# Supplementary Information

**Article title**: Tick-Borne Encephalitis Vaccine Effectiveness and Barriers to Vaccination in Germany

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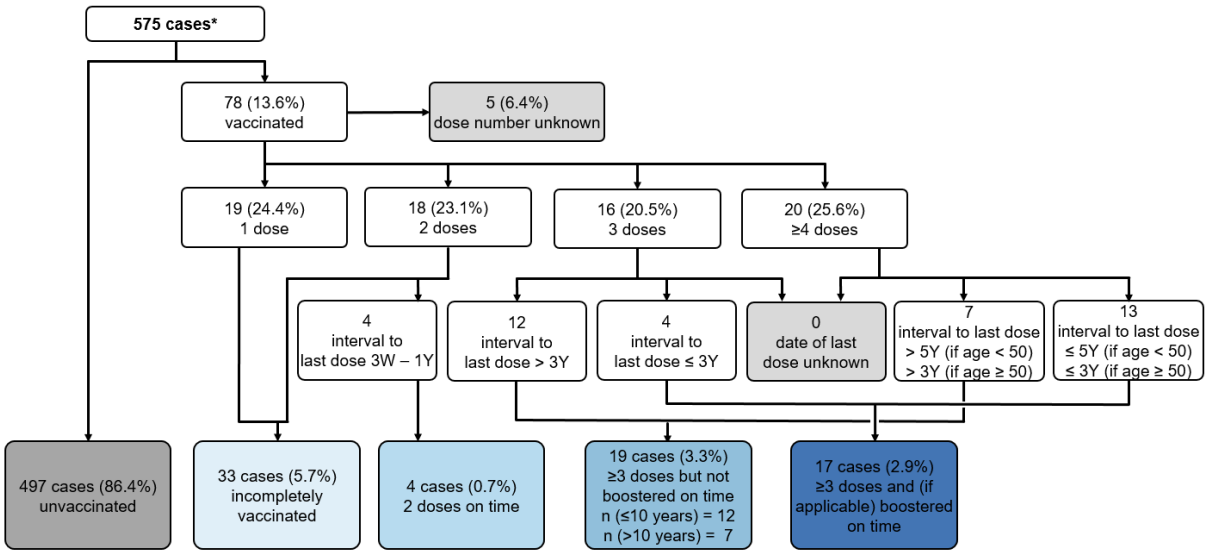
## Overview

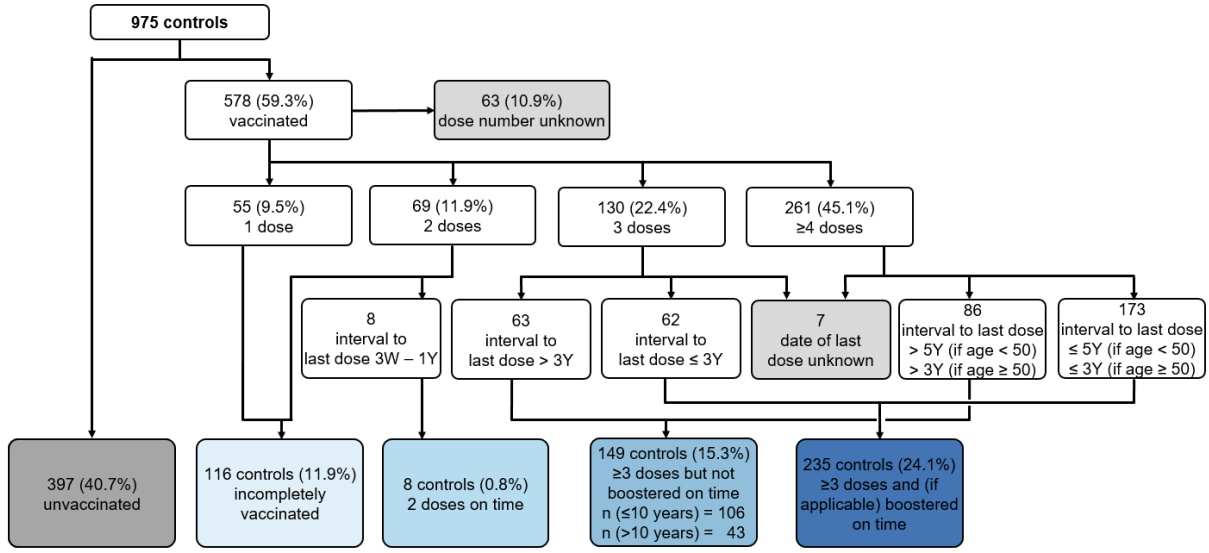
**Supplementary Figure 1**. Definition of TBE vaccination status based on time interval since last dose in 575* cases (**a**) and 975 controls (**b**). Manufacturers' instructions foresee booster intervals of 3 years from age 50 for one vaccine and from age 60 for the other. We applied the conservative cut-off at 50 years, irrespective of vaccine type

