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)

Wilbur Chen

CDC Lead

Susan Hills, DVBD

Ex Officio

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Steve Waterman, DVBD

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Jessica MacNeil, NCIRD

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Terms of Reference for TBE Vaccine Work Group

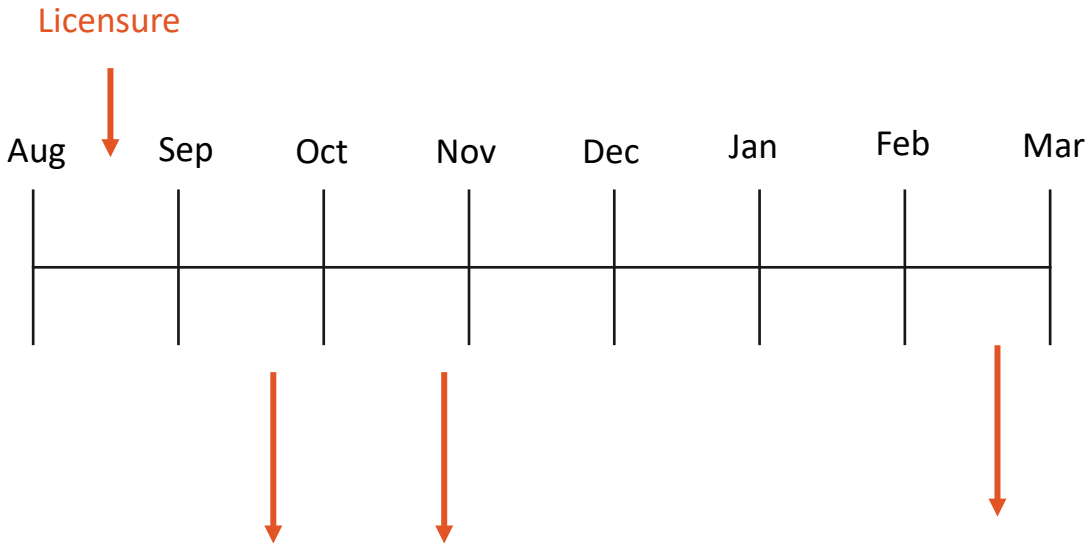
- To review information on TBE, including its epidemiology, clinical presentation, diagnosis, treatment, and outcome
- To review data on infection risk and burden for travelers and laboratory workers
- To review data on vaccine safety, immunogenicity, and effectiveness
- To provide evidence-based recommendation 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



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

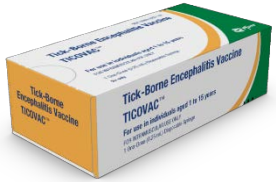
1976	Licensed in Austria
1999	Thimerosal removed
2000	Transition in origin of production virus seed to chick embryo fibroblast cells
2001	Licensure of current formulation of vaccine in Europe
2003	Introduction of pediatric formulation
By 2021	>75 million doses of new formulation have been used in ~30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

Barrett PN et al. Vaccine 2003.

TBE vaccine

Vaccine type	Inactivated, whole virus
TBE virus strain	Neudorfl (European subtype)
Substrate	Chick embryo fibroblast cells
Adjuvant	Aluminum hydroxide
Preservative	None
Stabilizer	Human serum albumin
Other ingredients	Sodium chloride, dibasic sodium phosphate, monobasic potassium phosphate
Substances used in manufacturing	Formaldehyde, sucrose, protamine sulfate, neomycin, gentamicin

