Analysis of Tick-borne Encephalitis vaccination coverage and compliance in adults in Switzerland, 2018

Baroutsou, Vasiliki ; Zens, Kyra D ; Sinniger, Philipp ; Fehr, Jan ; Lang, Phung

Abstract: BACKGROUND Overall incidence and geographic range of Tick-borne Encephalitis (TBE), a vaccine preventable infection, have steadily increased in Switzerland over the last 50 years. While fully subsidized vaccination has been recommended in many areas for well over a decade, vaccine coverage and variables associated with vaccination compliance among Swiss adults are poorly understood. METHODS In 2018 we conducted a national, cross-sectional survey of vaccination cards evaluating TBE vaccination coverage and compliance among adults (18-79) in Switzerland. RESULTS Nationwide TBE vaccination coverage was 41.7% (range 14.3% to 60.3%) for 1 dose and 32.9% (range 8.4% to 50.4%) for a complete primary series (3 doses). There was a significant correlation between average disease incidence by canton (2009-2018) and vaccine coverage at both 1 and 3 doses. Of the overall population, 9.5% had received at least one TBE booster vaccination with large regional coverage variation. We estimated that 23% of adults in Switzerland would be protected from infection based on their vaccination history and 135 (95% CI: 112-162) TBE cases were prevented in 2018. Individuals reporting previous experience with tick-associated health problems, those frequently in nature or those with "high" perceived risk of contracting TBE, were significantly more likely to have received at least one vaccine dose, indicating a positive impact of awareness on vaccination compliance. We also calculated a TBE incidence rate of 6.83/100,000 among the unvaccinated adult population in Switzerland and estimated vaccine effectiveness at 91.5% (95% CI: 90.9-92.0%). CONCLUSIONS These findings provide an important reference for TBE vaccination levels in Switzerland and further suggest that public health interventions promoting knowledge of TBE health impacts and risk factors may be beneficial in improving TBE vaccination coverage but should be tailored to account for heterogeneity in vaccine uptake.

DOI: https://doi.org/10.1016/j.vaccine.2020.10.022

38(49):7825-7833.
DOI: https://doi.org/10.1016/j.vaccine.2020.10.022

Vaccine 38 (2020) 7825–7833

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Analysis of Tick-borne Encephalitis vaccination coverage and compliance in adults in Switzerland, 2018

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ARTICLE INFO

Article history:
Received 6 April 2020
Received in revised form 2 October 2020
Accepted 7 October 2020
Available online 21 October 2020

ABSTRACT

Background: Overall incidence and geographic range of Tick-borne Encephalitis (TBE), a vaccine preventable infection, have steadily increased in Switzerland over the last 50 years. While fully subsidized vaccination has been recommended in many areas for well over a decade, vaccine coverage and variables associated with vaccination compliance among Swiss adults are poorly understood.
Methods: In 2018 we conducted a national, cross-sectional survey of vaccination cards evaluating TBE vaccination coverage and compliance among adults (18-79) in Switzerland.
Results: Nationwide TBE vaccination coverage was 41.7% (range 14.3% to 60.3%) for 1 dose and 32.9% (range 8.4% to 50.4%) for a complete primary series (3 doses). There was a significant correlation between average disease incidence by canton (2009-2018) and vaccine coverage at both 1 and 3 doses. Of the overall population, 9.5% had received at least one TBE booster vaccination with large regional coverage variation. We estimated that 23% of adults in Switzerland would be protected from infection based on their vaccination history and 135 (95% CI: 112-162) TBE cases were prevented in 2018. Individuals reporting previous experience with tick-associated health problems, those frequently in nature or those with "high" perceived risk of contracting TBE, were significantly more likely to have received at least one vaccine dose, indicating a positive impact of awareness on vaccination compliance. We also calculated a TBE incidence rate of 6.83/100,000 among the unvaccinated adult population in Switzerland and estimated vaccine effectiveness at 91.5% (95% CI: 90.9-92.0%).
Conclusions: These findings provide an important reference for TBE vaccination levels in Switzerland and further suggest that public health interventions promoting knowledge of TBE health impacts and risk factors may be beneficial in improving TBE vaccination coverage but should be tailored to account for heterogeneity in vaccine uptake.

1. Introduction

Tick-borne Encephalitis (TBE) is a serious viral infection of the Central Nervous System which can result in severe disease, permanent disability, and death. The causative agent of TBE, the Tick-borne Encephalitis Virus (TBEV), is widespread throughout Russia, parts of Asia, the Baltic states, southern Sweden and Finland and a large part of Central Europe [1,2]. TBE was first described in Switzerland in 1969 and has, over the last 50 years, become endemic, spreading from the north-eastern part of the country progressively west and southward [3–5]. Switzerland is now among the most affected countries in Central Europe and, in 2018, the average disease incidence reached 4.37 cases/100,000 individuals – just short of the World Health Organization (WHO) definition of $\geq$ 5.0 cases/100,000 as "highly endemic" [6,7]. Incidence, however, is not homogenous. In both Switzerland and in other affected countries, disease generally occurs in geographically-localized areas where TBEV circulates between local tick vector and small mammal reservoir populations. Additionally, incidence is higher among men compared to women and among individuals from 60 to 79 compared to other age groups [6].

Currently, two TBE vaccines (FSME-Immun; Pfizer and Encepur; Bavarian Nordic) are licensed in Europe and available in Switzerland. Conventional primary vaccination is a series of 3 immunizations administered over 6–15 months, depending on vaccine type.

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https://doi.org/10.1016/j.vaccine.2020.10.022
0264-410X/

Both vaccines elicit viral neutralizing antibody responses which are thought to protect from infection. Complete primary vaccination results in antibody responses which persist for many years. To maintain titres, both manufacturers recommend an initial booster 3 years after completion of the primary series, and every 5 years until age 50 for Encepur and 60 for FSME-Immun, then every 3 years thereafter [8–10]. In Switzerland, however, a simplified scheme has been adopted with boosters beginning every 10 years after completion of the primary series regardless of age [11].

