

Evidence to Recommendations

TBE virus and transmission

- Flavivirus, related to Powassan virus
- European, Siberian, and Far Eastern subtypes
- Transmitted by *Ixodes* species ticks
 - Infections usually acquired in wooded areas during recreational or occupational activities



Risk locations

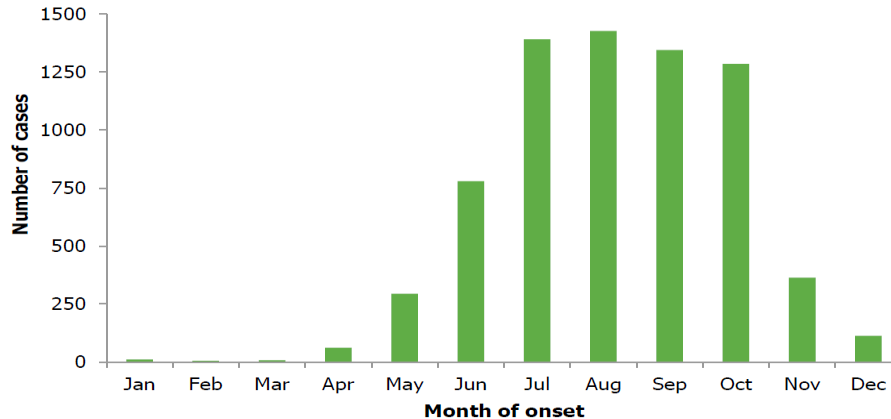
- Focal areas
- Incidence variable
 - Country-to-country
 - Within countries
 - Year-to-year



Source: Dobler et al, Wien Med Wochenschr 2012

Risk period

- Seasonal risk from April to November when ticks are active



TBE cases in nine European countries, 2000–2010

TBE in endemic areas

- Approximately 5,000–10,000 cases reported annually
- Range of TBE virus transmission is increasing in Europe

Disease risk and outcome

- Very low numbers of cases among US persons
 - 11 cases in US civilian travelers, 2001–2020
 - 9 cases in military personnel, 2006–2020



- Potentially high morbidity and mortality
 - Case fatality rates 1–20%
 - Sequelae rates 10–50%

TBE vaccine licensure in the United States



- In August 2021, TICOVAC™ approved for individuals aged ≥ 1 year
 - Adult (0.5mL) and pediatric (0.25mL) formulations
- Schedule
 - 3 primary doses
 - 1 booster dose

TBE vaccine (TICOVAC™) use internationally

- Current formulation available > 20 years
- > 75 million doses administered
- Marketed in ~ 30 countries, primarily in Europe



