were selected from among a database of individuals participating in a 2018 cross-sectional study of TBE vaccination in Switzerland [12, 13]. In brief, adults with a Swiss mailing address in each of three age groups (18-39, 40-59, 60-79) were selected from each of the seven Swiss geographical regions (European NUTS-2 level) by disproportional stratified random sampling. Selected individuals (n=26,880; 1,280 from each age group and region) were requested by mail to submit a copy of their vaccination record. A total of 4,626 individuals submitted vaccination records. From these, date(s) of TBE immunization were recorded into a database. All participants in this database were eligible for inclusion into this study. One case was excluded due to missing information on vaccine dose number (final n=4,625, Figure 1).

Matching: Cases and controls were matched on sex, age (within 5-year intervals) and canton of residence (half-cantons were combined). All possible matches for each case were considered. Matching was performed using nearest neighbor matching with the *matchit* function in R v 4.0.3 [16], R Foundation for Statistical Computing, Vienna, Austria).

Analysis: For cases and controls, the total number of TBE vaccine doses received and the time since the most recent vaccination were determined. Individuals were classified as being "unvaccinated" (0 doses), "incomplete" (1-2 doses) or "complete" (3+ doses). Among those with "complete" vaccination, individuals were further classified by the time since the last dose was received (<5 years, 5-10 years, or 10+ years). Based on these criteria, a conditional logistic regression model was used to calculate Vaccine Effectiveness (VE: 100 x [1- odds ratio]) for each of the defined vaccination status categories. Statistical analyses were performed using Stata v.17.0 (StataCorp, LLC, College Station, TX, USA) and GraphPad Prism v.8.0 (GraphPad Software, Inc., San Diego, CA, USA); p values <0.05 were considered statistically significant.

Ethics Statement: Mandatory reporting data for TBE cases were provided to us by the Swiss FOPH, which maintains the national disease surveillance system. Data were provided to us in an anonymized form and were treated confidentially throughout the analysis, therefore, ethical approval was not necessary. For the cross-sectional TBE vaccination coverage database used to select controls, potential participants were sent a letter explaining the study's purpose and stating that, by submitting vaccination records, they were voluntarily consenting to participation [12, 13]. All data were anonymized and treated confidentially throughout the analysis. The procedure and method of consent for the cross-sectional study were approved by the Department of Data Protection of the University of Zurich and the Ethics Committee of the Canton of Zurich (approval number 2017-02-027).

Patient and Public Involvement: There was no patient and/or public involvement in the design, conduct, or dissemination plans of this research study.

RESULTS

In total, 1,828 cases and 3,667 controls were matched for our study (Figure 1, Table 1). Among cases, 8.3% (n=151) had received at least 1 TBE vaccine dose, compared to 45.2% (n=1,656) of controls (p<0.0001 Chi-squared test). Of vaccinated cases, 49.7% were "incomplete" (1-2 doses) and 50.3% were "complete" (3+ doses). Of vaccinated controls, 16.8% were "incomplete" and 83.2 were "complete" (p<0.0001 Chi-squared test).

VE for incomplete vaccination was 76.8% (Table 1). For complete vaccination, overall VE was 95.0%. When the most recent dose was received <5 years prior VE was 91.6%, 95.2% when the most recent dose was received 5-10 years prior, and 98.5% when the most recent dose was received 10+ years prior. Compared to <5 years prior, VE 10+ years prior was significantly higher (p<0.0001 conditional logistic regression). These values were also comparable between those aged 18-39, 40-59, and 60-79 (Figure 2).

Among incompletely vaccinated TBE cases, the median time since last vaccination was 1.3 years (15.5 months), compared to 6.7 years (79.8 months) for incompletely vaccinated controls (p<0.0001 Mantel-Cox Log-rank test) (Figure 3a). 37.5% of incompletely vaccinated cases occurred within 2 months of last vaccination. For completely vaccinated TBE cases, median time since last vaccination was 3.8 years (46.0 months) compared to 7.8 years (93.3 months) for controls (p<0.0001 Mantel-Cox Log-rank test, Figure 3b). Comparing timing of last vaccination to the recommended booster vaccination scheme, 63.2% of cases had been last vaccinated within the preceding 5 years, 26.3% within the preceding 5-10 years and 10.5% had been last vaccinated more than 10 years prior. For controls, 38.0%, 28.8% and 33.3% of individuals had received a last vaccination <5, 5-10, or 10+ years prior, respectively (p<0.0001 Chi-squared test).