*6 of 581 cases were previously unvaccinated, but received 1 dose within 30 days after onset (in 5 cases 1–8 days post onset, in 1 case 28 days). These were excluded, hence *n* = 575

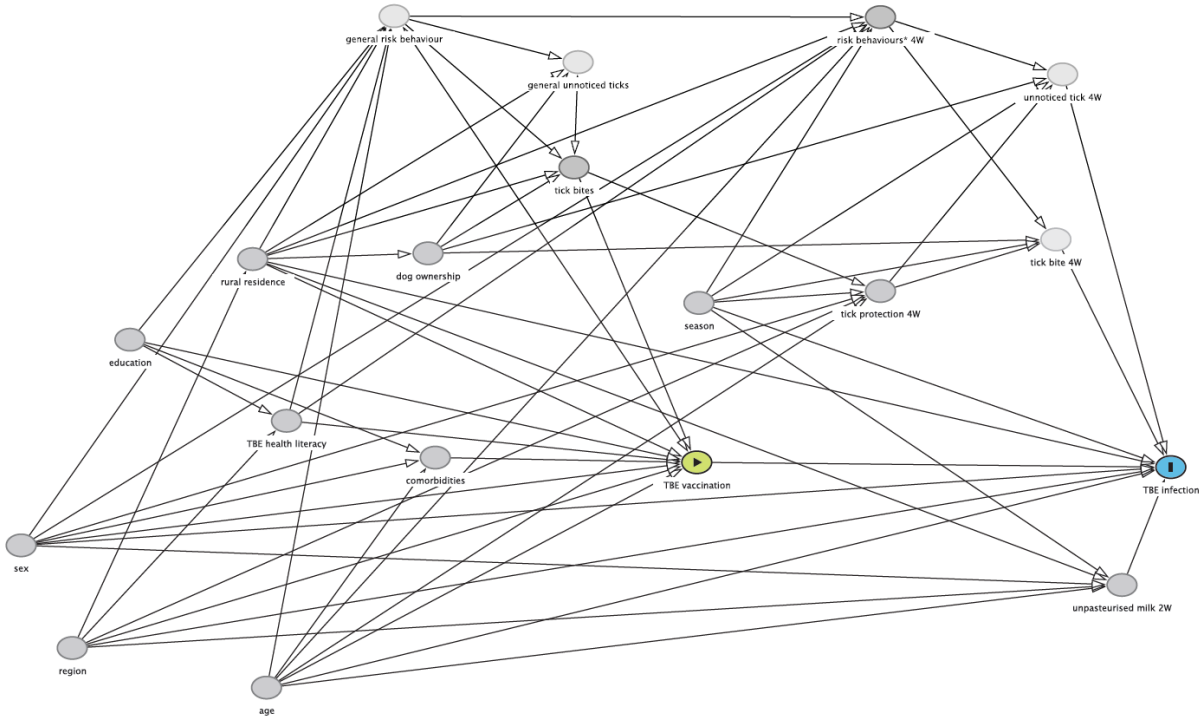
**a**




**b**



**Supplementary Figure 2.** Directed acyclic graph (DAG) of the causal structure underlying TBE vaccine effectiveness. Determined by subject-specific knowledge and created with Dagitty [1]




4W = refers to 4-week period of exposure time (cases) or reference period (controls). 2W = refers to 2-week period. Blue node = outcome. Light grey nodes = unobserved parameters. Green node = exposure of interest. The minimal sufficient adjustment set of covariates required to estimate the adjusted total causal effect of TBE vaccination on the outcome included the matching factors (age, sex, region) and the parameters tick bites, dog ownership, risk behaviours 4W (taking walks, gardening, other outdoor activities, not staying on paths), season, and rural residence in settlements with < 5000 inhabitants

* includes taking walks, gardening, other outdoor activities, not staying on paths

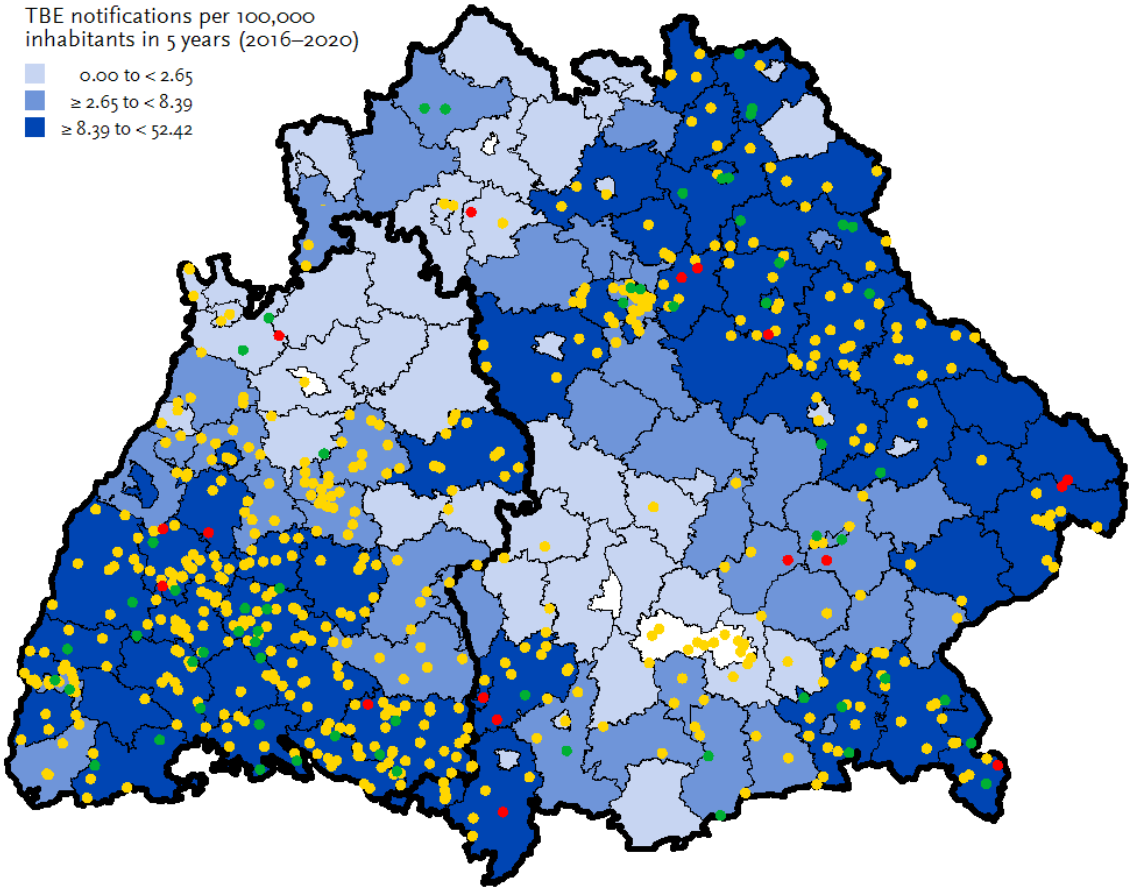
**Reference**

1. Textor J, van der Zander B, Gilthorpe MS, Liskiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. Int. J. Epidemiol. 2016;45(6):1887-94. doi:https://doi.org/10.1093/ije/dyw341

**Supplementary Table 1**. Univariable estimates for TBE vaccine effectiveness and number of participants with specific outcomes, *n* = 570 cases, 964 controls