**Persons who travel abroad:
Evidence to Recommendations**

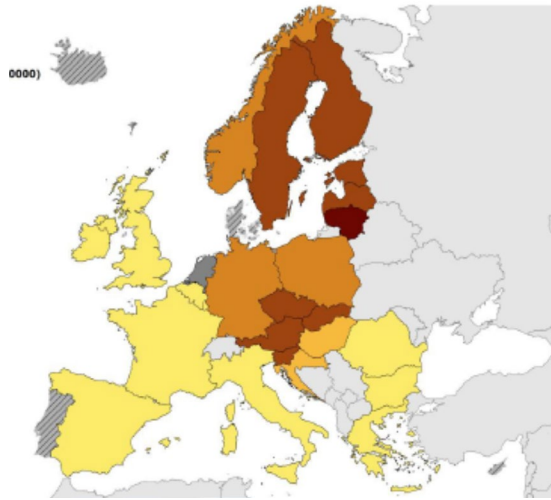
Policy question

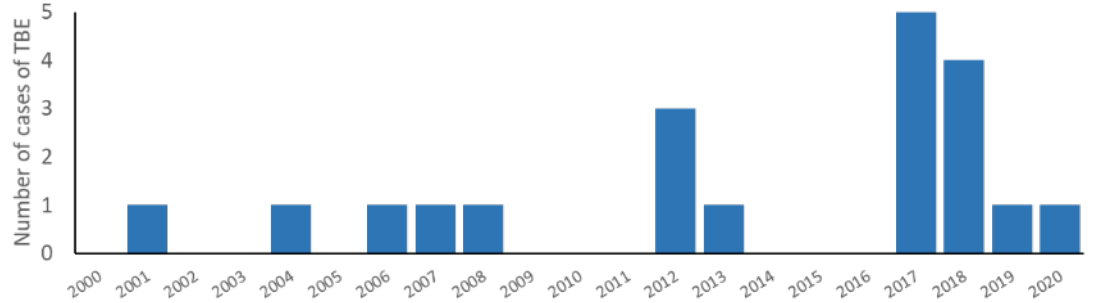
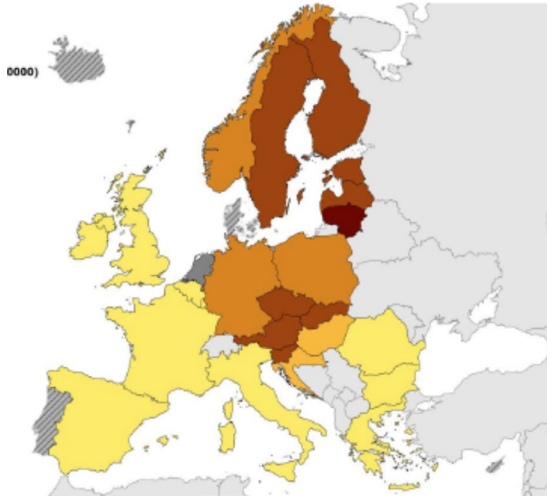
Should TBE vaccine be recommended for use in persons aged ≥ 1 year traveling to or residing in TBE risk areas?

Domain 1. Public health problem

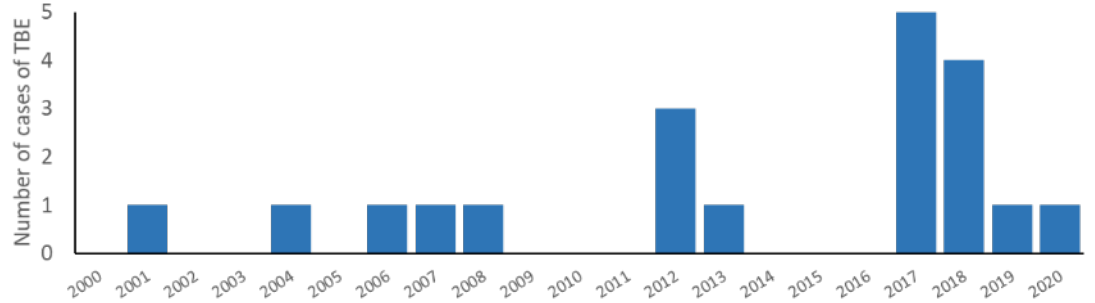
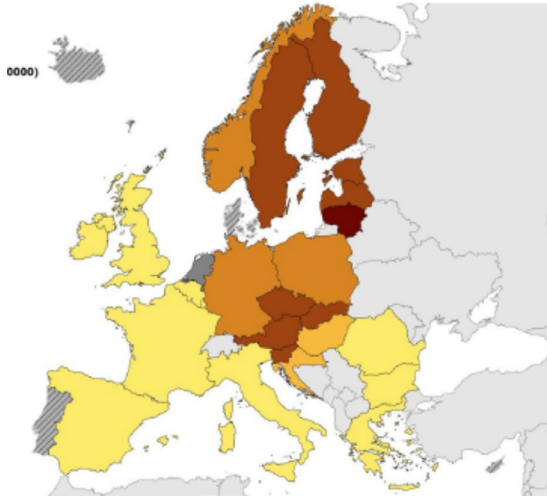
Is TBE of public health importance?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know