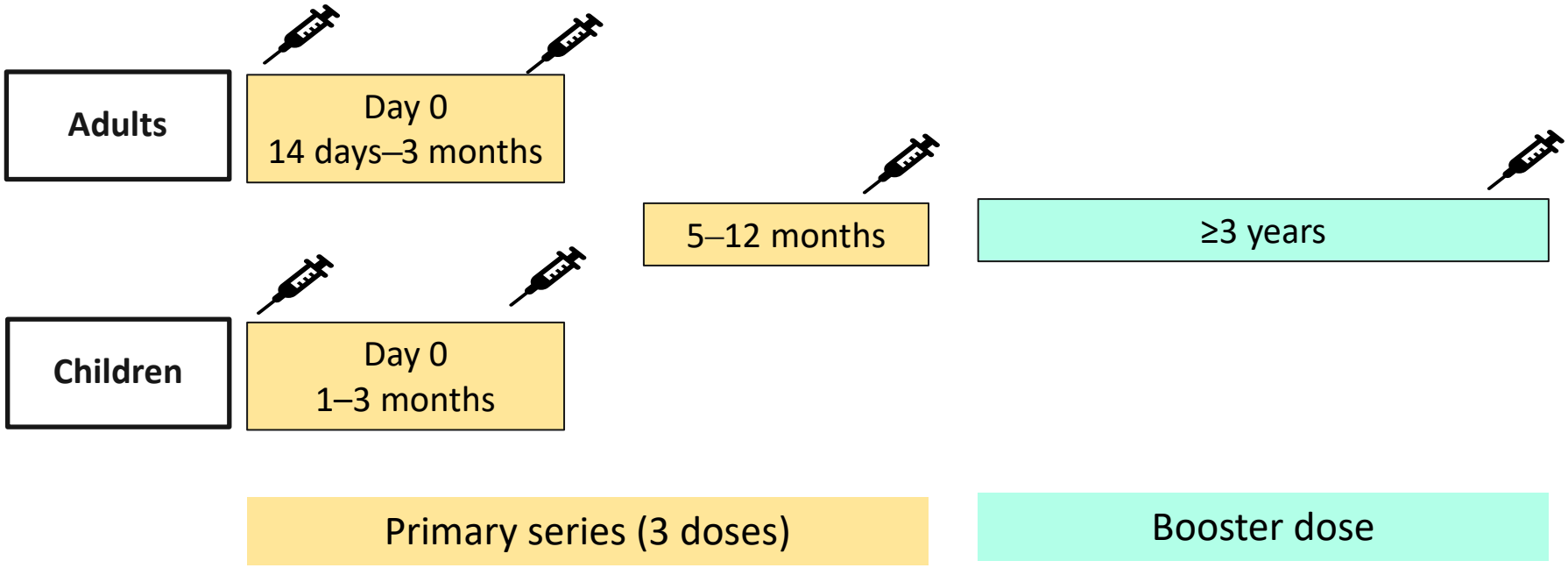
TBE vaccine administration



Packaging subject to minor changes before distribution

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

TBE vaccination schedule*



*All intervals are following previous 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

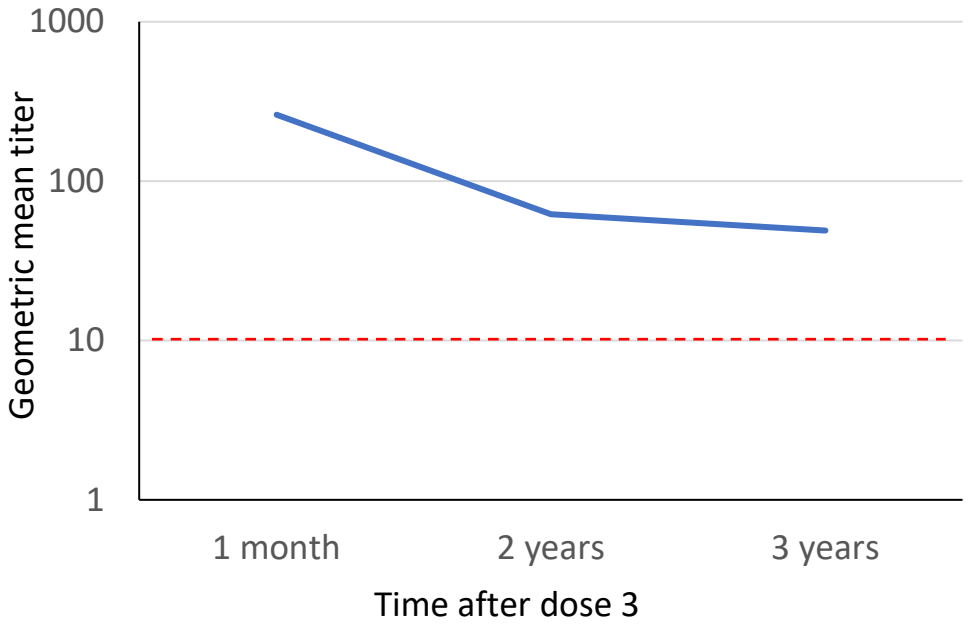
- TBE virus neutralizing antibodies believed to confer protection against disease
  - Neutralizing antibody titer ≥10 generally used in vaccine studies
  - No formal correlate of protection and no standardized reference reagents