Table 1. Demographic Breakdown of Cases and Controls and Vaccine Effectiveness by Vaccination Status

	Controls (n = 3,667)	Cases (n = 1,828)	% Vaccine Effectiveness (1-OR)*100	95% CI Lower	95% CI Upper	p Value
Male	1,925 (52.5%)	1,159 (63.4%)	-	-	-	-
Female	1,742 (47.5%)	669 (36.6%)	-	-	-	-
18-39	1,060 (28.9%)	463 (25.3%)	-	-	-	-
40-59	1,257 (34.3%)	800 (43.8%)	-	-	-	-
60-79	1,350 (36.8%)	565 (30.9%)	-	-	-	-
Unvaccinated	2,011 (54.8%)	1,677 (91.7%)	Ref.	-	-	-
1-2 Doses (Incomplete)	279 (7.6%)	75 (4.1%)	76.8	69.0	82.6	<0.001

3+ Doses (Complete) <5 years	522 (14.2%)	48 (2.6%)	91.6	88.4	94.0	<0.001
3+ Doses Complete 5-10 years	397 (10.8%)	20 (1.1%)	95.2	92.4	97.0	<0.001
3+ Doses Complete >10 years	458 (12.5%)	8 (0.4%)	98.5	96.8	99.2	<0.001
3+ Doses (Complete) Any time	1,377 (37.6%)	76 (4.2%)	95.0	93.5	96.1	<0.001

DISCUSSION

Here we used a retrospective, matched case-control study design to investigate TBE VE in Switzerland considering both incomplete and complete vaccination, and, among completely vaccinated individuals, different time intervals since last vaccination. Of the 8.3% of cases that had received at least one vaccine dose, 50.3% were completely vaccinated (3+ doses). Based on this definition, we estimate a failure rate of 4.2%, which is in line with TBE vaccine failure rates estimated in other studies [10, 17-20], including two previous studies also using Swiss mandatory reporting data from the national database which we draw from here [21, 22].

Importantly, nearly half of vaccinated cases were among recipients of only 1-2 doses. Here, we calculated VE for incomplete vaccination at 76.8%, which was substantially and significantly less than that for complete vaccination (95.0%). Furthermore, we found that nearly 40% of the cases among incompletely vaccinated individuals occurred within 2 months of their last dose, suggesting they were exposed before they had developed a protective immune response to vaccination. As TBE is a strongly seasonal disease (peaking from April to October), and because primary vaccination for TBE according to the "conventional" schedule takes a minimum of 5-9 months, vaccination should ideally begin in the fall or winter of the year prior to planned exposure. Alternatively, a rapid immunization scheme (0, 7 and 21 days plus a fourth dose after 12-18 months for Encepur or 0 and 14 days plus a third dose after 5-12 months for FSME-Immun [3, 4]), could potentially provide an option to limit a period of reduced protection. Previous studies have not found substantial differences in serological response to TBE vaccination based on use of the "rapid" or "conventional" schedules [8, 23, 24]. While our dataset did not include complete timing of TBE vaccination history, which could allow us to investigate VE by vaccination schedule, such an analysis could be informative.

Among completely vaccinated individuals, overall TBE VE was 95.0%. Interestingly, we did not observe a decrease in VE with increasing time since the last vaccine dose was received, consistent with the findings of a recent study evaluating TBE cases in vaccinated individuals using a different methodology [21]. If anything, VE was lower in the first 5 years following last vaccination compared to last vaccination 10+ years prior. We further observed the median time to vaccine failure among completely vaccinated cases was 3.8 years (46.0 months). While not completely clear, this observation could potentially be explained by a fraction of individuals which remained insufficiently protected by vaccination. The median time to

vaccine failure did not, however, differ between cases having received 3 doses or those having received 4+ doses (not shown), suggesting no impact of adding an additional dose. It should also be noted that we did not observe appreciable differences in overall VE or VE over time between age groups (in agreement with findings summarized in a recent systematic review of TBE vaccine booster intervals [25]).