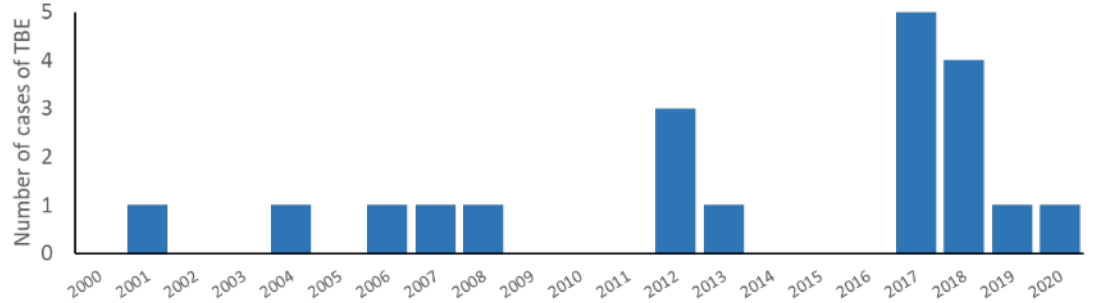
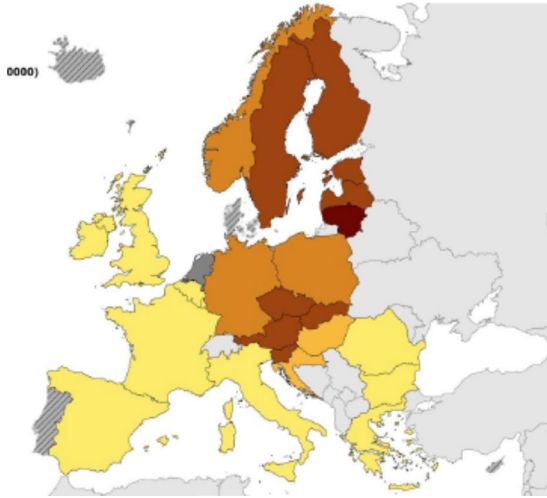


Estimated risk is <1 case of TBE per million trips



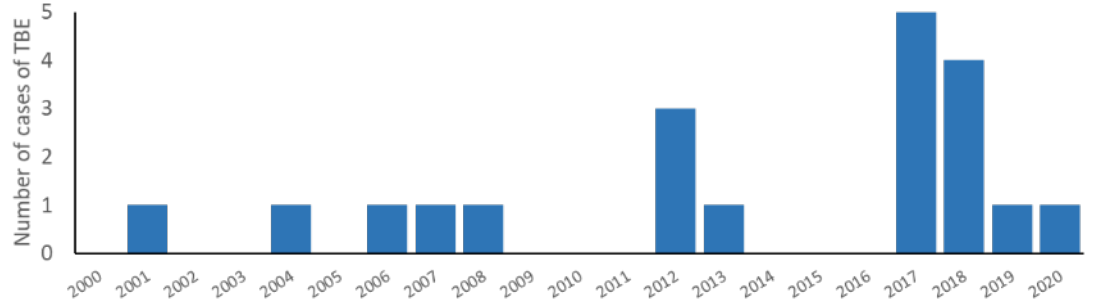
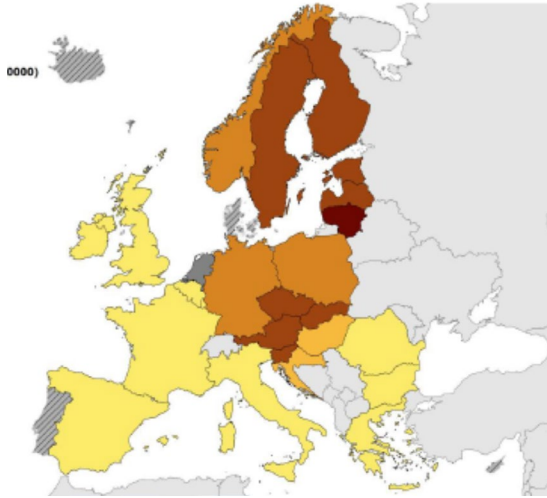
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Public health problem

Is TBE of public health importance?

