TICK-BORNE ENCEPHALITIS (TBE) VACCINE

Katherine Poehling, M.D.
Chair, ACIP TBE Vaccine Work Group
September 29, 2021
Background

- Food and Drug Administration approved a TBE vaccine (manufactured by Pfizer as TICOVAC) on August 13, 2021
- No TBE vaccine previously licensed in the United States
- No existing ACIP TBE vaccine recommendations
- TBE Vaccine Work Group was formed in September 2020 to review use of TBE vaccine in U.S. adults and children traveling abroad
TBE Vaccine Work Group members and participants

**ACIP**

Katherine Poehling (Chair)  
David Shlim, ISTM

Wilbur Chen  
Mark Sawyer, AAP

**CDC Lead**

Susan Hills, DVBD  
Alan Barrett, Univ Texas Galveston  
Lin Chen, Mount Auburn Hosp

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Melinda Wharton, NCIRD

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Terms of Reference for TBE Vaccine Work Group

- To review information on TBE, including its epidemiology, clinical presentation, diagnosis, treatment, and outcome
- To review data on infection risk and burden for travelers and laboratory workers
- To review data on vaccine safety, immunogenicity, and effectiveness
- To provide evidence-based recommendation options for ACIP
- To identify areas in need of further research for informing potential future vaccine recommendations
- To publish ACIP recommendations in the Morbidity and Mortality Weekly Report (MMWR)
Today’s topics

- Summary of immunogenicity and safety of TBE vaccine
  - Susan Hills (CDC/NCEZID)

- Next steps for TBE Vaccine Work Group
  - Susan Hills (CDC/NCEZID)
Work Group timeline (planned), Aug 2021–Mar 2022

- Present to ACIP (today): TBE vaccine immunogenicity and safety
- Present to ACIP: Evidence to Recommendations
- ACIP vote on vaccine recommendations and finalize MMWR
TICK-BORNE ENCEPHALITIS (TBE) VACCINE: IMMUNOGENICITY AND SAFETY

Susan Hills, MBBS, MTH
Medical Epidemiologist
Arboviral Diseases Branch
Centers for Disease Control and Prevention

September 29, 2021
Today’s topics

1. TBE vaccine and its administration
2. Immunogenicity after the primary series
3. Immunogenicity after a booster dose
4. Safety
5. Vaccine effectiveness
6. Special populations
7. Conclusion
TBE vaccine and its administration
TBE vaccine development history

1976  Licensed in Austria
1999  Thimerosal removed
2000  Transition in origin of production virus seed to chick embryo fibroblast cells
2001  Licensure of current formulation of vaccine in Europe
2003  Introduction of pediatric formulation
By 2021 >75 million doses of new formulation have been used in ~30 countries

## TBE vaccine

<table>
<thead>
<tr>
<th><strong>Vaccine type</strong></th>
<th>Inactivated, whole virus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TBE virus strain</strong></td>
<td>Neudorfl (European subtype)</td>
</tr>
<tr>
<td><strong>Substrate</strong></td>
<td>Chick embryo fibroblast cells</td>
</tr>
<tr>
<td><strong>Adjuvant</strong></td>
<td>Aluminum hydroxide</td>
</tr>
<tr>
<td><strong>Preservative</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>Stabilizer</strong></td>
<td>Human serum albumin</td>
</tr>
<tr>
<td><strong>Other ingredients</strong></td>
<td>Sodium chloride, dibasic sodium phosphate, monobasic potassium phosphate</td>
</tr>
<tr>
<td><strong>Substances used in manufacturing</strong></td>
<td>Formaldehyde, sucrose, protamine sulfate, neomycin, gentamicin</td>
</tr>
</tbody>
</table>
### TBE vaccine administration

| **Dose**       | Adult dose: ≥16 years (0.5mL)  
|                | Pediatric dose: 1–15 years (0.25mL) |
| **Presentation** | Prefilled syringe |
| **Route**      | Intramuscular |

Packaging subject to minor changes before distribution
TBE vaccination schedule*

*All intervals are following previous dose

Adults
- Day 0
- 14 days–3 months

Children
- Day 0
- 1–3 months

Primary series (3 doses)

5–12 months

≥3 years

Booster dose
Immunogenicity after primary series
Measuring vaccine protection against TBE

- No vaccine efficacy trials because of low disease incidence
  - Evidence for protection based on immunogenicity endpoints

- TBE virus neutralizing antibodies believed to confer protection against disease
  - Neutralizing antibody titer ≥10 generally used in vaccine studies
  - No formal correlate of protection and no standardized reference reagents
Immunogenicity after 3-dose primary series: Adults

- Observational study conducted in Poland
  - Subjects aged 16–64 years

- Seropositivity at 1 month after dose 3 (initial study)
  - 99% (411/416) seropositive

- Seropositivity at 3 years after dose 3 (follow up study)
  - 94% (229/243) seropositive