An important limitation of our study is the relatively small number of vaccinated cases (n=151). Furthermore, we do not have data on other factors which might impact the response to vaccination such that we could control for them in our analysis. Whether individuals have a chronic medical condition or immunosuppression [26-29], the age at which the person was first vaccinated, [17, 20, 30, 31], whether they were regularly vaccinated in their primary series [10, 11], and possibly whether they received a "conventional" or "rapid" schedule, could potentially have an impact on our assessment of VE. An additional limitation is that, while we found TBE VE appeared similar between age groups, as we matched cases and controls by age we were unable to directly compare VE values. While some studies have demonstrated reduced serological responses to TBE vaccination and increased vaccine breakthrough in older individuals [17, 20, 30, 31], other work has shown vaccination breakthrough to be comparable between older and younger age groups, and that VE remains high even among those aged 60+ [32, 33]. Clarifying how TBE VE is impacted by age remains an important area warranting further study.

Taken together, and despite our study limitations, these results do not indicate a consistent decrease in TBE VE over time among fully-vaccinated individuals, as might be predicted by antibody decay kinetics. These findings also highlight that antibody responses may not necessarily always be a suitable surrogate for VE estimates, which have been shown to decline with time in several publications [7, 9, 34, 35].

CONCLUSIONS

Despite that a substantial portion of the Swiss population has been vaccinated for TBE—42% coverage for 1 dose and 34% for 3 doses [12] —disease incidence continues to increase, indicating that current vaccination coverage is insufficient. To better address this, additional information related to vaccination uptake, schedule compliance, and effectiveness is needed. Our findings highlight the increased effectiveness of complete (3+ dose) versus incomplete (1-2 dose) TBE vaccination. That 40% of breakthroughs among incompletely vaccinated individuals occur within 1-2 months of vaccination suggests that individuals are being exposed before they have had time to develop a protective immune response to vaccination. That VE does not appreciably change or decrease among completely vaccinated individuals over 10+ years since last vaccination supports the longevity of the protective response following complete TBE vaccination; also among both younger and older age groups. In total, our findings support the effectiveness of 10-year TBE booster intervals currently used in Switzerland.

COMPETING INTERESTS STATEMENT

The authors declare no competing interests.

FUNDING STATEMENT

This work was funded, in part, by a competitive grant from the Swiss Federal Office of Public (grant number 19.002540) awarded to KDZ and PL. KDZ was additionally supported by awards from the EMDO Stiftung (award number 1053) and the University of Zurich Forschungskredit for post-doctoral researchers (award number FK-20-059). The funders had no role in the study design, data analysis, preparation of the manuscript, or decision to publish.

DATA AVAILABILITY STATEMENT

To ensure participant privacy, the datasets analyzed for this study are not publicly available. They are, however, available upon request, without undue reservation, by contacting the study authors (phung.lang@uzh.ch).

AUTHOR CONTRIBUTIONS

KDZ and PL conceived the study. KDZ, SRH and PL designed the study, KDZ and PL acquired study funding. AJS and EA provided case data. KDZ and SRH organized the database and analyzed the data, KDZ wrote the first draft of the manuscript. KDZ, SRH, AJS, EA, JSF, and PL critically reviewed the manuscript and approved the submitted version.

FIGURE LEGENDS

Figure 1. Study Flow Diagram.

Figure 2. Vaccine Effectiveness by Age. For each age group (18-39, 40-59, and 60-79), individuals were categorized as unvaccinated, incompletely vaccinated (1-2 doses), completely vaccinated (3+ doses) <5 years prior, 5-10 years prior, or 10+ years prior and VE was calculated using the formula (VE=100*1-Odds Ratio), with unvaccinated as the reference.

Figure 3. Time Since Last Vaccination Among Vaccinated Cases and Controls. (A) Among incompletely vaccinated cases (n=75) or controls (n=279), the percentage of individuals (with 95% Confidence Intervals) that received their last vaccine dose by indicated times. **(B)** Among completely vaccinated cases (n=76) or controls (n=1,377), the percentage of individuals (with 95% Confidence Intervals) that received their last vaccine dose by indicated times.

