FSME-IMMUN Development 2000 - 2020

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Global Viral Vaccines Medical and Scientific Affairs Lead, Pfizer

Pfizer Medical

Agenda

- **Background**
- Study Overview
- Adult Development: Main Studies
- Pediatric Development: Main Studies
- Long-term Protection: All Ages
- Breadth of Subtype Coverage
- Vaccine Effectiveness
- Additional Topics
- Summary

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Pfizer's Tick-borne Encephalitis Vaccine

- FSME-IMMUN is an inactivated whole-virus vaccine, developed and then first licensed in Austria in 1976
  - Suspension of purified TBEV-EU (strain Neudörfl) propagated in chicken embryo fibroblast cells derived from pathogen-free eggs
  - Highly purified by the use of continuous-flow zonal ultracentrifugation, free of thiomersal, HSA as stabilizer
- Approved Tradenames – Ex-USA
  - FSME-IMMUN / Tico Vac
    - 0.5mL with 2.4 µg TBEV-EU for use as of ≥ 16years of age
  - FSME-IMMUN Junior / Tico Vac Junior
    - 0.25mL with 1.2µg TBEV-EU for use in children and adolescents 1–15 years of age
- US tradename
  - TBD

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SMPC data on file; Barret et al. History of TBE vaccines; 2003; Loew-Baselli et al. (2011), Vaccine 29: 7307– 7319

FSME-IMMUN®

Historical Development[3]

1976	• First approved in Austria as vaccination for **high-risk groups**
1981	• **TBE mass vaccination** introduced in Austria
1999	• **Removal of thiomersal** (and its stabilizer) in fulfilment of Ph. Eur. Requirements
2000	• **Removal of human serum albumin** (HSA) and use of a production virus seed free of potential contaminating mouse brain protein, achieved by subjecting the master virus seed to 2 sequential passages in primary chick embryo cells • These changes to the manufacturing process and final formulation required a **new marketing authorization** to be obtained. The newly approved vaccine was called FSME-IMMUN® • **HSA removal** was associated with a **substantial increase in the rate of high fever** in infants and young children
2001	• **HSA again added** to the TBE vaccine, which was again named FSME-IMMUN® and licensed based on a new clinical development program • The incidence of adverse reactions decreased to expected levels
2003	• Launch of FSME-IMMUN Junior

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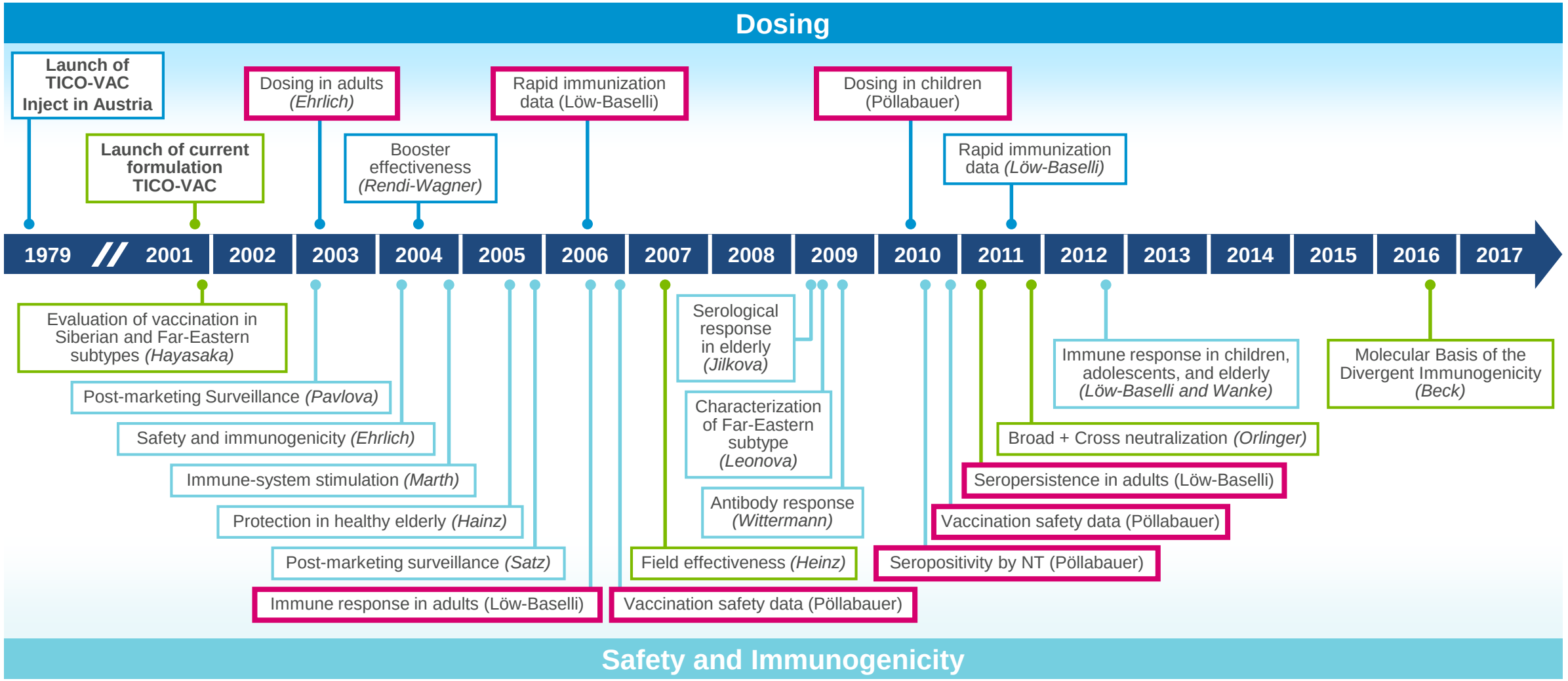
Loew-Baselli et al. (2011) *Vaccine* 29:7307– 7319