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

Loew-Baselli A et al. Vaccine 2006; Loew-Baselli A et al. Vaccine 2009

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

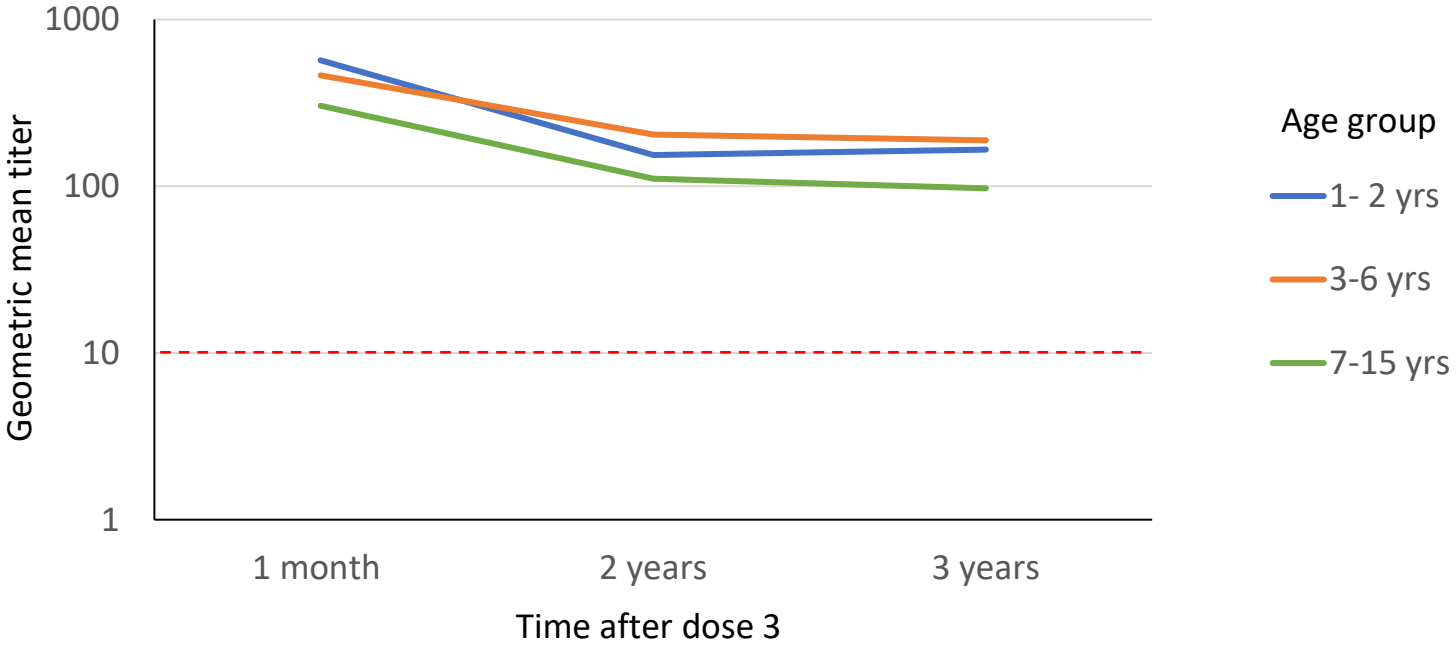
Loew-Baselli A et al. Vaccine 2009

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

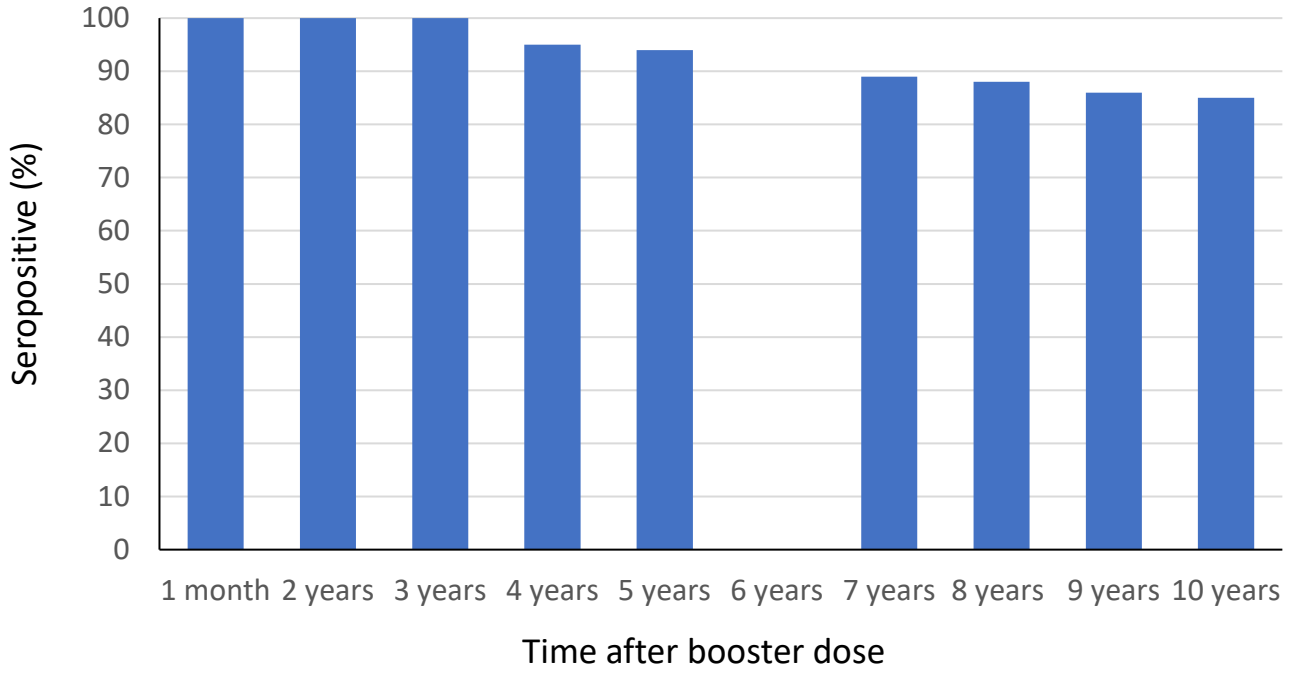
Poellabauer E et al. Vaccine 2019

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

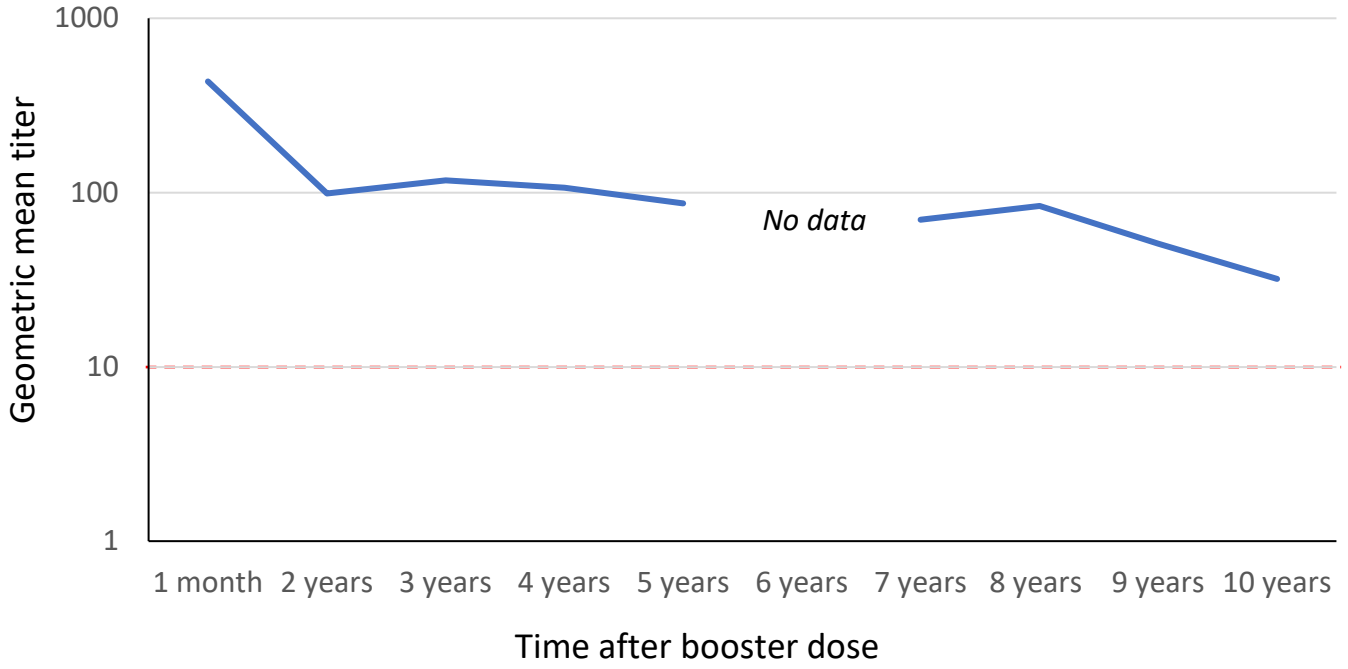
Immunogenicity after booster dose*: Adults (N=232)



*Administered at 3 years after dose 3 of primary series

Konior et al. Vaccine 2017; Pfizer

GMTs* at intervals after booster dose (N=232)

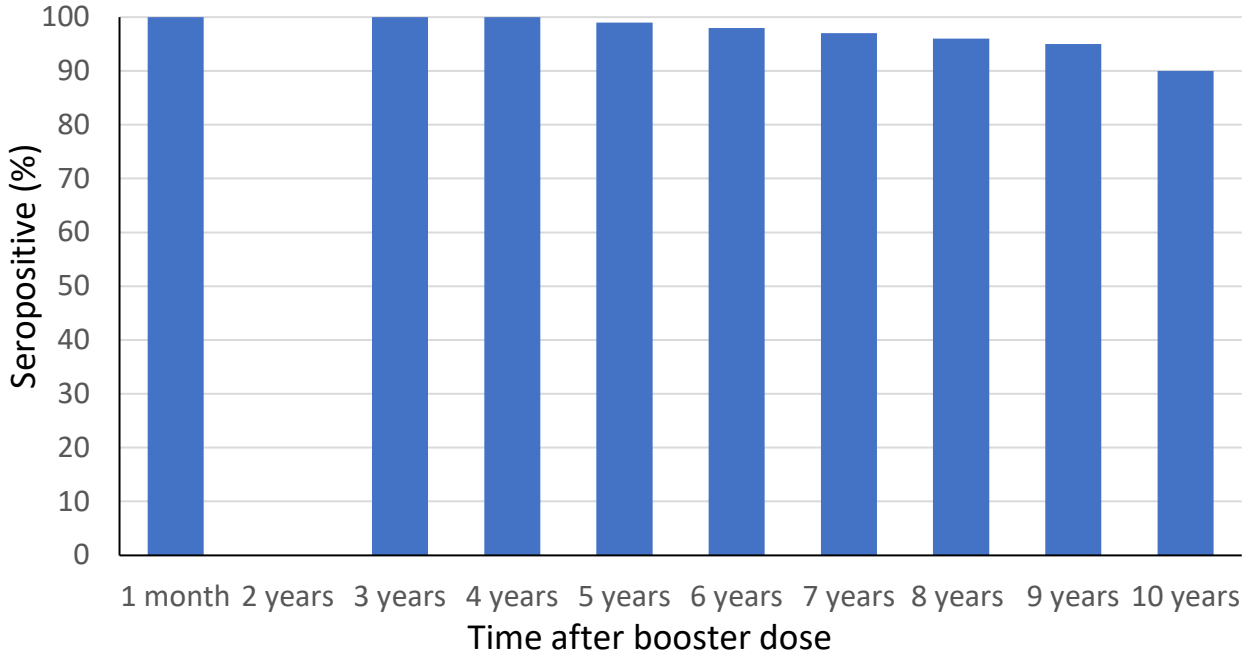


*Geometric mean titer of neutralizing antibodies

- - - - Neutralizing antibody titer ≥10 considered to confer protection

Konior et al. Vaccine 2017; Pfizer

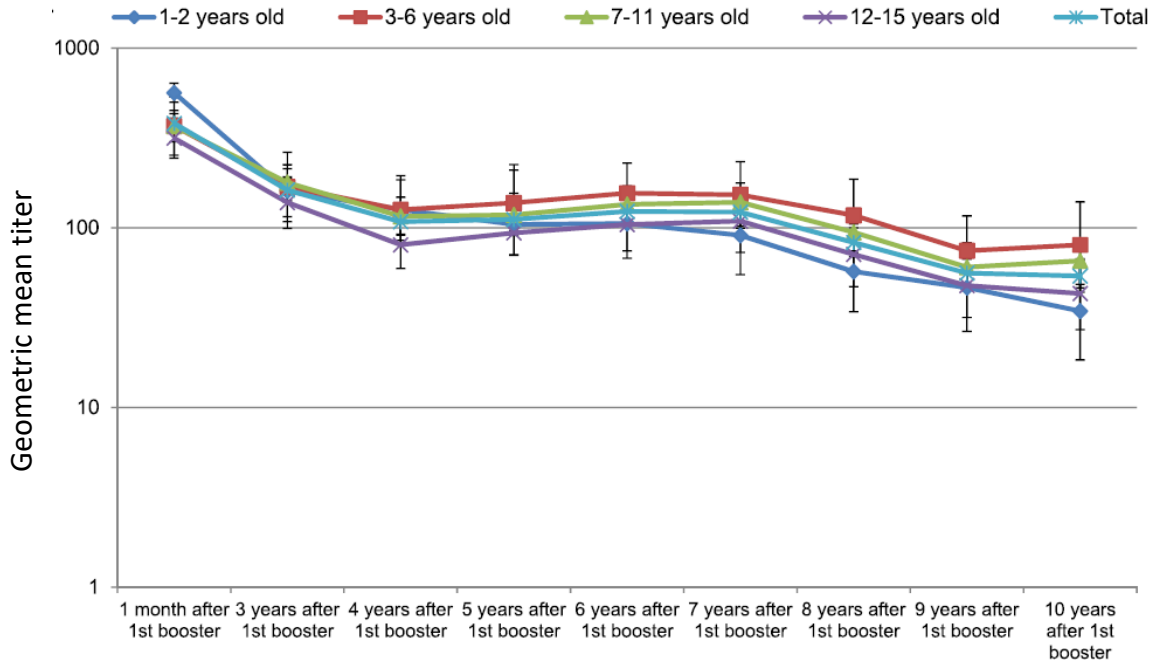
Immunogenicity after booster dose*: Children and adolescents (N=172)



*Administered at 3–5 years after dose 3 of primary series

Poellabauer E et al. Vaccine 2019

GMTs* at intervals after booster dose by age group (N=172)