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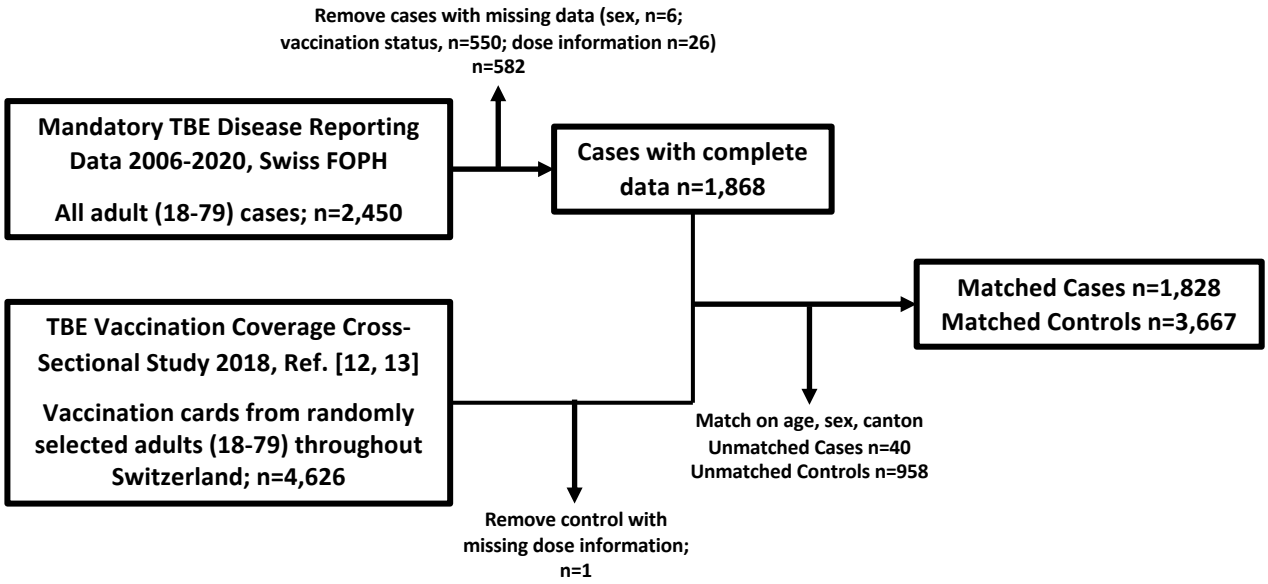

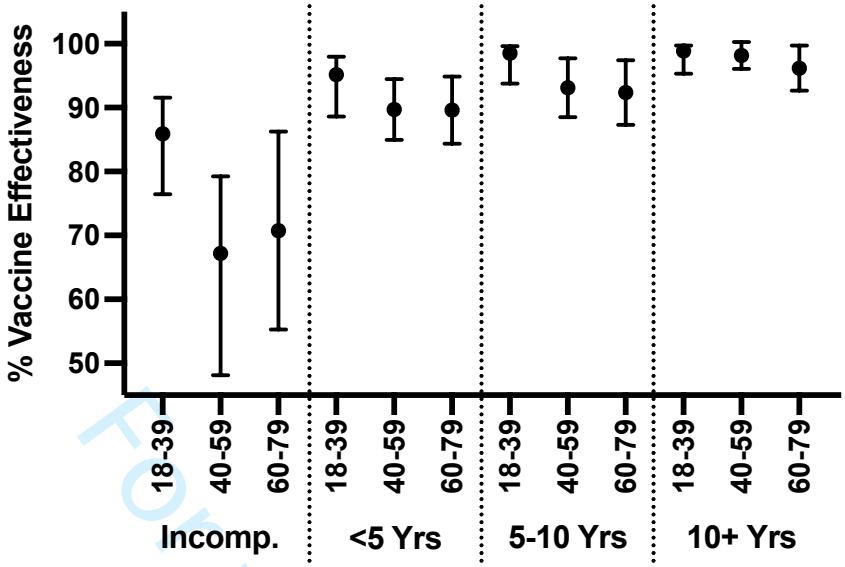

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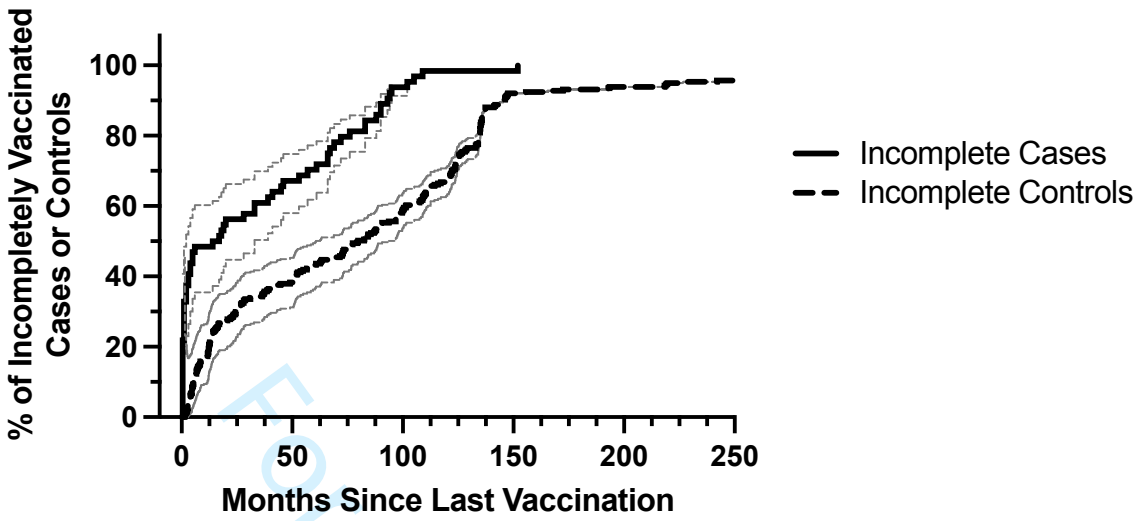