The Swiss Confederation is composed of 26 semi-autonomous cantons. Vaccination recommendations are made by the FOPH and are adopted at the cantonal level. While health insurance is privatized in Switzerland, all individuals are required to be covered, and FOPH-recommended vaccinations are reimbursed. Although TBE vaccination was previously available to individuals at personal expense, in 2006 the FOPH officially recommended TBE vaccination of all individuals from the age of 6 residing or spending significant time in TBEV risk areas within Switzerland, areas with 3 or more diagnosed cases of TBE or areas where TBEV has been found circulating in local tick populations [12]. The original recommendation included roughly 71 municipalities (of 2,212 total) in 15 Swiss cantons and has been periodically updated and expanded by the FOPH based on disease monitoring efforts through the comprehensive mandatory infectious disease reporting system. This system utilizes defined clinical and laboratory criteria for TBE infection and is in place in Switzerland since 1988 (https://www.ecdc.europa.eu/en/publications-data/country-profile-switzerland-tick-borne-encephalitis-tbe). Despite these recommendations, however, TBE incidence has continued to increase and, as a result, the FOPH dramatically expanded its recommendation in 2019 to include all Swiss cantons, with the exceptions of the cantons of Geneva (45 municipalities; 5.8% of the 2018 Swiss population) and Ticino (115 municipalities; 4.1% of the 2018 Swiss population), as risk areas [13]. Significantly, this increase in TBE disease incidence occurred even in cantons where vaccination was specifically recommended and reimbursed by compulsory health insurance, suggesting poor vaccine uptake among those at risk.

While TBE vaccination has been FOPH-recommended and reimbursed by compulsory health insurance in many areas for more than a decade, the overall level of vaccine coverage isn't known. Switzerland does not have a national, population-based immunization registry system and vaccination coverage among adults is not otherwise routinely monitored. Regional variations in coverage and how they relate to disease incidence and vaccination recommendations further remain unclear. In addition, individual-level variables impacting TBE vaccination compliance are incompletely understood. Understanding the frequency and distribution of vaccinated individuals can help to estimate the percentage of the adult population that is protected against TBE and may further have important impacts on the design of vaccination strategies and disease control. To address these knowledge gaps, we conducted a national survey evaluating TBE vaccination coverage and compliance among adults in Switzerland.

2. Methods

2.1. Study design

In collaboration with the Swiss FOPH and all 26 cantons since 1999, we have developed a robust system to monitor routine vaccination coverage in children aged 2, 8 and 16 years at the national and cantonal levels based on obtaining vaccination records by mail [14]. Therefore, to estimate the breadth and depth of TBE vaccination coverage among adults in Switzerland, we used a similar methodology to perform a national, cross-sectional study, where randomly selected adults aged 18–79 were requested by mail to submit a copy of their vaccination record. In addition, to assess knowledge of TBE infection, risk behaviours, and reasons for receiving or abstaining from vaccination, participants were further asked to complete a short questionnaire.

2.2. Selection and recruitment of participants

A comprehensive list of all individuals with a registered mailing address in Switzerland was provided by an external organization (Institute for Social Research, Zurich, Switzerland). This list was divided by the 7 statistical "large regions" defined by the Swiss Federal Statistical Office ((SFSO), Supplementary Table 1), and the population of each region was further divided into three age groups: 18–39, 40–59 and 60–79. From each region and age group, disproportional stratified random sampling was used to select 1,280 individuals invited to participate, for a total sample size of 26,880 (1,280 × 7 regions × 3 age groups).

Potential participants were contacted by mail beginning in February 2018. To participate, individuals were requested to submit a copy of their vaccination record and to complete a short questionnaire. Non-responders received a single reminder letter in May 2018. As Switzerland is a multilingual country, the language (German, French or Italian) of both the letter and questionnaire were matched to the official language of the municipality of each address. The total enrolment period was from February to October 2018. Participants submitting a completed questionnaire, a vaccination record, or both, were eligible for a lottery to receive one of three 1,000 CHF ($1,065) cash prizes with individuals submitting both a completed questionnaire and a copy of their vaccination record entered twice.

2.3. Data collection

2.3.1. Vaccination records

Both paper-based forms and private digital vaccination records (i.e. healthcare provider or meineimpfungen.ch) are used in Switzerland. Vaccination records contain dates of vaccination, vaccine names and lot numbers that are manually recorded by a health professional after a vaccination is administered. For this study, copies of paper-based forms or printouts of digital vaccinations records obtained from study participants were manually inspected and the number and date(s) of TBE immunization were recorded.

2.3.2. Self-reported questionnaire

The questionnaire consisted of four questions. Participants were asked to 1) Report whether they or someone that they know had experienced tick-related health problems; 2) Their frequency of episodes of time spent in nature, during tick season; 3) Self-estimation of the risk of contracting TBE; and 4) Reasons for abstaining from vaccination (in the event that they were not vaccinated for TBE). Completed questionnaires were manually inspected and responses recorded.

2.3.3. Statistical analyses

Prior to analysis, data were post-stratified according to age and gender. Vaccination coverage among study participants was calculated at national, large region (Supplementary Table 1) and cantonal levels by dose counting. Descriptive statistics with 95% confidence intervals (mean) were calculated for primary and booster vaccination coverage. Demographic variables and differences between groups were evaluated using Pearson chi-square test for categorical variables and Wilcoxon-Mann-Whitney test for continuous variables using R version 3.6.1 (R Foundation for Statistical

Table 1
Participant Demographics by Age and Region.

Region	Total Switz.* (Adults 18–79)		Sample Size (n)	Participants (n)	Response (%sample size)	
Overall	6,570,644		26,880	4,479	16.7	
Sex		**% Switz.**				**% Participants**
Male	3,282,778	50.0	14,790[§]	2,270	15.3	50.7
Female	3,287,866	50.0	12,009[§]	2,209	18.4	49.3
Age Groups		**% Switz.**				**% Participants**
18–39	2,447,156	37.2	8,960	1,339	14.9	29.9
40–59	2,486,310	37.8	8,960	1,552	17.3	34.7
60–79	1,637,178	24.9	8,960	1,588	17.7	35.5
Large Region		**% Switz.**				**% Participants**
Lake Geneva	1,251,746	19.1	3,840	473	12.3	10.6
Ticino	272,375	4.1	3,840	420	10.9	9.4
Midland Switzerland	1,440,871	21.9	3,840	708	18.4	15.8
Northwest Switzerland	895,062	13.6	3,840	667	17.4	14.9
Central Switzerland	627,917	9.6	3,840	721	18.8	16.1
East Switzerland	907,600	13.8	3,840	756	19.7	16.9
Zurich	1,175,073	17.9	3,840	734	19.1	16.4

*2018 Population data from Swiss Federal Statistical Office.
[§] 81 Individuals of Unknown Gender.

Computing, Vienna, Austria). Correlations between vaccination coverage and average disease incidence were performed using GraphPad Prism version 8.0 (GraphPad Software, Inc., San Diego, CA) and Pearson correlation coefficients calculated for each pair using a two-tailed test. Multiple logistic regression analysis evaluating the association between age, gender or questionnaire variables with the probability of being vaccinated at 1 and 3 doses was performed and Crude and Adjusted Odds Ratios (OR) with 95% confidence intervals were calculated using R version 3.6.1. For analysis of variables in the questionnaire, differences between groups were further evaluated using Pearson chi-square test with the Rao-Scott correction. For all analyses p-values ≤ 0.05 were considered as statistically significant.

2.4. Estimation of TBE incidence among unvaccinated and vaccine effectiveness

We estimated TBE incidence among unvaccinated adults for the study year 2018 taking the percentage of participants with 3 + vaccine doses as "vaccinated" and using adult (18–79) TBE case numbers from mandatory disease reporting data [6]. As case number data are not available by age group at the cantonal level, we estimated values based on national data where 92% of cases occur in adults [6]. As data for vaccine failure in TBE cases are not publicly available, we used a value of 4% for the vaccine failure rate based on a previous study of TBE cases in Switzerland from 2005 to 2011 [5].

2.5. Estimation of population-level protection

We estimated the percentage of the adult population "protected" from TBE infection based on immunization dates from vaccination records. We defined "protected" as having completed the primary series of 3 TBE vaccinations within the last 10 years or having completed the primary series and at least one booster vaccination within the last 10 years.

2.6. Ethical considerations

With each mailing, a letter was included explaining the study's procedures and objectives. Participation in the survey was voluntary and individuals had the possibility to withdraw submitted data at any time. Submission of the vaccination records and/or completed questionnaires were taken as informed consent. Data were treated confidentially and anonymized prior to analysis. The study was approved by the Office of Data Protection as well as the Ethics Committee of the Canton of Zurich.

3. Results

3.1. Participation

Of 26,880 randomly selected individuals, 8,448 (31%) responded. Individuals submitting only a questionnaire without a vaccination record (3,713, 14%) or a vaccination record without a completed questionnaire (256, 1%) were excluded from further analysis (Fig. 1). A total of 4,479 individuals (17%, Fig. 1, Table 1) submitted both a completed questionnaire and vaccination record and were included for analysis. For simplicity, we will henceforth refer to these individuals as "participants" or "respondents". 18% of invited females and 15% of invited males participated. In total, just under 51% of participants were male (Table 1). Participation by age group was 15% for those 18–39, 17% for those 40–59 and 18% for those 60–79 (Table 1). Participants tended to be older in comparison to the adult population of Switzerland (Table 1). Regionally, participation was highest in East Switzerland and lowest in Ticino (20 and 11% of contacted individuals, respectively, Table 1).

3.2. Primary vaccination coverage

Among participants, national TBE vaccination coverage was 42% for one dose but only 33% for a complete primary series of three doses (n = 4479, Table 2). Vaccination coverage was slightly higher among men than among women for one dose (46% vs 37%, $p < 0.001$) but comparable for 3 doses (34% vs 32%, $p = 0.17$). Similarly, coverage at one dose was higher among those from 18 to 39 (49%) compared to those aged 40–59 (37%) or 60–79 (37%) ($p < 0.001$), but comparable at three doses where coverage was 35%, 31% and 32% ($p = 0.17$), respectively (Table 2).

We observed that vaccination with at least 1 (59%) and 2 (56%) dose(s) was higher among males aged 18–39 than for any other age/gender group. Coverage with at least 3 doses (37%), however, was only slightly greater than for other age/gender groups (Table 2).

At the large region level, TBE vaccination coverage ranged from 14% (Ticino region) to 60% (Zurich region) for one dose and 8% (Ticino region) to 50% (Zurich region) for a series of 3 doses (Fig. 3, Supplementary Table 2). At the cantonal level coverage ranged from 2% (Geneva) to 72% (Thurgau) at one dose and 0 (Geneva)

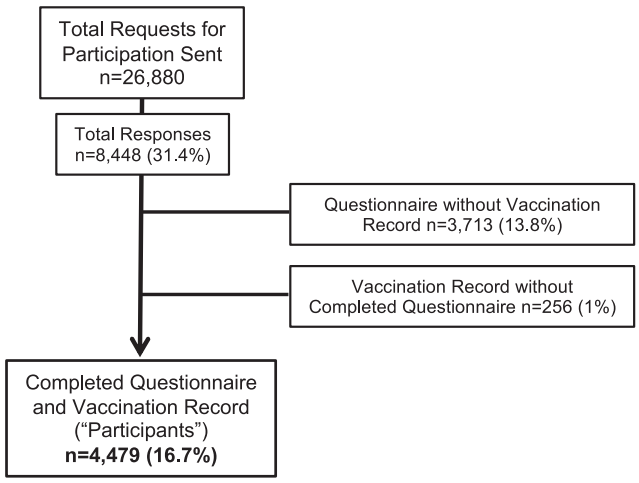

Fig. 1. Flow Chart of Study Respondents - A total of 26,880 requests for participation were sent to randomly selected individuals by mail. Individuals were included in the study if the submitted both a questionnaire and a vaccination card.

to 68% (Uri) at 3 doses (Supplementary Figs. 1 and 2, Supplementary Table 3). Coverage at ≥ 3 doses exceeded half of the adult population in only two cantons (Supplementary Figs. 1 and 2, Supplementary Table 3). There was a significant, positive correlation ($p < 0.001$) between average TBE incidence by canton (2009–2018) and TBE vaccine coverage at both 1 and 3 doses (Fig. 2). Mean vaccination coverage (at 1 dose, $p < 0.001$, and 3 doses $p < 0.01$) was higher in areas overlapping with TBE risk areas where vaccination was recommended by the FOPH as of 2018 (Supplementary Figs. 1 and 2).

3.3. Booster vaccination coverage

We found that TBE booster vaccination coverage (defined here as 4 + vaccinations) for adults 18–79 years was 9.5% of the overall population (Table 2 and Fig. 4). When evaluated as the percentage of individuals having previously completed the primary series of 3 vaccine doses, we found that 31% of adults 18–79 had received at least one booster vaccination and that coverage was higher among older adults 60–79 compared to younger adults aged 18–39 (36% versus 27%, respectively (($p < 0.01$)), with the highest coverage found among male seniors (41%).

At the large region level, booster vaccine coverage (4 + vaccinations) among participants was highest in Zurich (17%) and lowest in Lake Geneva (2%) and Ticino (2%) (Fig. 4, Supplementary Table 2). In general, booster coverage was greater in regions with increased TBE incidence with the exception of Central Switzerland (Fig. 4). When evaluating booster coverage by canton, Thurgau and Glarus had the highest coverage (24% and 23% of participants, Supplementary Fig. 3, Supplementary Table 3) and Geneva, Jura and Appenzell Innerrhoden had the lowest coverage (0% for all three). We found that there was a significant, positive correlation between average TBE incidence by canton (2009–2018) and TBE booster vaccine coverage ($r = 0.545$, $p < 0.01$, Supplementary Fig. 4).

3.4. Estimation of TBE incidence among unvaccinated adults

Based on vaccination coverage levels among study participants, we estimated 2018 TBE incidence among unvaccinated adults at the national level to be 6.83 cases/100,000 compared to 4.37 cases/100,000 [6] for all individuals (Table 3). At the cantonal level estimates for incidence among unvaccinated adults varied widely, ranging from no cases in Basel Land to a high of 90.07 cases/100,000 in canton Uri (Supplementary Table 4). According to these estimates, 16, rather than 10 cantons exceeded the WHO definition of a "highly endemic" area (≥5.0 cases/100,000 individuals) [7], representing just over 60% of the adult (18–79) population of Switzerland (Supplementary Table 3, Supplementary Table 4).

3.5. Estimation of prevented TBE cases and vaccine Effectiveness

Based on our estimate for national TBE incidence among unvaccinated adults, we further estimated that 112–162 TBE cases were prevented among adults 18–79 in 2018 (Table 3). Furthermore, from these values we calculated 90.9–92.0% Vaccine Effectiveness (Table 3).

3.6. Estimation of Population-Level protection

We next estimated the percentage of the adult population in Switzerland "protected" from TBE infection based on "current" immunization. We found that, at the national level, 23% of participants submitting vaccination records had received 3 or more TBE vaccine doses within the last 10 years. Of individuals with at least one booster vaccination, 84% had received this booster within the last 10 years.

3.7. Vaccination coverage by TBE awareness and perceived risk

We further explored whether previous experience with tick-borne illness or perceived risk of illness might impact TBE vaccine compliance. Participants reporting that they, or someone they know, had experienced such problems were significantly more

Table 2
TBE Vaccination Coverage at the National Level.

	≥ 1 Dose (95% CI)	≥ 2 Doses (95% CI)	≥ 3 Doses (95% CI)	≥ 4 Doses Total* (95% CI)	≥ 4 Doses Primary§ (95% CI)
All Ages	41.7% (40.1–43.3%)	39.9% (38.3–41.5%)	32.9% (31.3–34.5%)	9.5% (8.5–10.6%)	31.3% (29.3–33.0%)
Male	46.0% (43.7–48.3%)	43.7% (41.3–46.1%)	34.0% (31.6–36.4%)	10.0% (8.5–11.6%)	31.9% (27.2–37.0%)
Female	37.4% (35.3–39.6%	36.1% (33.9–38.3%)	31.8% (29.7–33.9%)	9.0% (7.8–10.4%)	28.6% (23.8–33.8%)
18–39	49.3% (46.3–52.4%)	46.9% (43.7–50.0%)	34.7% (31.5–38.0%)	8.6% (6.8–10.7%)	27.1% (23.7–30.8%)
Male	58.8% (54.4–63.1%)	55.8% (51.1–60.4%)	37.4% (32.5–42.5%)	8.8% (6.1–12.3%)	25.2% (20.3–30.7%)
Female	39.6% (35.4–43.9%)	37.6% (33.4–42.0%)	31.9% (27.9–36.1%)	8.4% (6.2–11.0%)	28.8% (23.9–34.0%)
40–59	37.0% (34.5–39.5%)	35.6% (33.2–38.1%)	31.3% (29.0–33.8%)	9.5% (8.0–11.1%)	29.3% (26.0–32.9%)
Male	38.9% (35.1–42.9%)	37.2% (33.4–41.1%)	32.0% (28.4–35.8%)	9.4% (7.2–11.9%)	29.3% (24.4–34.7%)
Female	35.0% (31.9–38.3%)	34.0% (31.0–37.2%)	30.7% (27.7–33.8%)	9.6% (7.6–11.9%)	29.3% (24.8–34.2%)
60–79	37.4% (34.9–39.8%)	35.9% (33.5–38.4%)	32.4% (30.1–34.8%)	11.0% (9.5–12.6%)	36.2% (32.8–39.6%)
Male	36.8% (33.9–39.9%)	34.8% (31.9–37.9%)	31.7% (28.8–34.6%)	12.9% (11.0–15.1%)	41.2% (36.8–45.6%)
Female	37.8% (34.0–41.8%)	36.9% (33.1–40.9%)	33.1% (29.4–37.0%)	9.2% (7.0–11.8%)	27.8% (22.7–33.2%)

* Percentage of participants (n = 4,479)
§ Percentage of participants which have completed the primary series of 3 doses (n = 1,473)

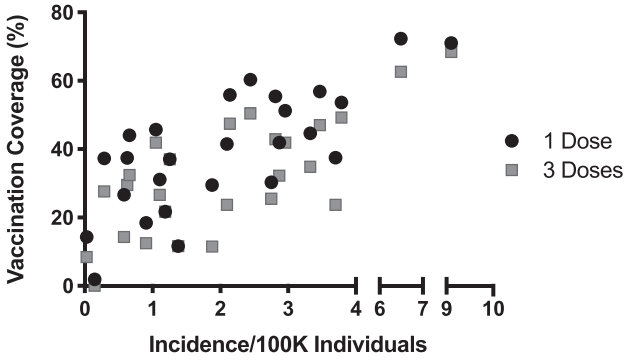

Fig. 2. Vaccination Coverage versus Average TBE Incidence by Canton - Average TBE incidence by canton was determined for the period between 2009 and 2018 and plotted against the percentage of respondents in each canton vaccinated with at least 1 or at least 3 doses of TBE vaccine. Pearson correlation coefficients were calculated for each pair using a two-tailed test. For 1 dose - Pearson r = 0.73, $p < 0.001$; For 3 doses - Pearson r = 0.75, $p < 0.001$.

likely to have received at least one dose of TBE vaccine (46% vaccinated who reported yes versus 37% vaccinated who reported no, Adjusted OR 1.2, Fig. 5, Table 4). Participants that reported being in nature 4 + times per month between the months of April and October (peak tick season) were significantly more likely to have received at least one dose of TBE vaccine (45% of individuals, Adjusted OR 1.7) compared to those reporting 1–3 nature days per month (29%) or being in nature "almost never" (21%). Additionally, participants reporting their perceived risk of contracting TBE to be "high" were significantly more likely to have received at least one dose of TBE vaccine (78% of individuals, Adjusted OR 12.7) compared to those who perceived their risk to be "middle" (50%) or "low" (22%) (Fig. 5, Table 4).

We additionally evaluated reasons for abstaining from TBE vaccination by asking participants to indicate which reason(s) had prevented them from being vaccinated: 1) at low risk; 2) not enough information about TBE; 3) not enough knowledge about the vaccine; 4) sceptical of vaccines in general; 5) not enough time; or 6) vaccine too expensive. We found that 43% of respondents listed "at low-risk" as a reason for abstaining from TBE vaccination.

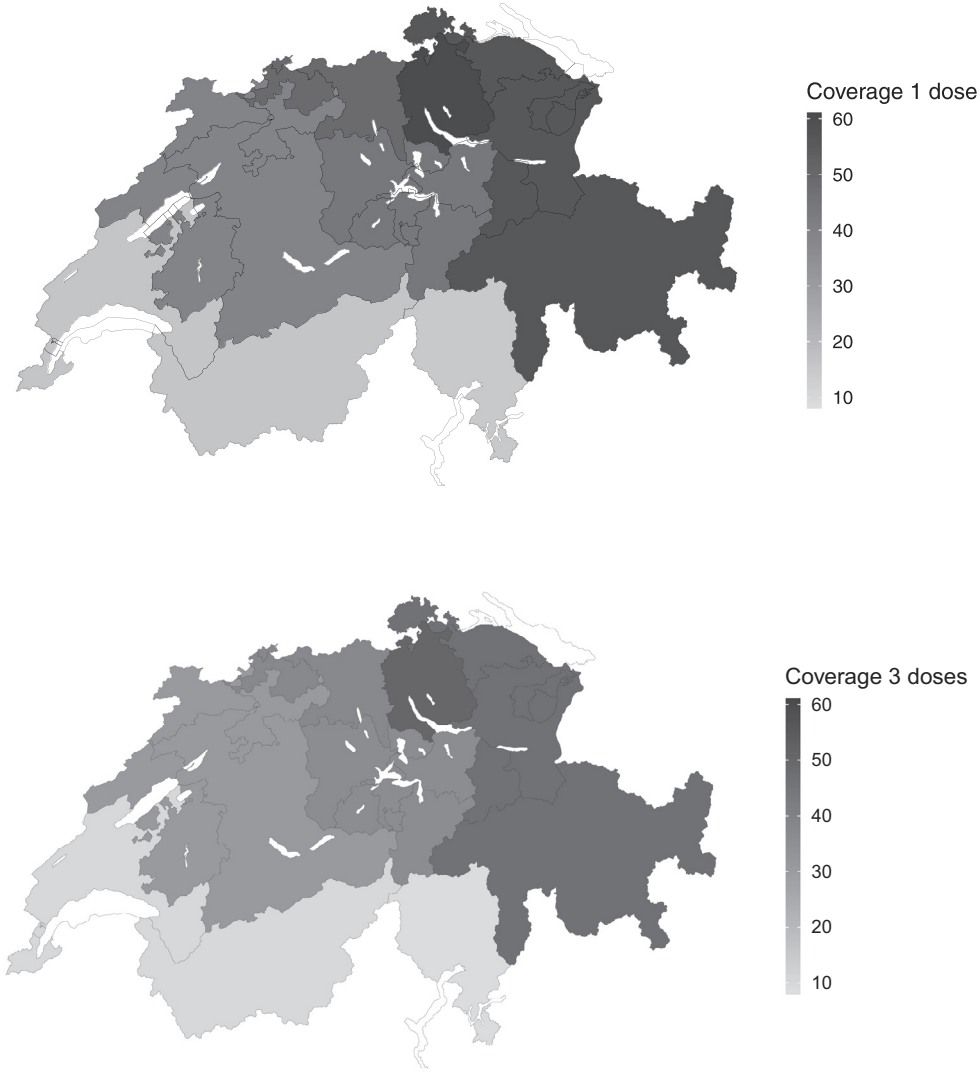

Fig. 3. Map of TBE Vaccination Coverage by Region - The percentage of respondents from each Swiss large region (Table 1) receiving at least 1 (top panel) or at least 3 (bottom panel) doses of TBE vaccine are shown.

Table 3
Estimated TBE Incidence Among Unvaccinated Adultsand Vaccine Effectiveness, 2018.

	Estimate	95% Confidence Interval
TBE Cases 18–79 (C_{tot}) [6]	314	–
TBE Vaccine Failure Rate (V_{fr}) [5]	4.0%	–
Fraction Population with 3 + TBE Doses (PPV)	32.9%	31.3–34.5%
Adult (18–79) Population, 2018 (P)*	6,570,644	–
Incidence Among Unvaccinated (I_{uv})**	6.83/ 100,000	5.97–7.81/100,000
Prevented Fraction in Population (PF_{pv})§	30.1%	28.6–31.6%
Prevented Cases in Population (PC)§§	135	112–162
Vaccine Effectiveness (VE)#	91.5%	90.9–92.0%

*2018 Population data from Swiss Federal Statistical Office
**Incidence Among Unvaccinated calculated as: $I_{uv} = (C_{tot} * (1 - V_{fr})) / ((1 - PPV) * P)$ and reported per 100,000 individuals
* Population data from Swiss Federal Statistical Office
** Incidence Among Unvaccinated calculated as: $I_{uv} = (C_{tot} * (1 - V_{fr})) / ((1 - PPV) * P)$ and reported per 100,000 individuals
§ Prevented Fraction in Population calculated as: $PF_{pv} = (((I_{uv} - (C_{tot} / P)) / I_{uv})$
§§ Prevented Cases in Population calculated as: $PC = P * I_{uv} * PF_{pv}$
# Vaccine Effectiveness calculated as: $VE = PF_{pv} / PPV$

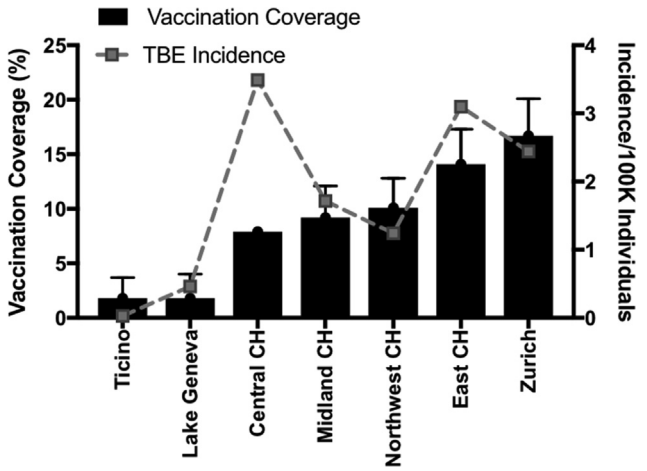

Fig. 4. TBE Booster Vaccination by Region - The left y axis shows the percentage of respondents in each Swiss large region having received at least one TBE booster vaccination (defined at 4 + vaccinations); the right y axis shows the average TBE disease incidence between 2009 and 2018 in each Swiss large region.

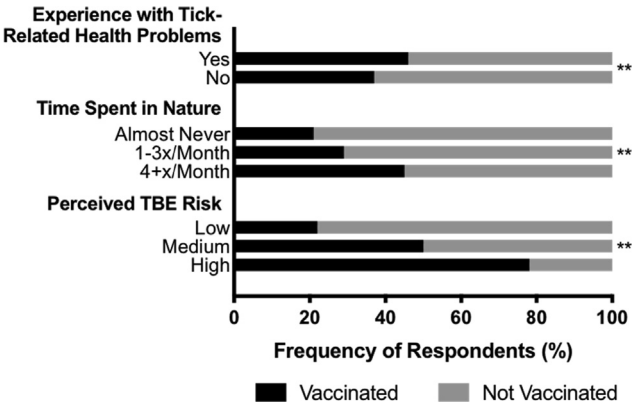

Fig. 5. Self-Reported Risk Factors and TBE Vaccination Status - Individuals were asked whether they or someone that the know had experienced tick-related health problems (yes or no), the amount of time that they spent in nature between April and October (almost never, 1–3 times a month or 4 + times a month), and what they perceived their personal risk of contracting TBE to be (low, medium, high). For each response, the percentage of individuals receiving at least 1 dose of TBE vaccine is indicated. For each question indicated on the y axis, frequencies of expected versus observed values were compared by Pearson's χ^2 test using the Rao & Scott adjustment. ** = $p < 0.01$ for each comparison.

40% of respondents listed "not enough information about TBE" and 32% of respondents listed "not enough knowledge about the vaccine". A further 32% listed that they were "sceptical of vaccines in general". Approximately 9% and 3% of individuals listed "not enough time" or "vaccine too expensive", respectively (Fig. 6).

4. Discussion

4.1. TBE vaccination coverage at the national level

In this nationwide, cross-sectional study we found that just over 40% of adult participants living in Switzerland have received at least 1 TBE vaccine dose, and that just under one-third have received at least 3 doses – thought to be necessary for establishing lasting immunity. In comparison, in Austria, which has the highest TBE vaccination rate in Europe, nearly 90% of the population has received at least one vaccine dose and nearly 60% have completed the primary series of 3 doses. Since the initiation of widespread vaccination campaigns in Austria in the early 1980s, annual disease incidence has declined substantially. Between 2000 and 2006

Table 4
Probabilities (Odds Ratio/Adjusted Odds Ratio) for Being Vaccinated with at Least 1 or 3 Doses of TBE Vaccine.

	Crude Odds Ratio (95% CI)		Adjusted Odds Ratio (95% CI)	
	≥ 1 Dose	≥ 3 Doses	≥ 1 Dose	≥ 3 Doses
Gender				
Male	1.28 (1.13–1.43)	1.13 (1.00–1.27)	Ref	Ref
Female	0.78 (0.70–0.88)	0.89 (0.79–1.00)	0.58 (0.50–0.68)	0.79 (0.67–0.93)
Age Group				
18–39	1.19 (1.04–1.35)	0.93 (0.81–1.06)	Ref	Ref
40–59	0.81 (0.71–0.91)	0.88 (0.78–0.99)	0.52 (0.43–0.63)	0.79 (0.65–0.97)
60–79	1.05 (0.93–1.19)	1.21 (1.07–1.37)	0.50 (0.41–0.60)	0.79 (0.64–0.96)
Experience with Tick-Related Health Problems				
Yes	1.78 (1.58–2.01)	1.92 (1.69–2.18)	1.21 (1.02–1.42)	1.32 (1.11–1.57)
No	0.56 (0.50–0.63)	0.52 (0.46–0.59)	Ref	Ref
Time Spent in Nature				
Almost Never	0.27 (0.17–0.43)	0.26 (0.15–4.45)	Ref	Ref
1–3 Times/Month	0.43 (0.36–0.52)	0.41 (0.34–0.50)	1.04 (0.53–2.05)	0.95 (0.46–1.99)
4 + Times/Month	2.58 (2.18–3.06)	2.68 (2.23–3.23)	1.72 (0.91–3.28)	1.50 (0.74–3.02)
Self-Perceived TBE Risk				
High	7.01 (5.72–8.60)	6.24 (5.18–7.51)	12.65 (9.48–16.88)	11.09 (8.46–14.53)
Middle	1.99 (1.76–2.24)	1.86 (1.64–2.11)	3.38 (2.82–4.04)	3.57 (2.92–4.36)
Low	0.17 (0.15–0.20)	0.16 (0.14–0.19)	Ref	Ref

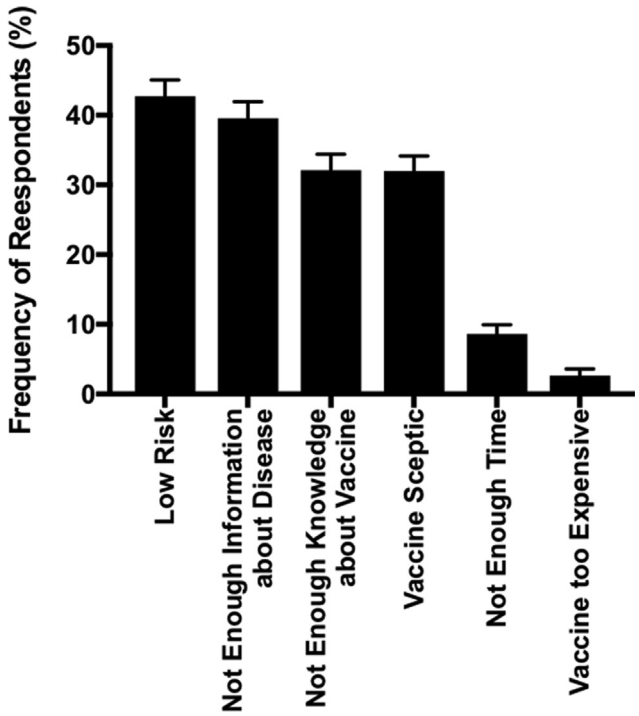

Fig. 6. Self-Reported Reasons for Abstaining from TBE Vaccination - From a list of possibilities (x axis) individuals who had not been vaccinated for TBE (as confirmed by vaccination card) were asked to indicate why they had not been vaccinated with more than one answer possible. Percentages of individuals indicating each response are given.

alone, TBE vaccination in Austria was estimated to have prevented 2800 cases of illness and 20 deaths [15–17]. In contrast, in Switzerland, annual TBE incidence has continued to increase over the last decades, despite vaccination efforts.

4.2. Demographic differences

When considering demographics, we found that coverage at 1 and 2 doses was significantly higher among males aged 18–39 than for other age/gender groups. In Switzerland, an 18-week military service is compulsory for young males and vaccinations are provided as part of basic training. During this time individuals could potentially receive the first two TBE immunizations. This could explain the increased vaccination coverage in this group for doses 1 and 2, but not dose 3, which is given 5–12 months after the second.

While individuals between the ages of 60 and 79 have the highest average disease incidence in Switzerland, vaccination coverage was not significantly higher among study participants in this age group compared to younger individuals, who have a substantially reduced disease incidence. In an Austrian study, vaccination rates tended to be lower in individuals $\geq$ 60 compared to those 16–49 and 50–59 [16], while, in contrast, two Swedish studies demonstrated that those $\geq$ 60–65 tended to be better vaccinated than younger adults and children [18,19] These conflicting findings suggest that, despite increased risk, age is not necessarily a consistent driver of TBE vaccination.

4.3. Regional variation

We further found that vaccination coverage varied widely throughout Switzerland with coverage at the cantonal level ranging from approximately 8–70% and approximately 14–60% at the large region level. In both cases, coverage was higher in areas where vaccination was recommended for residents (as of 2018) by the FOPH due to TBE risk. There was a significant correlation between average TBE incidence and TBE vaccination coverage by canton at both $\geq$ 1 and $\geq$ 3 doses. These findings support the idea that FOPH recommendations, as well as potentially increased TBE awareness among healthcare providers, the public, or both, help to promote vaccine uptake. A follow-up study to investigate the influence of the recent 2019 change in national TBE vaccination recommendations on vaccination uptake is warranted, especially with the further rise in reported TBE cases in 2020 [6]. Importantly, while national policy changes impact TBE vaccine uptake, cantonal differences in the implementation of these policies could be a source of variability in coverage. For example, 21 of 26 cantons permit vaccination in pharmacies, and only 19 of these offer TBE vaccination [20].

4.4. TBE incidence among Unvaccinated, prevented Cases, and vaccine Effectiveness

It is further worth noting that TBE incidence, both at the national and cantonal levels, has continued to increase despite vaccination efforts, suggesting that immunization based on risk areas alone may not be enough to protect from disease. We estimated 2018 TBE incidence among unvaccinated adults at 6.83 cases/100,000 compared to 4.37 cases/100,000 for all (vaccinated and unvaccinated) individuals. We further estimated that, as a result of vaccination, 112–162 TBE cases were prevented among adults 18–79 in Switzerland in 2018 alone. Although our analysis was not comprehensive, and we did not have access to raw case data and, therefore needed to make several assumptions, we estimated Vaccine Effectiveness at 90.9–92.0%, which is in line with the more systematic analysis performed by Heinz et al [17]. At the cantonal level we found that 16, rather than 10, cantons exceeded the WHO definition of a "highly endemic" area ($\geq$5.0 cases/100,000 individuals), representing more than 60% of the adult population. Together, these findings indicate that many individuals remain at risk for TBE and that substantially more adults should be vaccinated in order to reduce disease incidence.

4.5. Population-Level protection

While we found that vaccination coverage is higher in endemic areas, coverage at $\geq$ 3 doses exceeded half of the adult population in only two cantons suggesting that a large proportion of the population remains susceptible to TBE, even in areas where TBE is a significant risk. When we considered whether participants were "current" for TBE vaccination, we found that less than one-quarter met these criteria and could be assumed to have protective immunity. For comparison, just over 40% of the population resides in the 10 cantons that, in 2018, fell within the WHO definition of a "highly endemic" area and just over 80% of the population resides in the 17 cantons with known TBE-endemic areas (and FOPH TBE vaccination recommendations as of 2018) [6,12].

4.6. Impact of disease perceptions and attitudes

Of the three areas examining perception and knowledge that might influence TBE vaccination uptake, we found that risk perception was the most significantly correlated, with participants reporting a "high" perceived risk of contracting TBE nearly 13 times more likely to have received at least one dose of TBE vaccine compared to those who estimated their risk to be "middle" or "low". Furthermore, low risk perception, along with lack of knowledge, was cited as the most frequent reason for not getting a TBE vaccination. In a recent survey conducted in 11 European coun-

tries, the strongest motivators for TBE vaccination were fear of disease (38%) and residence or time spent in high-risk areas (31–35%), while vaccination coverage studies in Sweden found an increased likelihood of being vaccinated among those reporting $\geq$ 2 weeks of outdoor exposure in known risk areas or frequent visits to forests or other areas with TBE risk [16,19,21]. In the same studies, the major reasons for not receiving vaccination were the beliefs that vaccination was unnecessary (33%), that there was no risk of contracting disease (23%) [16] and lack of perceived risk (29%) [19]. However, more individuals listed lack of time (23%) and vaccine expense (26%) as reasons for not being vaccinated compared to in our study (9 and 3%, respectively) [19]. Although cost does not appear to be a major factor in not receiving TBE vaccination in Switzerland at the national level, this effect may vary by region as vaccine costs are only reimbursed by compulsory health insurance in FOPH-recommended areas. Taken together, these findings support the positive impact of awareness of health consequences and risk perceptions and behaviours on TBE vaccination and compliance, suggesting that public health interventions promoting such knowledge might be beneficial in improving vaccine compliance not only in Switzerland, but also in countries searching for methods to combat the same problem.

5. Limitations

An important limitation in this study was the participation rate. Approximately 17% of contacted individuals submitted both a completed questionnaire and a vaccination record, which is low, but not unusual for a study design based on response by mail. While we obtained a high enough response rate to evaluate coverage at the regional level (as per our study design), responses were not sufficient to extend all analyses to the cantonal level. Furthermore, participation was highest among individuals aged 60–79 (35.5%, Table 1) although this group represents the smallest portion of the adult Swiss population (24.9%). Similarly, participation was lowest in those 18–39 (29.9% of adults) although this group is nearly as large as those 40–59 (37.2% of adults), demographically speaking. To adjust for this, data were post-stratified prior to analysis. Moreover, although the sampling frame used is comprehensive, it is not exhaustive and there were inaccuracies in the list of addresses used to contact individuals based on household movement, deaths, etc. Approximately 3% of the letters were returned as "undeliverable" suggesting that this represents a relatively small fraction of the overall sample.

Such a study design also comes with the risk that individuals interested in a topic are more likely to participate. It is possible that individuals that have been vaccinated for TBE, those having some previous knowledge of TBE disease, or those with increased risk due to occupation or other exposure to ticks, were more likely to participate than those that have not been vaccinated, were not aware of illness caused be TBEV, or who had a lower risk of exposure. In this case, vaccination coverage would appear artificially high, as would the frequency of individuals reporting some previous knowledge of TBE or tick-borne disease. From a separate analysis of the complete set of 8,192 questionnaires that we received, we found that individuals reporting that they had not been vaccinated were more likely to not submit a vaccination card, compared to individuals who did report being vaccinated (data not shown). Similarly, the percentage of individuals reporting via questionnaire that they had been vaccinated was lower among those submitting only a questionnaire compared to those submitting both a questionnaire and a vaccination record (35% versus 42%, data not shown), indicate some level of bias in our study. Moreover, the use of an incentive to increase participation may have introduced an additional bias.

A further limitation of this study is that the use of a cross-sectional design allows only correlations, but no causal effects to be determined. A nationwide vaccination registry would be ideal for rapid and accurate assessment of vaccination uptake. Unfortunately, such a representative registry is not yet available in Switzerland. Consequently, personal vaccination records are currently used to collect and evaluate vaccination data. However, despite being completed by healthcare providers, vaccination records may contain errors, or they may be incomplete (i.e. if an individual does not bring their record to a vaccination appointment or update it afterward). Regarding our estimation of protection from TBE, as we did not collect serum to evaluate TBEV antibody titres, we could only estimate protection based on vaccination history, assuming that 3 doses were and boosters at appropriate intervals where necessary and sufficient for seropersistence (Reviewed in [22]).

6. Conclusions

Vaccination coverage in Switzerland is highly variable between regions, highlighting the impact of heterogeneous disease incidence and corresponding heterogeneous vaccination recommendations and implementations at the cantonal level. Despite the trend toward increasing disease incidence over the last decades, only a third of adults in Switzerland have completed the primary TBE vaccination series. Public health interventions focusing on awareness of health consequences and risk perceptions and behaviours will be effective in improving TBE vaccination coverage.

Declaration of Competing Interest

PL received monetary compensation for a presentation at a Pfizer training workshop; Pfizer also covered her cost to attend the ISW-TBE meeting (International Scientific Working group on TBE) in 2019. All other authors have no other conflicts of interest to declare.

Acknowledgements

We would like to thank Anna Fraefel, Carlotta Superti-Furga and Stefan Olarte for their help with data collection and organization during the study, Sarah Haile for statistical consultation and Monika Kotur for critical reading of this manuscript. This study was supported by a grant from Pfizer WI233989. The funders had no role in the design, implementation or evaluation of the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.10.022.

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