*Geometric mean titer of neutralizing antibodies

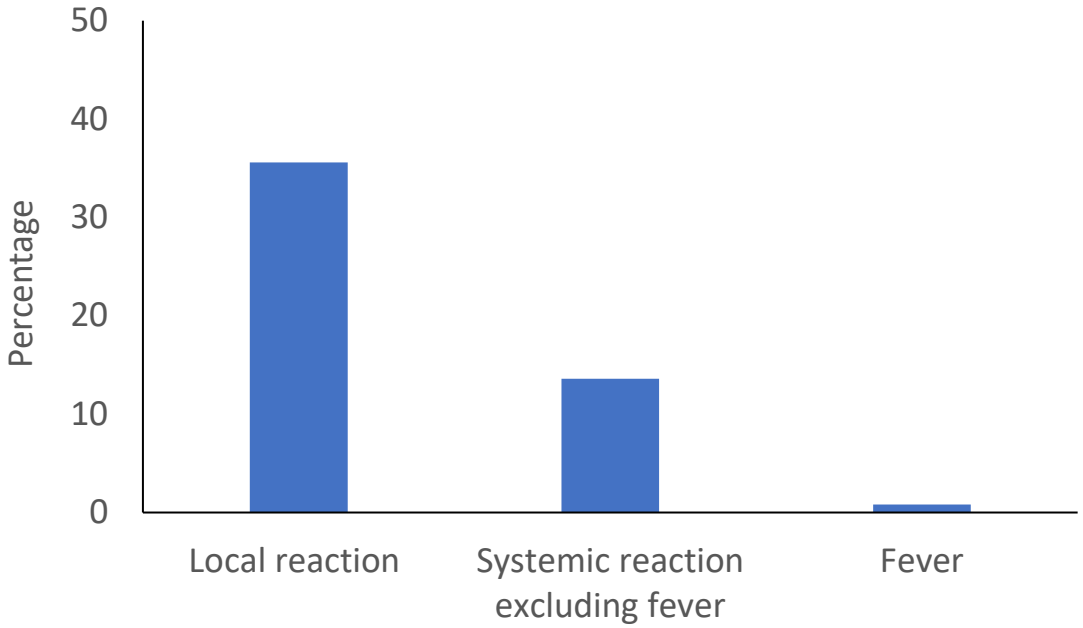
Source: Poellabauer E et al. Vaccine 2019

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

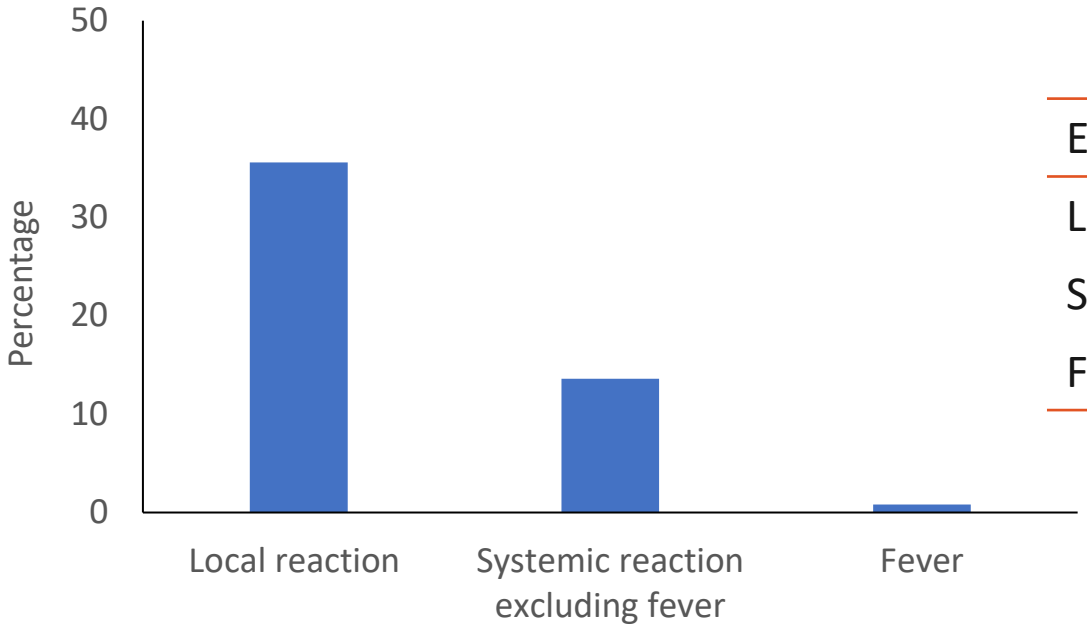
Safety: Adults
Solicited adverse events after dose 1 (N=2,977)*



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

Loew-Baselli A e al. Vaccine 2006.

Severity of adverse events after dose 1



Event	Severe (%)
Local	0.1
Systemic	0.03
Fever*	0

*Severe fever defined as >40^{o}C

Loew-Baselli A e al. Vaccine 2006.

Commonest systemic reactions after dose 1

Type of event	(%)
Fatigue	7
Headache	6
Malaise	5

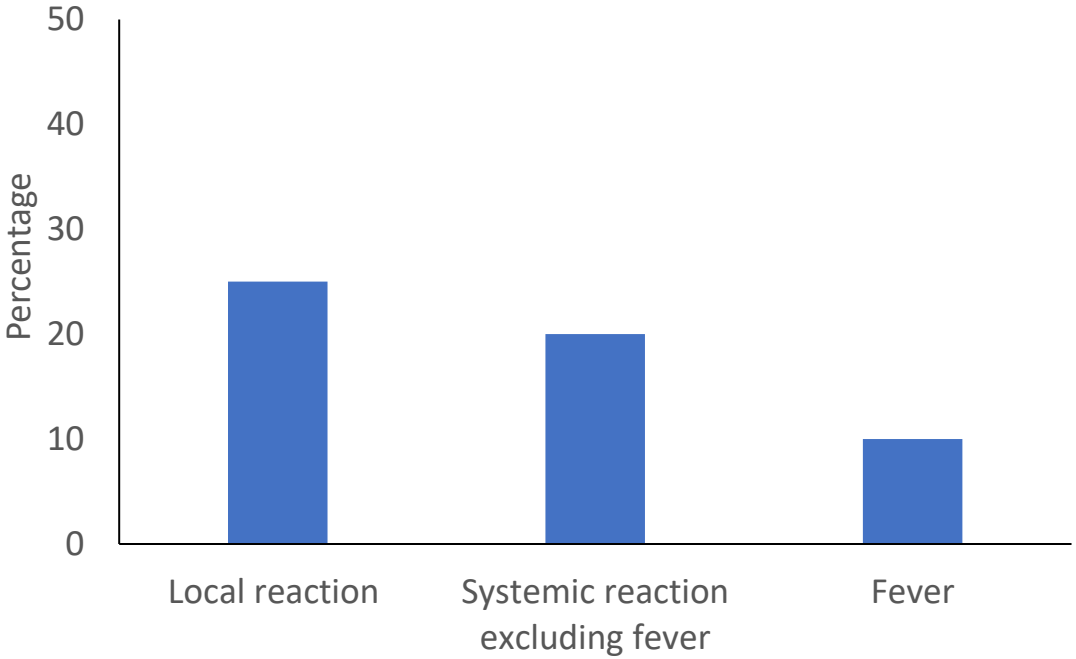
Loew-Baselli A e al. Vaccine 2006.

Serious adverse events (N=2,977)

- No vaccine-related serious adverse events

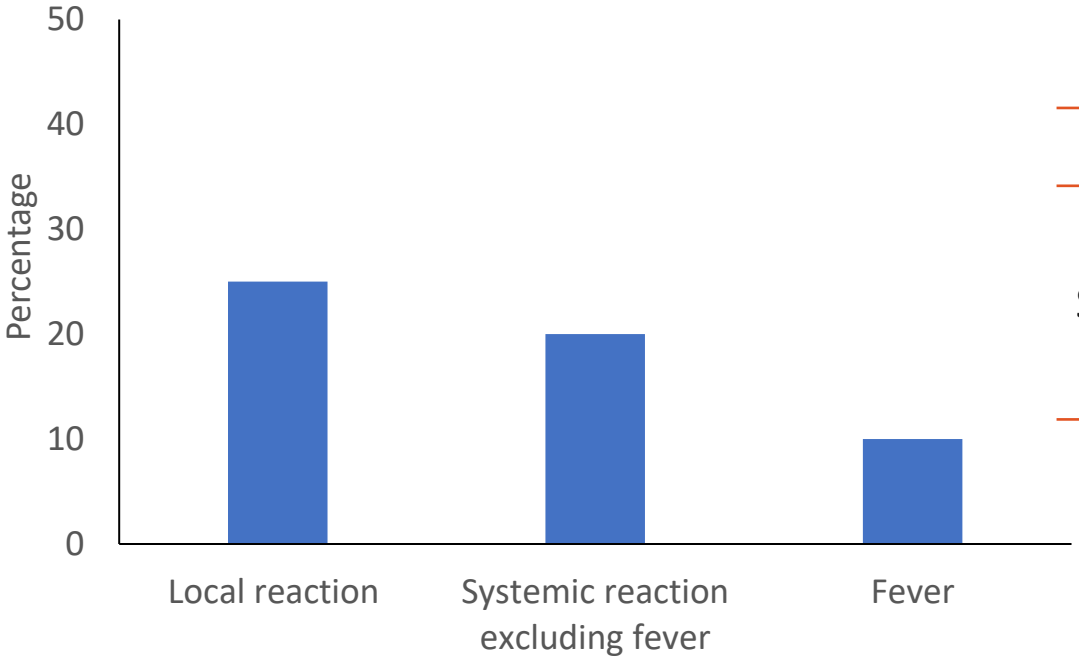
Loew-Baselli A e al. Vaccine 2006.

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



Event	Severe (%)
Local	0.2
Systemic	0.1
Fever*	0

*Severe fever defined as >40^{o}C

Pöllabauer EM et al. Vaccine 2010

Fever rates after dose 1* by age group (N=2,417)

Age group	No.	Any fever (%)	38.0–38.4°C (%)	38.5–38.9°C (%)	39.0–40.0°C (%)	>40.0°C
1–2 years	186	36	24	6	6	0
3–6 years	563	13	5	5	3	0
7–15 years	1,668	6	3	2	<1	0
Total	2,417	10	5	3	1	0

TICOVAC package insert

Fever rates after dose 1* by age group (N=2,417)

Age group	No.	Any fever (%)	38.0–38.4°C (%)	38.5–38.9°C (%)	39.0–40.0°C (%)	>40.0°C
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3–6 years	563	13	5	5	3	0
7–15 years	1,668	6	3	2	<1	0
Total	2,417	10	5	3	1	0

TICOVAC package insert

Fever rates after doses 2 and 3

Dose	No. with fever	No. in group	(%)
2	39/	2,410	(1.6)
3	31/	2,390	(1.3)

TICOVAC package insert

Commonest systemic reactions after dose 1

Type of event	Age group	(%)
Headache	1-15 years	11
Restlessness	1-5 years	9
Fatigue	6-15 years	6

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^{o}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*

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

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

Heinz FX et al. Vaccine 2007.

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

Manufacturer safety database, 1976–2020 (N=138)

Mother outcome	Infant outcome	n
Healthy	Healthy	60
Healthy	Unknown	48
+/- AE*	+/- AE*	30

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[1]
- No studies have assessed safety of TBE vaccination in lactating women

Manufacturer safety database, 1976–2020 (N=25)

Infant	n
No adverse event	11
Unknown	8
Adverse event	6

[1]International 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

*Prelog M et al. Vaccine 2008; Zielinski CC at al. Cancer 1986; Panasiuk B et al. Infection 2003; Einarsdottir et al. Vaccine 2021; Harrison et al. NPJ Vaccines 2020.

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]

[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

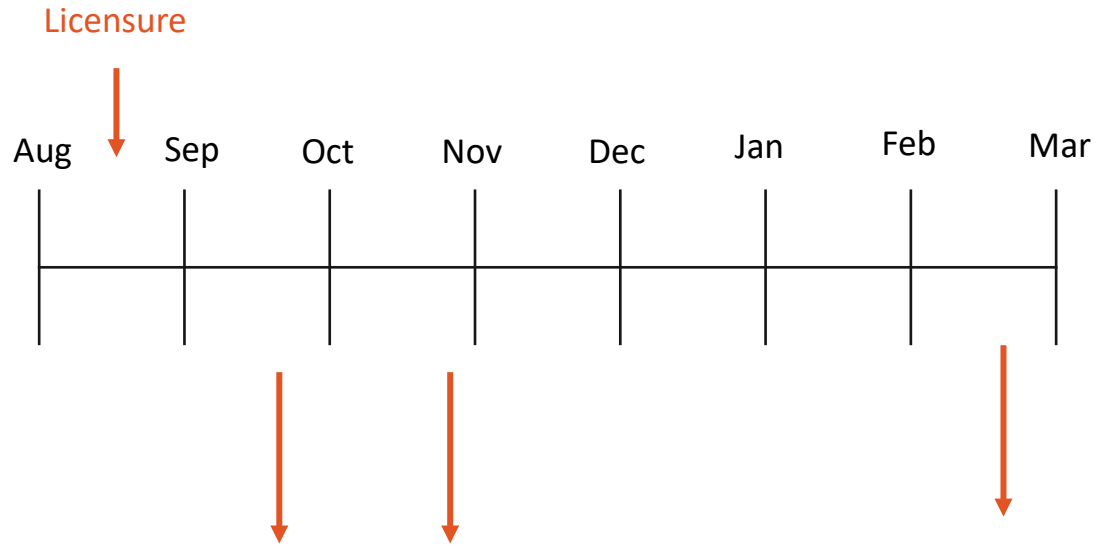
- Good immunogenicity results with high seropositivity rates
  - Following completion of 3-dose primary series
  - Following booster dose at 3 years
  - In adults and children
- Acceptable safety profile
  - Vaccine relatively well tolerated with few severe local or systemic reactions
- Limited data 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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