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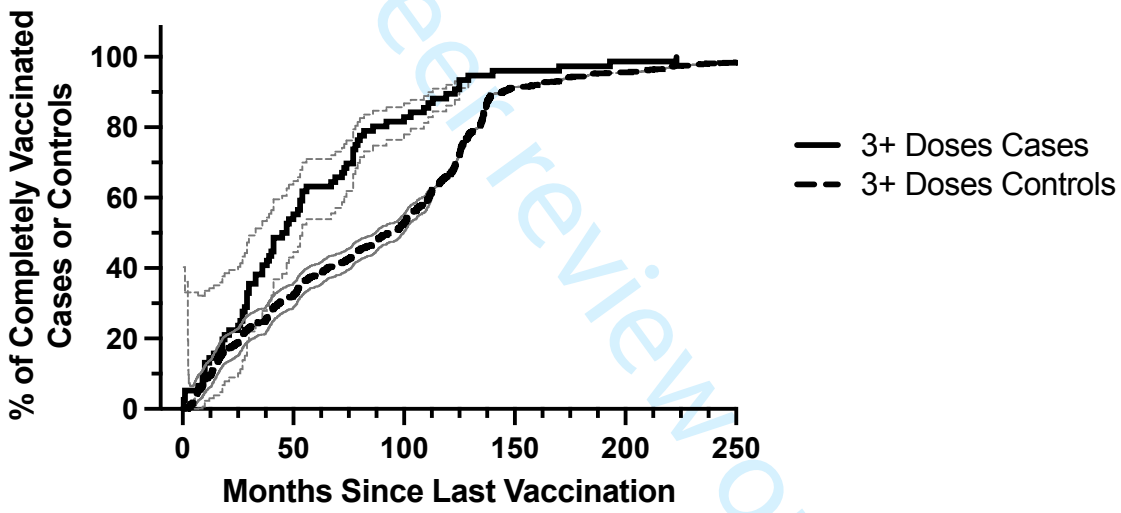

Reporting checklist for case-control study.

Based on the STROBE case-control guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE case-controlreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	2, 3
Objectives	#3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	#4	Present key elements of study design early in the paper	3
Setting	#5	Describe the setting, locations, and relevant dates, including periods	3

		of recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	3
Eligibility criteria	#6b	For matched studies, give matching criteria and the number of controls per case	3
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for cases and controls.	3, 4
Bias	#9	Describe any efforts to address potential sources of bias	NA
Study size	#10	Explain how the study size was arrived at	3
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	3, 4
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	4
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	4
Statistical methods	#12c	Explain how missing data were addressed	3, 4
Statistical methods	#12d	If applicable, explain how matching of cases and controls was addressed	3, 4
Statistical methods	#12e	Describe any sensitivity analyses	NA
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give	3, Figure 1, Table 1

		information separately for cases and controls.	
Participants	#13b	Give reasons for non-participation at each stage	3, Figure 1
Participants	#13c	Consider use of a flow diagram	Figure 1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	Table 1
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	3, Figure 1, Table 1
Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	Table 1
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	4, Table 1
Main results	#16b	Report category boundaries when continuous variables were categorized	4, Table 1
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	4, Figure 2, Figure 3
Discussion			
Key results	#18	Summarise key results with reference to study objectives	5, 6
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	6
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	6, 7
Generalisability	#21	Discuss the generalisability (external validity) of the study results	7
Other Information			

Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	7

Notes:

- 13a: 3, Figure 1, Table 1
- 13b: 3, Figure 1
- 14b: 3, Figure 1, Table 1
- 17: 4, Figure 2, Figure 3 This checklist was completed on 18. January 2022 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai