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Effectiveness of TBE vaccination in southern Germany and Latvia

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ABSTRACT

Background: Tick-borne encephalitis (TBE) is a vaccine-preventable disease which may cause long-term sequelae and even death. The data on the long-term effectiveness of TBE vaccines are limited. Additionally, the vaccination schedule is complex which in part contributes towards sub-optimal uptake in TBE-endemic areas. The current ecological study measures vaccine effectiveness (VE) in two European countries.

Methods: TBE VE was measured from 2007 to 2018 in Latvia and Southern German states by age group, vaccination history, and schedule compliance. TBE cases and vaccination history were obtained from the public health agencies for Latvia and the southern German federal states of Bavaria and Baden-Wuerttemberg. Cases were "within schedule" if a TBE infection was diagnosed within the time interval preceding the next scheduled dose and "outside schedule" if the diagnosis occurred after the next scheduled dose. Vaccine uptake was estimated via representative nationwide surveys.

Results: VE after 2, 3, and $\geq$4 doses was high in both countries at 97.2%, 95.0%, and 95.4% for southern Germany, and 98.1%, 99.4%, and 98.8% for Latvia while within- schedule, and only showed marginal differences outside schedule at 90.6%, 89.9%, and 95.6% for southern Germany, and 97.4%, 98.4%, and 99.0% for Latvia regardless of age groups.

Conclusions: In both countries, VE after two and three primary doses within-schedule was very high in all age groups. Once receiving booster doses, high VE continued to be observed even in persons with extended intervals since the last dose received, suggesting that longer and more flexible booster intervals may be considered for sustainable long-term protection.

1. Introduction

Tick-borne encephalitis (TBE) is a vaccine-preventable vector-borne disease caused by a flavivirus (TBE virus, TBEV) that can cause long-term neurological sequelae and death. It is transmitted to humans by ticks, or rarely by consumption of unpasteurised dairy products.

The TBEV is known to circulate in the non-tropical Eurasian forest belt. Based on sequence homology the European (TBEV-EU), the Siberian (TBEV-SIB) and the Far Eastern (TBEV-FE) subtypes can be differentiated [1–3] with a case fatality rate of 1–2%, 6–8% and up to 20% respectively [4].

The overall disease burden is underestimated as diagnostic testing is not universally implemented or even available in many affected countries [4]. Further, the European Centres for Disease Control and Prevention (ECDC) utilizes a conservative case definition of TBE—only considering persons with serologically confirmed TBE infection [5] having clinical (hospital-based) manifestation of inflammation of the CNS—therefore, many non-CNS cases likely remain unreported. Official reporting in western Europe has identified between 4379 and 7350 cases annually from 2007 to 2020 [6]. Overall, the number of reported TBE cases in Europe has increased by up to 193.2% in the last 30 years [7], which is thought to be associated with the emergence of new endemic areas, increased awareness and testing, and changes in working and leisure time activities that have increased exposure.

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No specific treatment for TBE is available to date and this is why prevention by vaccination is recommended by local and national health authorities, the ECDC, and the World Health Organization (WHO), for anyone living in, or travelling to, highly endemic areas [8,9]. Two vaccines are available in western Europe, FSME-IMMUN (Pfizer) and Encepur (Bavarian Nordic, formerly GSK). Although licensing had been accomplished through studies of the respective vaccine-seed virus as the antigen to document seroconversion, geometric mean antibody titres and seropersistence [10,11], the final proof for the success of vaccines depends on the evaluation of their effectiveness in the field which is outlined in the European Medicines Agency (EMA) Guideline on Clinical Evaluation of Vaccines [12]. The only population-based TBE-vaccine effectiveness (VE) calculations so far were performed in Austria, a country with an especially high vaccine coverage, indicating high effectiveness in all age groups [13,14]. However, it has been suggested that an inferior vaccine response, as measured by antibody titres or neutralisation tests, may possibly lead to vaccine breakthrough disease, particularly with increasing age [15–17].

The purpose of this study was to investigate the VE of TBE vaccination by doses received in Germany and Latvia, where TBE is highly endemic and TBE vaccine coverage rates are lower as in Austria. Germany is the most populous western European country, of which the southern German federal states of Bavaria and Baden-Wuerttemberg (hereafter named "southern Germany") bear the greatest burden of TBE. And in Latvia all three major TBEV subtypes are known to circulate [18]. Additionally, this study examines whether the first two doses are sufficient to provide short term (seasonal) protection for travellers to risk areas, and whether age or adherence to the recommended timing of doses [19] influence the calculated VE.

2. Methods

Data used for calculating VE were: (1) annual numbers of reported TBE cases confirmed by laboratory diagnosis, (2) vaccination history of these cases, (3) estimated TBE vaccine uptake and schedule adherence data, and (4) population estimates. TBE cases were defined as any serologically confirmed TBE infection following the ECDC definition [5] and the country specific (German, Latvian) diagnostic criteria and definitions, irrespective of clinical presentation.

2.1. TBE cases

All TBE cases for the period from 2007 to 2018 reported in southern Germany and Latvia were collected by the German federal state health authorities of Bavaria and Baden-Wuerttemberg and the Centre for Disease Prevention and Control of Latvia (CDPC), respectively. These health authorities also provided aggregated counts by age group, vaccination status, vaccine doses, and schedule adherence for this study.

The Robert Koch Institute (RKI), which collects mandatory reported TBE cases in Germany [20], has classified southern Germany as TBE endemic. [21–32]. TBE has been a notifiable disease in Latvia since 1973 and all cases are reported to the CDPC.

Both countries report all laboratory confirmed TBE infections, including cases with any non– CNS specific symptoms (so-called "febrile forms"). In Latvia, about a quarter of hospitalized patients with serologically confirmed TBEV infection were without any clinical signs of CNS disease, however hospitalization was warranted due to fever, malaise, and no other symptom of CNS contribution than headaches [33]. Approximately half of such cases were without CNS disease in Germany. Demographics and vaccination history were obtained via a questionnaire sent out and/or an interview by the responsible local public health offices [20,21–32].

2.2. TBE vaccination schedule

The standard vaccination schedule consists of up to 6 dosing intervals for an individual. The primary series consists of two doses administered 1–3 months apart followed by a third dose either 5 or 9–12 months thereafter (depending on the product). After receipt of the third dose, the primary series is considered "complete". The first booster (4th) dose is recommended 3 years after the completion of the primary series. Subsequent booster doses are administered in 5-year intervals until the age of 50, for Encepur, or 60, for FSME-IMMUN, after which the booster interval decreases to every three years to account for immunosenescence.

If a vaccinated individual was diagnosed with TBE, the time between the most recent dose received and the diagnosis date was calculated. If the time was within the recommended interval until the next scheduled dose, the case was classified as "within schedule". If the time exceeded the recommended timing for the next scheduled dose, the case was classified as "outside schedule". For example, a 75-year-old patient diagnosed with TBE with a history of 8 doses who had received the most recent booster dose 8 years prior to the TBE diagnosis would be classified as "outside schedule". However, if the most recent dose was only 2 years prior, then the case would be "within schedule".

According to the Summary of Product Characteristics (SPC) for FSME-IMMUN, two doses can provide a sufficient level of protection preceding a tick season, though optimal protection is expected with completion of the 3-dose primary series and booster doses at recommended intervals [34]. Therefore, VE was calculated for individuals having received $\geq$2 vaccine doses. Individuals who only received one dose were excluded from the analysis. Similarly, if vaccination history could not be determined for a TBE case, the case was excluded from VE calculations.

2.3. TBE vaccine uptake

TBE vaccine uptake was estimated via nationwide surveys, which have been detailed in a previous publication [19]. Briefly, participants were recruited via online panels and completed questionnaires at home. Respondents were asked to utilise documentation of vaccination (*eg*, vaccination cards) to verify entries for questions related to vaccine uptake (*ie,* doses received and schedule adherence). Participants were broadly representative of the respective country in terms of age, region, and gender, but outcome measures were weighted accordingly to account for sampling variability.

2.4. VE calculation and statistical analysis

Vaccine breakthrough cases were defined as patients with documented TBE despite having received $\geq$2 vaccine doses at least 2 weeks prior to onset of disease symptoms, and with the last dose given within the guidance of the vaccine label.

Available data were stratified by: (1) the number of TBE doses administered (0 for unvaccinated, 2, 3, and $\geq$4); (2) age group (0–17, 18–59, $\geq$60) and (3) adherence to the vaccination schedule as outlined above based on the time interval from administration of the last vaccine dose to the onset of disease (within schedule versus outside schedule).

VE was calculated applying the general formula $VE = 100 \times \left(1 - \frac{I_v}{I_n}\right)$ where I_v and I_n are the annualized incidences in vaccinated and not vaccinated, respectively. Confidence inter-

vals (CIs) were calculated for significance testing at 95% using the Wald method [35].

3. Results

TBE case numbers showed marked annual fluctuations. Southern Germany reached peak levels in 2018 and also 2020 (2020 data not shown in the Figure) while cases in Latvia had decreased by 59% since its peak in 2010 (Fig. 1). A total of 4040 TBE cases had been reported over the 12-year observation period nationally in Germany, of which Bavaria and Baden-Wuerttemberg contributed 3446 (85%) of cases. Of these 3446 cases, 127 (3.7%) did not have a vaccinated vs. unvaccinated status, while a further 42 (1.2%) had an unknown number of TBE vaccine doses or the dose dates could not be determined. After removal of these 169 cases (4.9%), there were 3277 cases left with complete vaccination history available. Among these, 3010 TBE cases (91.9%) occurred among unvaccinated patients, while 267 (8.1%) cases were among patients who had received one or more TBE vaccine dose ever. Of the 267 cases, 77 (28.8%) had only ever received a single dose, leaving 190 breakthrough cases for our analysis.

In Latvia, there were 3106 TBE cases reported for the 12-year period, of which 4 (0.1%) did not have a vaccinated vs. unvaccinated status, and an additional 4 (0.1%) were known to be vaccinated, but the number of doses or vaccination dates could not be determined. After excluding these 8 cases (0.26%), there were 3098 cases included in the analysis. Of these, 3044 (98.3%) occurred among patients who did not have a record of any TBE vaccination, while 54 (1.7%) cases had received at least one TBE vaccine dose at any time. Of the 54 cases, 7 (13.0%) had a single vaccine dose only, leaving 47 breakthrough cases for analysis.

Approximately 24.1 million people lived in southern Germany in 2018 with 9.7 million unvaccinated (people never received any dose of a TBE vaccine); the annualized incidence of TBE among the unvaccinated was 2.57 per 100,000 population (Table 1a). Of the 1.9 million people who lived in Latvia in 2018, 0.8 million remained unvaccinated and the annualized incidence of TBE among the unvaccinated was 31.7 per 100,000 population (Table 1a).

Overall TBE vaccine effectiveness (VE) for vaccinated persons (≥2 doses), irrespective of age group or time since the most recent dose, was 93.9% (95% CI: 92.9–94.7%) in southern Germany and 98.6% (95% CI: 98.2–99.0%) in Latvia. For those who had received only the first 2 doses of the primary series, completed the primary series (prior to starting booster doses), or had at least one booster dose, the VEs were outlined in Table 1a, 1b, and 1c respectively.

For southern Germany, overlapping 95% Cis were observed by age for those who had received only the first 2 doses (Table 1a) or had received at least one booster dose (Table 1c). However, for those who had only completed the primary series without any booster doses, the ≥60 year olds age group had lower VE compared to 18–59 year olds (Table 1b). For Latvia, overlapping 95% CIs were observed by age for those who had only completed the primary series without any booster doses or who had received at least one booster dose. For those who had only received the first 2 doses, a lower VE was observed among ≤17 year olds compared to older age groups. (Table 1a).

When the time of the most recent dose an individual had received prior to TBE diagnosis extended beyond the recommended interval of the next scheduled dose (*ie.* "outside schedule"), VE in southern Germany was found to be lower. Of those who had received only the first 2 doses of the primary series, the VE was 97.2% (95% CI: 94.9–98.4%) for those within schedule versus 90.6% (95% CI: 87.7–92.8%) for those who were not (Table 1a). Similarly, for those who had completed the 3 dose primary series, but have not yet received any booster doses, the VE was 95.0% (95% CI: 92.8–96.5%) and 89.9% (95% CI: 86.5–92.5%) for those who were within schedule versus those who were not respectively (Table 1b). Although examination by age groups found these schedule compliance-associated differences among the age groups of 18–59 year olds and ≥60 year olds in Southern Germany, individuals whose last dose was a booster (≥4 doses, Table 1c) exhibited overlapping 95% CIs regardless of schedule compliance. Time since the last dose did not show any significant differences in Latvia for any age groups (Tables 1a, 1b, 1c).

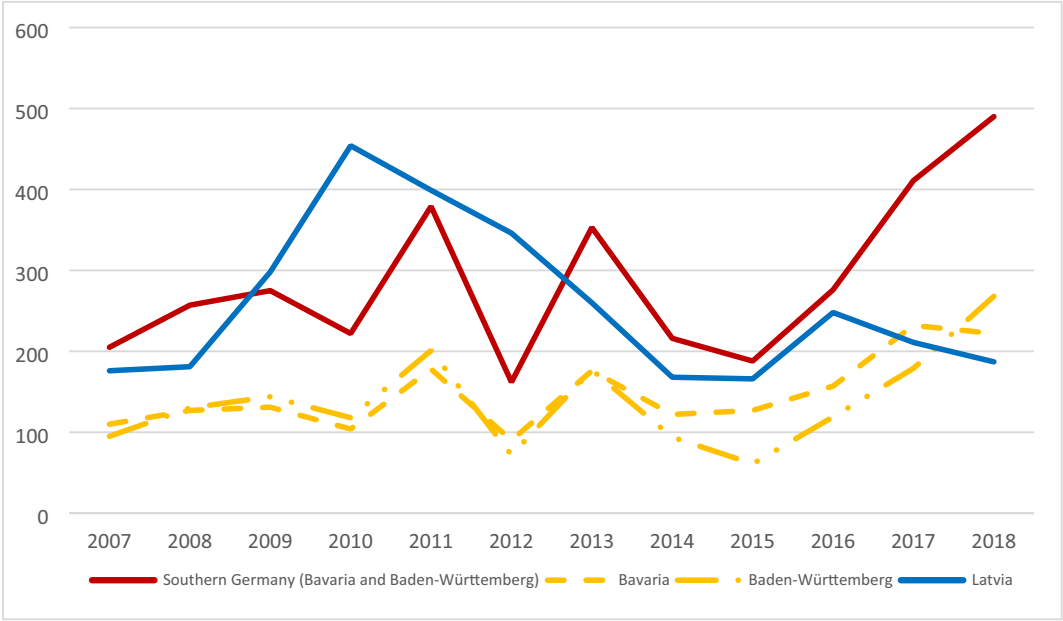

Fig. 1. Total TBE cases in Bavaria, Baden-Wuerttemberg (individually and combined; "southern Germany"), and Latvia (2007–2018).

Table 1a
Comparisons of TBE vaccine effectiveness (VE) in southern Germany and Latvia by vaccination history (2 doses only), schedule timing, and by age groups (2007–2018).

Age Group / Schedule Compliance	Unvaccinated			Last Dose Received Second Dose w/o Subsequent Third (2 Doses Only)				
	Pop.	TBE Cases	Annual Inc.	Pop.	TBE Cases	Annual Inc.	VE (%)	95% CI
SOUTHERN GERMANY *(Bavaria and Baden-Württemberg)*								
All ages	9,747,843	3010	2.57	3,123,015	65	0.17	93.3	91.4–94.7
Within schedule				1,259,861	11	0.07	97.2	94.9–98.4
Outside schedule				1,863,154	54	0.24	90.6	87.7–92.8
≤17 years old	1,422,456	294	1.72	560,227	9	0.13	92.2	84.9–96.0
Within schedule				317,262	4	0.11	93.9	83.6–97.7
Outside schedule				242,965	5	0.17	90.0	75.9–95.9
18–59 years old	5,589,398	1857	2.77	1,924,410	44	0.19	93.1	90.7–94.9
Within schedule				697,843	6	0.07	97.4	94.2–98.8
Outside schedule				1,226,567	38	0.26	90.7	87.1–93.2
≥60 years old	3,064,222	859	2.34	693,935	12	0.14	93.8	89.1–96.5
Within schedule				302,703	1	0.03	98.8	91.6–99.8
Outside schedule				391,232	11	0.23	90.0	81.8–94.5
LATVIA								
All ages	800,481	3044	31.69	179,156	16	0.74	97.7	96.2–98.6
Within schedule				69,054	5	0.60	98.1	95.4–99.2
Outside schedule				110,101	11	0.83	97.4	95.3–98.5
≤17 years old	153,895	163	8.83	49,108	6	1.02	88.5	73.9–94.9
Within schedule				34,575	3	0.72	91.8	74.3–97.4
Outside schedule				14,533	3	1.72	80.5	38.9–93.8
18–59 years old	424,119	2002	39.34	97,930	10	0.85	97.8	97.4–99.7
Within schedule				23,201	2	0.72	98.2	97.0–99.4
Outside schedule				74,728	8	0.89	97.7	98.4–99.5
≥60 years old	222,467	879	32.93	17,960	0		100.0	
Within schedule				1885	0		100.0	
Outside schedule				16,075	0		100.0	

Table 1b
Comparisons of TBE vaccine effectiveness (VE) in southern Germany and Latvia by vaccination history (3 doses only), schedule timing, and by age groups (2007–2018).

Age Group / Schedule Compliance	Unvaccinated			Last Dose Received Primary Series Completion (3 Doses Only)				
	Pop.	TBE Cases	Annual Inc.	Pop.	TBE Cases	Annual Inc.	VE (%)	95% CI
SOUTHERN GERMANY *(Bavaria and Baden-Württemberg)*								
All ages	9,747,843	3010	2.57	3,366,349	75	0.19	92.8	90.9–94.3
Within schedule				1,886,192	29	0.13	95.0	92.8–96.5
Outside schedule				1,480,157	46	0.26	89.9	86.5–92.5
≤17 years old	1,422,456	294	1.72	619,308	7	0.09	94.5	88.4–97.4
Within schedule				309,654	4	0.11	93.8	83.2–97.7
Outside schedule				309,654	3	0.08	95.3	85.4–98.5
18–59 years old	5,589,398	1857	2.77	1,932,003	41	0.18	93.6	91.3–95.3
Within schedule				1,165,951	11	0.08	97.2	94.9–98.4
Outside schedule				765,208	30	0.33	88.2	83.1–91.8
≥60 years old	3,064,222	859	2.34	696,673	27	0.32	86.2	79.7–90.6
Within schedule				420,437	14	0.28	88.1	79.9–93.0
Outside schedule				275,931	13	0.39	83.2	70.9–90.3
LATVIA								
All ages	800,481	3044	31.69	308,420	13	0.35	98.9	98.1–99.4
Within schedule				163,621	4	0.20	99.4	98.3–99.8
Outside schedule				144,799	9	0.52	98.4	96.9–99.2
≤17 years old	153,895	163	8.83	62,656	2	0.27	97.0	87.8–99.3
Within schedule				52,587	1	0.16	98.2	87.2–99.7
Outside schedule				10,050	1	0.83	90.6	32.9–98.7
18–59 years old	424,119	2002	39.34	171,273	9	0.44	98.9	97.9–99.4
Within schedule				75,837	3	0.33	99.2	97.4–99.7
Outside schedule				95,506	6	0.52	98.7	97.0–99.4
≥60 years old	222,467	879	32.93	282,915	2	0.23	99.3	97.2–99.8
Within schedule				205,832	0	0.00	100.0	
Outside schedule				77,083	2	0.33	99.0	96.0–99.7

4. Discussion

The objective of the present study was to calculate VE of TBE vaccination using population-based surveillance data from the southern German federal states Bavaria and Baden-Wuerttemberg, and from Latvia, covering the 12 years from 2007 to 2018. While disease incidences in unvaccinated persons differed by more than a log fold between these two countries (2.57 per 100,000 population in Germany, 31.69 per 100,000 population in Latvia), overall VE estimates in individuals with ≥ 2 doses were high in both countries with 94% in southern Germany and 99% in Latvia. Importantly, when stratified by age groups, doses of TBE vaccine received, and adherence to recommended dosing intervals (based on the time from the most recent dose until the TBE diagno-

Table 1c
Comparisons of TBE vaccine effectiveness (VE) in southern Germany and Latvia by vaccination history (≥4th doses), schedule timing, and by age groups (2007–2018).

Age Group / Schedule Compliance	Unvaccinated			Last Dose Received Any Booster Dose (≥4th Dose)				
	Pop.	TBE Cases	Annual Inc.	Pop.	TBE Cases	Annual Inc.	VE (%)	95% CI
SOUTHERN GERMANY *(Bavaria and Baden-Württemberg)*								
All ages	9,747,843	3010	2.57	3,530,490	50	0.12	95.4	93.9–96.5
Within schedule				2,650,748	38	0.12	95.4	93.6–96.6
Outside schedule				878,303	12	0.11	95.6	92.2–97.5
≤17 years old	1,422,456	294	1.72	702,487	8	0.09	94.5	88.9–97.3
Within schedule				525,246	5	0.08	95.4	88.9–98.1
Outside schedule				177,241	3	0.14	91.8	74.5–97.4
18–59 years old	5,589,398	1857	2.77	2,717,459	24	0.07	97.3	96.0–98.2
Within schedule				1,878,008	18	0.08	97.1	95.4–98.2
Outside schedule				839,451	6	0.06	97.8	95.2–99.0
≥60 years old	3,064,222	859	2.34	979,905	18	0.15	93.4	89.5–95.9
Within schedule				677,202	15	0.18	92.1	86.8–95.3
Outside schedule				302,703	3	0.08	96.5	89.0–98.9
LATVIA								
All ages	800,481	3044	31.69	407,183	18	0.37	98.8	98.2–99.3
Within schedule				298,215	14	0.39	98.8	97.9–99.3
Outside schedule				108,968	4	0.31	99.0	97.4–99.6
≤17 years old	153,895	163	8.83	35,483	2	0.47	94.7	78.5–98.7
Within schedule				34,053	1	0.24	97.2	80.2–99.6
Outside schedule				1,430	1	5.83	34.0	−371.2–90.8
18–59 years old	424,119	2002	39.34	282,915	12	0.35	99.1	98.4–99.5
Within schedule				205,832	9	0.36	99.1	98.2–99.5
Outside schedule				77,083	3	0.32	99.2	97.4–99.7
≥60 years old	222,467	879	32.93	107,312	4	0.31	99.1	97.5–99.6
Within schedule				65,489	4	0.51	98.5	95.9–99.4
Outside schedule				41,823	0	0.00	100.0	

sis), VE rarely fell below 90%. The implications of these findings are significant for the efficient prevention of TBE and are examined in context below.

4.1. Vaccine effectiveness overall

Though southern Germany exhibited a lower VE as compared to Latvia, the breakthrough rate was within margins of previous publications [13,14,36]. Further, these data are consistent with prior studies in Austria that found overall VE between 93 and 98% [13,14]. The high VE, especially in Latvia is reassuring, as all 3 TBEV subtypes (European, Siberian and Far-Eastern), against which vaccines have to be protective, are circulating [1–3].

Several considerations may be given to why the VE in Latvia is higher than in southern Germany. One might speculate that the differences in VE calculation between Latvia, southern Germany and Austria may be due to the quite different number of reported febrile cases without CNS symptoms between these regions. About a quarter cases in Latvia [33] and approximately half of the reported cases in Germany [20] were without any CNS symptoms. In contrast, in Austria almost no cases with only febrile disease were documented, which could be due to the high vaccination rate and therefore little suspicion of TBE in febrile disease, especially in the childhood population. Hence the Austrian VE calculation covers TBE infections with CNS symptoms only [13,14]. Future analyses are needed to explore the impact of disease severity in the context of age, compliance to the schedule and vaccination history on VE estimation. VE might be different in persons who get their primary vaccine course in childhood versus at an older age. This question has never been addressed so far, but in southern Germany paediatricians are more reserved on vaccination of children than maybe in Latvia. Also, the place of vaccination maybe considered. In Germany TBE vaccination is primarily provided by general practitioners as there are no vaccination centers or specialized vaccination ambulances.

Prior studies have suggested a major risk factor for vaccine breakthrough is only receiving the first 2 doses of the 3-dose primary series [37,38]. Similarly, a serological study observed a dose-dependent relationship where subjects with only 3 doses experienced a ∼15% decrease of geometric mean titers measured by the neutralization test annually, while subjects with ≥4 doses had annual decline rates of only ∼1% [39]. However, in our real-world field effectiveness measurement, we found consistently high VEs ranging from 95% to 99% (with overlapping 95% CI) in both countries among those who had only 2, only 3, or ≥4 doses with the most recent dose received within recommended dosing intervals. This is an important finding supporting results from Austria [14] that the first two doses of the basic immunization schedule may effectively provide short term protection (e.g., for travelling into endemic areas). Further, future studies could examine the protection provided after only 2 doses for laboratory workers who are challenged with a potential exposure to higher viral loads and via different media (e.g., aerosol, percutaneous).

4.2. Vaccine effectiveness by age

Age is said to be another predictive parameter for lower post-vaccination titres, earlier loss of antibodies, and consequently a higher vaccination failure rate in elderly vaccinated persons [37,38,40], for whom the risk of severe forms of TBE and sequelae appears to be highest. For this reason, it has been suggested to add an extra priming dose in the age group of 50 years or older [37,38]. Although our data demonstrated that VE rates for those who had ≥2 doses were consistently high across all age groups, we did observe lower VE for older adults in southern Germany for those who had only completed the primary series (86.2% [95% CI: 79.7–90.6%] versus 93.6% [95% CI: 91.3–95.3%] for 18–59 year olds), as well as for children and adolescents in Latvia for those who had only received the first 2 doses of the primary series (≤17 year olds: 88.5% [95% CI: 73.9–94.9%]; 18–59 year olds: 97.8% [95% CI: 97.4–99.7%]; ≥60 year olds: 100%). However, these differences were no

longer observed (confidence limits overlapped) at completion of the 3-dose primary series in Latvia, and once individuals had received booster (≥4) doses in both countries. These findings are consistent with Heinz et al. (2007 and 2013), which also showed that the rate of vaccine failure is not associated with age after primary series completion [13,14].

4.3. Vaccine effectiveness by schedule adherence

We conducted a sub-analysis by age groups, of VE by timing of the last dose received relative to the recommended interval to the next scheduled dose, comparing those who remained within the recommended intervals ("within schedule") versus those who had missed the next expected dose and were beyond the recommended interval ("outside schedule").

Though the younger age group (≤17 year-olds) had substantial variability due to low TBE case counts, time since the last dose did not negatively influence VE as all estimates, regardless of the number of doses or being within schedule versus outside schedule, had overlapping 95% confidence intervals. Similarly, for both the 18–59 year-old and ≥ 60 year-old age groups in Latvia there were no significant differences associated with time since the last dose. However, data from southern Germany did suggest lack of adherence to the recommended intervals of the primary schedule did negatively impact VE for the adult age groups by as much as −10%.

For those individuals whose last dose was a booster (≥4 doses), there were no longer significant differences associated with delayed timing for any age groups in either country. These data further supports that extended booster intervals ("outside schedule") are not a predisposing factor for higher vaccine failure rates, which is consistent with findings from Austria [13,14], Latvia [33], and Switzerland [41].

The consistently high VEs we found among those outside of the recommended dosing intervals, especially with the lack of differentiation among those having received booster doses, brings into question the relevance of seropositivity as the sole marker for vaccine-induced protection. A possible explanation of any discrepancy between serological results of clinical studies and population impact data was examined by Poellabauer et al., [17] in that boostability, even after prolonged intervals [42] and a rapid anamnestic immune response [11] after encounter with the antigen might prevent onset of the disease in most instances. Future studies could explore the impact of VE at various booster intervals, with age stratification to account for immunosenescence [43].

4.4. Limitations

First, country-specific differences in clinical and diagnostic practices may affect the proportion of cases captured and reported to public health authorities. These differences may contribute to the low incidence among the unvaccinated population in southern German (2.57 per 100,000 population) as compared to Latvia (31 per 100,000 population). Though differences may exist, it is expected that these would affect each country's respective vaccinated populations similarly, so it would have minimal impact to our VE calculations. Second, as some subgroups may have a small number of TBE cases for the basis of VE calculations, some results may need to be interpreted with caution as only directional or limited meaningful conclusions may be drawn, especially when there are wide confidence intervals around point estimates. Although certain strata have limited sample size, our study provides robust VE estimates based on a near-census of TBE cases in both countries. Third, it is possible for vaccination status, doses, and/or timing to have been misclassified, particularly if a patient's vaccinations had not been adequately recorded, or if the vaccination status was ascertained using methods that may have particular biases, such as patient recall. However, this is expected to be minimal due to the extensive medical record systems of the contributing public health authorities and follow-up routinely conducted to verify vaccination status for these cases.

Finally, although TBE vaccines are considered comparable in terms of their effectiveness, there is laboratory evidence from serological studies and from mouse challenge models that the two vaccines do not perform equally well against specific TBEV subtypes [44–47]. The two vaccines available in western Europe for the prevention of TBE are based on different seed virus strains, with one vaccine having an immunodominant point mutation of the seed virus that does not exist in nature [44]. Given that there may be differences in the market shares of the different vaccines used in our study countries, and these may even differ by age groups, the relative performance of the different vaccines is unknown and may impact overall VE measurement. Future studies however, have to validate these differences in real-world settings.

5. Conclusion

TBE vaccination proves to be highly effective as demonstrated by our study and other well-controlled studies [13,14,36]. We measured consistently high VEs that typically exceeded 90% regardless of age group, number of prior doses (2, 3 or ≥4), or adherence to recommended dosing intervals. We did not find that vaccine failure rates were enhanced among elderly persons who had completed the 3-dose primary series. Vaccines offered a high degree of protection for all age groups as of receipt of the 2nd dose of the primary series, especially when individuals stayed within schedule of the recommended primary series dosing intervals, supporting the use of two primary doses for travellers for seasonal protection. After receipt of booster doses, VE estimates could no longer be differentiated in any group between those within schedule versus outside schedule. TBE vaccination continues to be a critical component for the prevention of TBE and should be recommended and administered to all persons potentially exposed to TBEV. However, the complexity of currently recommended vaccination schedules may be a major barrier to uptake of TBE vaccination in highly endemic countries. The evidence presented here suggests that a simplified schedule with fewer doses (including extended booster intervals) may be considered effective to provide a broad and sustainable protection for the populations at risk.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: WE, FK, LJ, and HJS are full time employees of Pfizer Vaccines and may hold stock or stock options.

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