Geometric mean titers (GMTs)* at intervals after dose 3 of primary series

*Geometric mean titer of neutralizing antibodies

Neutralizing antibody titer ≥10 considered to confer protection

Loew-Baselli A et al. Vaccine 2009
Immunogenicity after 3-dose primary series: Children and adolescents

- Observational study conducted in Poland, Austria and Germany
  - Subjects aged 1–15 years

- Seropositivity at 1 month after dose 3 (initial study)
  - 99% (358/360) seropositive

- Seropositivity at 3 years after dose 3 (follow up study)
  - 98% (345/352) seropositive

Pöllabauer EM et al. Vaccine 2010; Poellabauer E et al. Vaccine 2019
GMTs* at intervals after dose 3 of primary series by age group (N=358)

*Geometric mean titer of neutralizing antibodies

Neutralizing antibody titer ≥10 considered to confer protection

Poellabauer E et al. Vaccine 2019
Summary of immunogenicity after a 3-dose primary series
Adults and children

- High seropositivity rates (99%) at 1 month after completion of primary series
- High seropositivity rates (≥94%) persist through 3 years after primary series
- Moderate decrease in GMT but little change between years 2 and 3
Immunogenicity after booster dose
Immunogenicity after booster dose*: Adults (N=232)

*Administered at 3 years after dose 3 of primary series

Konior et al. Vaccine 2017; Pfizer
GMTs* at intervals after booster dose (N=232)

*Geometric mean titer of neutralizing antibodies

Neutralizing antibody titer ≥10 considered to confer protection

Konior et al. Vaccine 2017; Pfizer
Immunogenicity after booster dose*:
Children and adolescents (N=172)

*Administered at 3–5 years after dose 3 of primary series
GMTs* at intervals after booster dose by age group (N=172)

*Geometric mean titer of neutralizing antibodies

Source: Poellabauer E et al. Vaccine 2019
Summary of immunogenicity after a booster dose among adults and children

- High seropositivity rates (100%) at 1 month after booster dose
- High seropositivity rates (≥85%) persist through 10 years after booster dose
- Moderate decrease in GMT initially followed by slow decrease through 10 years
Safety: Adults
Solicited adverse events after dose 1 (N=2,977)*

*N=2,947 for subjects included in fever (≥38°C) assessment

Severity of adverse events after dose 1

*Severe fever defined as >40°C

### Commonest systemic reactions after dose 1

<table>
<thead>
<tr>
<th>Type of event</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>7</td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
</tr>
<tr>
<td>Malaise</td>
<td>5</td>
</tr>
</tbody>
</table>

Serious adverse events (N=2,977)

- No vaccine-related serious adverse events

Safety: Children and adolescents
Solicited adverse events after dose 1 (N=2,417)*

Pöllabauer EM et al. Vaccine 2010
Severity of adverse events after dose 1

<table>
<thead>
<tr>
<th>Event</th>
<th>Severe (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>0.2</td>
</tr>
<tr>
<td>Systemic</td>
<td>0.1</td>
</tr>
<tr>
<td>Fever*</td>
<td>0</td>
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*Severe fever defined as >40°C

Pöllabauer EM et al. Vaccine 2010
Fever rates after dose 1* by age group (N=2,417)

<table>
<thead>
<tr>
<th>Age group</th>
<th>No.</th>
<th>Any fever (%)</th>
<th>38.0–38.4°C (%)</th>
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<th>39.0–40.0°C (%)</th>
<th>&gt;40.0°C</th>
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<tr>
<td>1–2 years</td>
<td>186</td>
<td>36</td>
<td>24</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>3–6 years</td>
<td>563</td>
<td>13</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>7–15 years</td>
<td>1,668</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>2,417</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>0</td>
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TICOVAC package insert
Fever rates after dose 1* by age group (N=2,417)

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<td>10</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

TICOVAC package insert
## Fever rates after doses 2 and 3

<table>
<thead>
<tr>
<th>Dose</th>
<th>No. with fever</th>
<th>No. in group</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>39/2,410</td>
<td></td>
<td>1.6</td>
</tr>
<tr>
<td>3</td>
<td>31/2,390</td>
<td></td>
<td>1.3</td>
</tr>
</tbody>
</table>

TICOVAC package insert
<table>
<thead>
<tr>
<th>Type of event</th>
<th>Age group</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>1-15 years</td>
<td>11</td>
</tr>
<tr>
<td>Restlessness</td>
<td>1-5 years</td>
<td>9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6-15 years</td>
<td>6</td>
</tr>
</tbody>
</table>

Pöllabauer EM et al. Vaccine 2010
Serious adverse events (N=2,417)

- No vaccine-related serious adverse events

Pöllabauer EM et al. Vaccine 2010
Summary of safety of vaccination among adults and children

- After dose 1
  - Local adverse events in 36% of adults and 25% of children and adolescents
  - Systemic adverse events in 14% of adults and 20% children and adolescents
  - Fever rates variable by age group but mainly mild and no fever >40°C

- Severe adverse events were uncommon

- Lower adverse events rates after subsequent doses
Vaccine effectiveness
Vaccine effectiveness (VE) studies

- No VE study for Pfizer’s TBE vaccine alone

- VE study in Austria with partially relevant data with limitations
  - Most but not all vaccine in use was Pfizer’s TBE vaccine (90–95%)
  - When TBE occurred in vaccinated person no information on which vaccine used
  - Most vaccinated persons would have had previous formulations of TBE vaccine
  - VE measured based on vaccination according to the recommended Austrian vaccination schedule
# VE in Austria, 2000–2006*

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Unvaccinated person incidence€</th>
<th>Vaccinated person incidence€</th>
<th>VE (%)</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–15</td>
<td>1.44</td>
<td>0.06</td>
<td>96</td>
<td>(84–99)</td>
</tr>
<tr>
<td>16–49</td>
<td>4.96</td>
<td>0.04</td>
<td>99</td>
<td>(98–100)</td>
</tr>
<tr>
<td>50–59</td>
<td>6.44</td>
<td>0.12</td>
<td>98</td>
<td>(95–99)</td>
</tr>
<tr>
<td>≥60</td>
<td>6.79</td>
<td>0.11</td>
<td>98</td>
<td>(97–99)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5.92</td>
<td>0.08</td>
<td>99</td>
<td>(98–99)</td>
</tr>
</tbody>
</table>

*Completed 3-dose primary schedule with or without one or more booster doses
€Per 100,000 population

Updated VE estimate in Austria, 2018–2020

- VE for all age groups: 96%

Pfizer, data on file
Special populations
TBE disease and vaccination in pregnant women

- TBE disease in pregnant women and their babies
  - Pregnant women similar spectrum of illness to non-pregnant persons
  - Transplacental transmission of TBE virus not established

- No studies have assessed safety or immunogenicity of TBE vaccine in pregnancy

<table>
<thead>
<tr>
<th>Mother outcome</th>
<th>Infant outcome</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>Healthy</td>
<td>60</td>
</tr>
<tr>
<td>Healthy</td>
<td>Unknown</td>
<td>48</td>
</tr>
<tr>
<td>+/- AE*</td>
<td>+/- AE*</td>
<td>30</td>
</tr>
</tbody>
</table>

AE: adverse event
*No patterns of AEs seen in mother or infant
TBE disease and vaccination in breastfeeding women

- TBE virus transmission via breastfeeding
  - Two reports show transmission with variable outcomes in infants

- No studies have assessed safety of TBE vaccination in lactating women

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<thead>
<tr>
<th>Infant</th>
<th>n</th>
</tr>
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<tr>
<td>No adverse event</td>
<td>11</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
</tr>
<tr>
<td>Adverse event</td>
<td>6</td>
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Manufacturer safety database, 1976–2020 (N=25)

1International Scientific Work Group on TBE (presentation by Jana Kerlik MD)
TBE disease and vaccination in persons with altered immune status

- Persons with altered immune status can have severe TBE and have higher risk of fatal outcome

- Limited data on TBE vaccine use in persons with altered immunocompetence*
  - Some studies used previous formulation of vaccine and/or modified schedule

- Immunogenicity results were variable but typically lower in immunocompromised persons
  - When adequate response occurred, it was often delayed

- Safety data suggested vaccination was well-tolerated

TBE disease and vaccination in older persons

- Incidence and severity of disease are highest in older persons

- High seropositivity rates after 3-dose primary series
  - 99% (136/137) of elderly adults ≥70 years seropositive at 1 month\(^1\)

- Some concern about duration of seropositivity after booster dose over longer term (≥5 years) but very limited data\(^2\)

- Adverse event rates comparable to younger persons\(^3\)

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\(^1\) Wanke et al. Clin Microbiol Infect 2012; \(^2\) Konior et al. Vaccine 2017; \(^3\) Pfizer study 690601
Coadministration with other vaccines
Administration of TBE vaccine with other vaccines

- No data on co-administration of TBE vaccine and other vaccines
Conclusions
Summary of immunogenicity and safety

- Good immunogenicity results with high seropositivity rates
  - Following completion of 3-dose primary series
  - Following booster dose at 3 years
  - In adults and children

- Acceptable safety profile
  - Vaccine relatively well tolerated with few severe local or systemic reactions

- Limited data among special populations
  - No major safety issues identified
  - Some persons with altered immunocompetence might have reduced immune response
Limitations of immunogenicity data

- Interpretation of seropositivity data
  - No formal immunologic correlate of protection

- Level of protection from TBE vaccine based on a European subtype TBE virus for other TBE virus subtypes unclear
  - Available data and genetic and antigenic similarity between the three subtypes suggest likely is cross-protection
  - However, data on cross-protection are limited and vaccine effectiveness has not been demonstrated
Next steps
Work Group timeline (planned), Aug 2021–Mar 2022

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