| TBE vaccination | | Number of participants | Number of cases | VE | 95% CI lower | 95% CI upper |
|---|---|---|---|---|---|---|
| *Interval since last dose* | Unvaccinated | 881 | 492 | 1 | | |
| | ≥ 3 doses, on-time | 251 | 17 | 94.3% | 90.4% | 96.6% |
| | ≥ 3 doses, not on-time, ≤ 10 years | 118 | 12 | 91.0% | 83.5% | 95.1% |
| | ≥ 3 doses, not on-time, > 10 years | 49 | 7 | 86.8% | 70.3% | 94.1% |
| | 2 doses, on-time | 12 | 4 | 60.5% | -32.3% | 88.2% |
| | 1–2 doses | 148 | 33 | 77.3% | 65.8% | 84.9% |
| | ≥ 1 dose, additional data missing | 75 | 5 | 94.4% | 85.9% | 97.7% |
| *Type of vaccine* | Unvaccinated | 881 | 492 | 1 | | |
| | ≥ 3 doses ENCEPUR | 113 | 8 | 94.0% | 87.5% | 97.1% |
| | ≥ 3 doses FSME-IMMUN | 117 | 13 | 90.1% | 82.1% | 94.5% |
| | ≥ 3 doses mixed | 108 | 7 | 94.5% | 88.1% | 97.5% |
| | ≥ 3 doses, type unknown | 70 | 8 | 89.8% | 78.4% | 95.2% |
| | < 3 or unknown doses | 228 | 42 | 82.1% | 74.4% | 87.5% |
| | ≥ 1 dose TicoVac | 17 | 0 | - | - | - |
| *Primary immunisation* | Unvaccinated | 881 | 492 | 1 | | |
| | timing as recommended | 142 | 11 | 93.4% | 87.5% | 96.5% |
| | irregular timing | 184 | 12 | 94.5% | 89.9% | 97.0% |
| | exact dates missing | 99 | 13 | 88.0% | 78.3% | 93.4% |
| | incomplete / doses unknown | 228 | 42 | 82.1% | 74.4% | 87.5% |
| *Number of doses* | Unvaccinated | 881 | 492 | 1 | | |
| | 1 dose | 74 | 19 | 72.7% | 53.2% | 84.1% |
| | 2 doses | 86 | 18 | 79.1% | 64.2% | 87.8% |
| | 3 doses | 145 | 16 | 90.2% | 83.2% | 94.3% |
| | ≥ 4 doses | 280 | 20 | 93.9% | 90.2% | 96.2% |
| | ≥ 1 dose, additional data missing | 68 | 5 | 93.7% | 84.2% | 97.5% |
| *Age group* | 2–13 years, ≥ 4 doses | 14 | 1 | 97.1% | 75.8% | 99.6% |
| | 14–64 years, ≥ 4 doses | 201 | 11 | 95.4% | 91.3% | 97.5% |
| | ≥ 65 years, ≥ 4 doses | 65 | 8 | 86.8% | 70.9% | 94.0% |
| *Sensitivity analysis: Interval since last dose, no imputed dates* | Unvaccinated | 881 | 492 | 1 | | |
| | ≥ 3 doses, on-time | 211 | 15 | 93.9% | 89.6% | 96.5% |
| | ≥ 3 doses, not on-time, ≤ 10 years | 94 | 10 | 90.6% | 81.6% | 95.2% |
| | ≥ 3 doses, not on-time, > 10 years | 35 | 5 | 86.8% | 65.7% | 94.9% |
| | 2 doses, on-time | 19 | 5 | 71.8% | 20.9% | 89.9% |
| | 1–2 doses | 141 | 32 | 76.8% | 64.8% | 84.7% |
| | ≥ 1 dose, additional data missing | 153 | 11 | 93.9% | 88.5% | 96.7% |

**Supplementary Figure 3.** Spatial distribution of participating TBE cases across the study area (*n* = 581)




Yellow = unvaccinated cases; Green = cases with partial/expired vaccination or with missing details; Red = cases with vaccine breakthrough infections. Cases were mapped at random points within their district of notification. Background shading in blue reflects TBE incidence 2016–2020 in areas classified as TBE risk areas in 2020. Districts with white shading were not classified as risk areas.

The map was created with RegioGraph Analyse, Version 2018 (GfK GeoMarketing GmbH, https://shop.gfk-geomarketing.de/de/regiograph.html).

**Supplmentary Table 2**. Comparison of characteristics of unvaccinated TBE cases and controls, who lived in or visited TBE risk areas

| | **Cases** | **Controls** | **p-value** |
|---|---|---|---|
| | *n* = 473 | *n* = 389 | |
| Age group | n (%) | n (%) | |
| ≤18 years | 53 (11%) | 25 (6%) | |
| 18–64 years | 331 (70%) | 273 (70%) | 0.023 |
| ≥65 years | 89 (19%) | 91 (23%) | |
| Demographics | | | |
| Male | 299 (63%) | 257 (66%) | 0.384 |
| ≥1 comorbidity (self-reported) | 98 (21%) | 96 (25%) | 0.166 |
| Home in TBE risk area | 462 (98%) | 379 (97%) | 0.816 |
| Rural residence (< 5,000 inhabitants) | 224 (48%) | 162 (43%) | 0.095 |
| Highest level of completed secondary education* (duration in years) | | | |
| Abitur (12–13 years) | 138 (29%) | 123 (32%) | |
| Fachabitur (12–13 years) | 48 (10%) | 21 (5%) | |
| Realschulabschluss (10 years) | 116 (25%) | 120 (31%) | 0.013 |
| Hauptschulabschluss (9 years) | 115 (24%) | 94 (24%) | |
| still in school/none/missing | 56 (12%) | 31 (8%) | |

* English translations: Abitur = general qualification for university entrance; Fachabitur = subject-related entrance qualification; Realschulabschluss = intermediate school-leaving certificate; Hauptschulabschluss = completion of compulsory basic secondary schooling.