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- Yes
- Varies
- Don't know

Domain 2. Benefits and harms of TBE vaccine

How substantial are the desirable anticipated effects?

- Minimal
- Small
- Moderate
- Large
- Varies
- Don't know

Outcomes assessed

- Aimed to assess protection from disease after the 3-dose primary series and after booster dose at 3 years after primary series
 - No efficacy data
 - Low TBE incidence would make such trials infeasible
- Immunogenicity data reviewed but limitations
 - No established correlate of protection
 - Vaccine based on European subtype TBE virus; likely protection for other TBE virus subtypes but limited data

Seropositivity after the primary series and booster dose

Dose	No. of studies	Age group (No. of studies)	Type of studies	Time point	Seropositivity
Primary series	10	Adult (n=7) Pediatric (n=3)	Observational	1 month	≥96%*
	2	Adult (n=1) Pediatric (n=1)	Observational	3 years [¥]	≥94%
Booster dose	2	Adult (n=1) Pediatric (n=1)	Observational	1 month	100%
	2	Adult (n=1) Pediatric (n=1)	Observational	5 years	≥94%
	2	Adult (n=1) Pediatric (n=1)	Observational	10 years	≥85%

*9 of 10 studies; [¥]Immediately prior to booster dose

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How substantial are the desirable anticipated effects?

- Minimal Small Moderate Large Varies Don't know

How substantial are the undesirable anticipated effects?

- Minimal
- Small
- Moderate
- Large
- Varies
- Don't know

Serious adverse events (SAE)

- 4 randomized controlled trials and 9 observational studies
 - 6,912 adults and children received ≥ 1 dose of vaccine in primary series
 - No vaccine-related SAEs
- 3 active post marketing surveillance studies
 - 2,679 adults and children received primary series dose or booster dose
 - One vaccine-related SAE of febrile convulsion in child with possible contributing factors

How substantial are the undesirable anticipated effects?

- Minimal
- Small
- Moderate
- Large
- Varies
- Don't know

Do the desirable effects outweigh the undesirable effects?

Favors
intervention

Favors
comparison

Favors
both

Favors
neither

Varies

Don't
know

Balance of desirable and undesirable effects

- High seropositivity rates and no serious safety concerns
- Prevents a rare but potentially serious, untreatable disease
- Healthcare provider should discuss balance with individual travelers based on their itinerary and activities
 - As with any vaccine, rare SAEs can occur
 - For some travelers, even low probability of SAE might be higher than disease risk
 - Target vaccine to travelers at higher risk for disease

Do the desirable effects outweigh the undesirable effects?

Favors
intervention

Favors
comparison

Favors
both

Favors
neither

Varies

Don't
know

What is the overall certainty of this evidence for the critical outcomes?

- No studies found
- 4 (Very low)
- 3 (Low)
- 2 (Moderate)
- 1 (High)

What is the overall certainty of the evidence for protection from TBE?

○ No studies found ○ 4 (Very low) ○ 3 (Low) ○ 2 (Moderate) ○ 1 (High)

- Observational studies only
- Indirectness as no efficacy data and unconfirmed cross-protection for non-vaccine TBE virus subtypes
- Magnitude of effect



What is the overall certainty of the evidence for serious adverse events?

No studies found 4 (Very low) 3 (Low) 2 (Moderate) 1 (High)

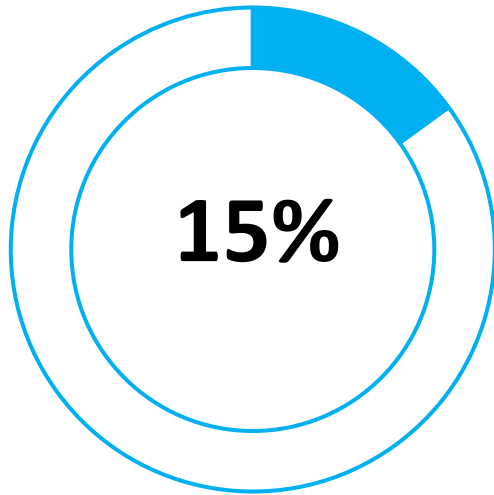
■ Risk of bias 

Domain 3. Values

Does the target population feel that the desirable effects are large relative to undesirable effects?

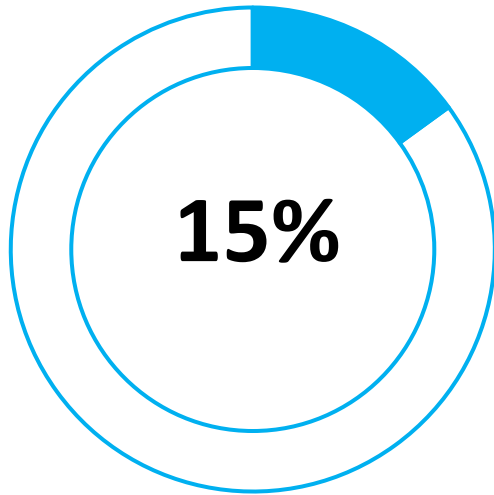
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- Probably no
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TBE vaccination practices of non-US travelers to TBE endemic countries engaging in at-risk activity for TBE

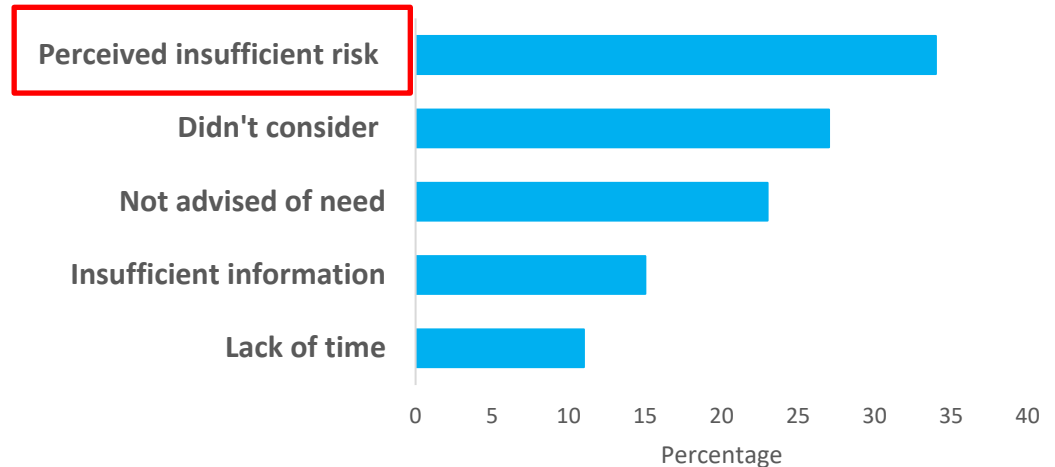


Travelers with high risk activities who were **vaccinated** before travel (56 of 375)

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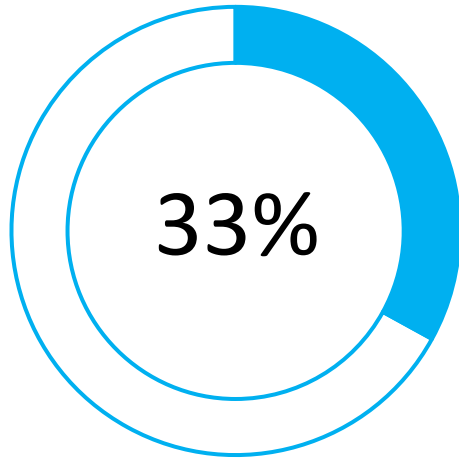


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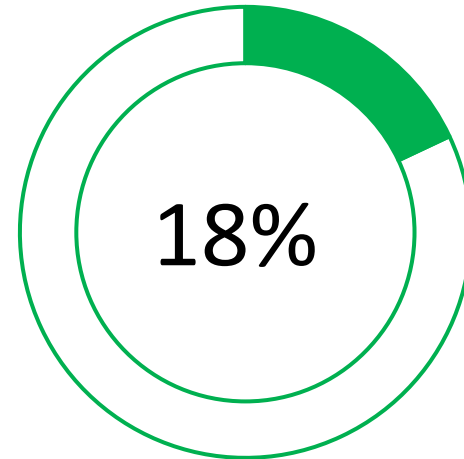


Reasons for no vaccination

TBE vaccination rates of residents of TBE endemic country with vaccination paid for out-of-pocket



Residents of **risk areas**



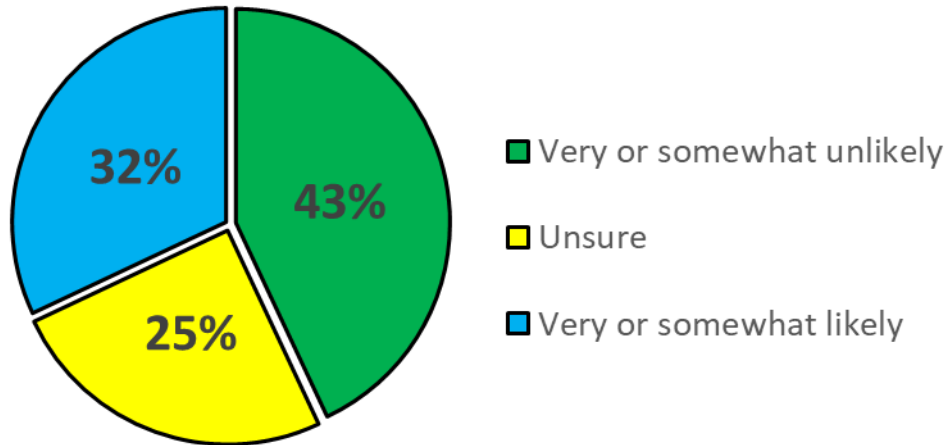
Residents of **other areas**

US population perceptions of vaccination when considering Japanese encephalitis (JE) and JE vaccine

- Similarities between JE and TBE
 - Disease risk for travelers low
 - Potential impact of disease high
 - Vaccines are safe and effective
 - Vaccines are high cost

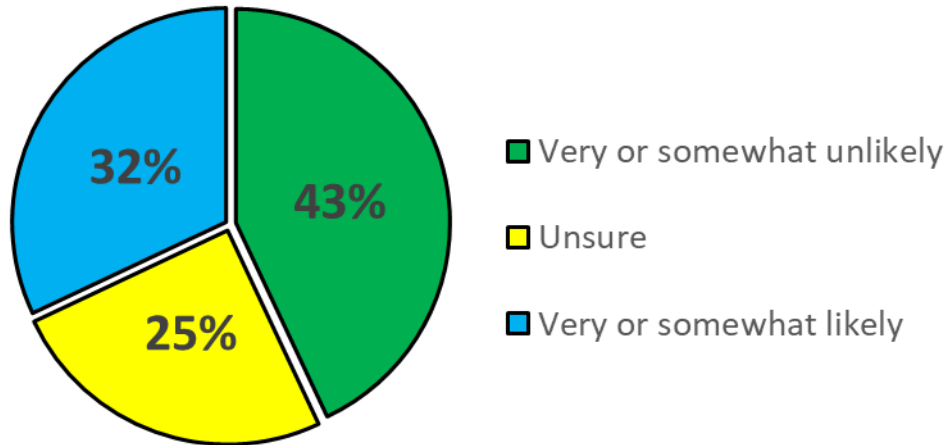
Perceptions of a similar travel vaccine

Likelihood of vaccination (N=6,427)



Perceptions of a similar travel vaccine

Likelihood of vaccination (N=6,427)



Factors in decision

Prevention of a disease with potentially serious outcomes and no treatment



Expensive vaccine with possibility of rare serious side effects

Values

Does the target population feel that the desirable effects are large relative to undesirable effects?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Important uncertainty or variability

Probably important uncertainty or variability

Probably not important uncertainty or variability

No important uncertainty or variability

No known undesirable outcomes

Domain 4. Acceptability

Is TBE vaccine acceptable to key stakeholders?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

Acceptability to key stakeholders



- Healthcare providers
 - TBE vaccine available in Europe and recommended by European providers



- Travelers
 - Option for protection from a potentially severe disease

Acceptability

Is the intervention acceptable to key stakeholders?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

Domain 5. Resource use

Is TBE vaccination a reasonable and efficient allocation of resources?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

Cost-effectiveness considerations

- No cost-effectiveness analysis (CEA)
 - Most travel vaccines are not cost-effective
 - TBE vaccine for travelers is not likely to be cost-effective
- CEA less relevant for a travel vaccine
 - Decision is for individual traveler and not for population
 - Vaccine paid for by traveler and generally not covered by insurance
 - Not covered under Vaccines for Children program
- CEAs in endemic countries
 - Variable results with incidence and vaccine cost important variables

Resource allocation considerations

- Vaccine recommendations targeting higher risk travelers probably reasonable allocation of resources
 - Financial implications borne by travelers most at risk and who benefit most
 - Variation based on actual disease risk, likelihood of use of other tick prevention measures, and opportunity costs
- Healthcare costs for TBE presenting as neurologic illness potentially large

Resource use

Is TBE vaccination a reasonable and efficient allocation of resources?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

Domain 6. Equity

What would be the impact on health equity?

- Reduced
- Probably reduced
- Probably no impact
- Probably increased
- Increased
- Varies
- Don't know

Health equity considerations

- TBE vaccine paid for out-of-pocket, by insurance companies, or by employers
 - Prevention currently by tick prevention measures
 - Vaccine availability could lead to health disparities
- Absolute risk of TBE is low and vaccine use among limited group, so not cause substantial disparities
- TBE vaccine recommendations cannot address this issue

Equity

What would be the impact on health equity?

- Reduced
- Probably reduced
- Probably no impact
- Probably increased
- Increased
- Varies
- Don't know

Domain 7. Feasibility

Is the intervention feasible to implement?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

Barriers to implementation

- Primary vaccination schedule requires minimum 5 months to complete
- Possible lack of healthcare provider understanding of who might benefit most from vaccination
 - CDC will post resources once recommendations approved

Feasibility

Is the intervention feasible to implement?

- No Probably no Probably yes Yes Varies Don't know

Balance of consequences

- Undesirable consequences *clearly outweigh* desirable consequences in most settings
- Undesirable consequences *probably outweigh* desirable consequences in most settings
- The balance between desirable and undesirable consequences *is closely balanced or uncertain*
- Desirable consequences *probably outweigh* undesirable consequences in most settings
- Desirable consequences *clearly outweigh* undesirable consequences in most settings
- There is insufficient evidence to determine the balance of consequences

Proposed policy option category

- TBE vaccination for persons who travel abroad based on **shared clinical decision-making**

Draft recommendation

TBE vaccine should be considered for persons aged ≥ 1 year traveling or moving abroad to TBE-endemic areas if they are at risk of TBE virus exposure through engaging in outdoor activities during the transmission season in environments where ticks are likely to be present

Information accompanying recommendations

- Factors that increase risk of TBE virus exposure
- Need for travelers to use preventive measures to avoid tick bites
- Advice to avoid consumption of unpasteurized dairy products
- General factors to consider in decision whether to vaccinate