Over >40 Years FSME Accumulated a Large Body of Evidence and Extensive Experience

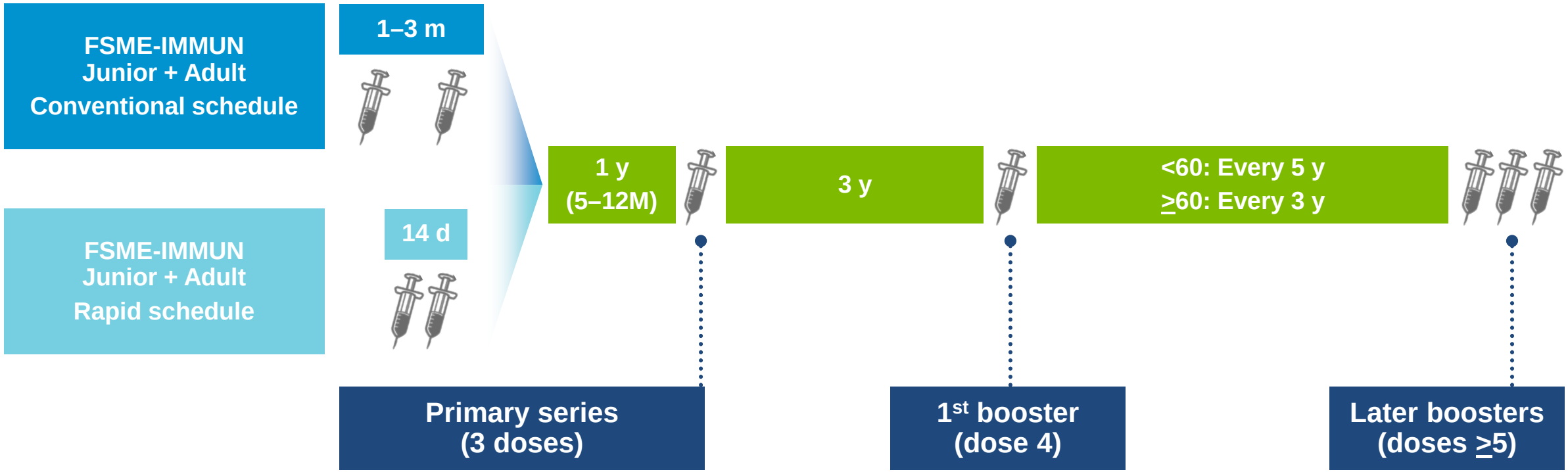


Studies Reviewed in Current Presentation

Pfizer Medical

Heinz et al. (2013) *Emerg Infect Dis.* 2013;19(1):69-76; Heinz et al. (2015) *Euro Surveill.* 2015;20(13):9-16.
Loew-Baselli et al. (2011) *Vaccine* 29: 7307–7319; Pfizer, data in file.

FSME-IMMUN Vaccination Schedule



FSME-Immun SmPC; data on file

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Assays Used in Clinical Studies with FSME-IMMUN

In Clinical Studies with FSME-IMMUN, the Following Assays for Assessing the Immunogenicity of the Vaccine Were Used

Enzyme-linked immunoassay (ELISA)

- **Immunozym FSME-IgG** (strain Neudörfl), PROGEN Biotechnik Heidelberg, Germany
- Based on over 20 years of field experience, serum IgG levels

  >126 VIE U/ml are considered **positive**

  63−126 VIE U/ml are considered **borderline**

  <63 VIE U/ml are considered **negative**

NOTE: There is no serological correlate of protection for TBE

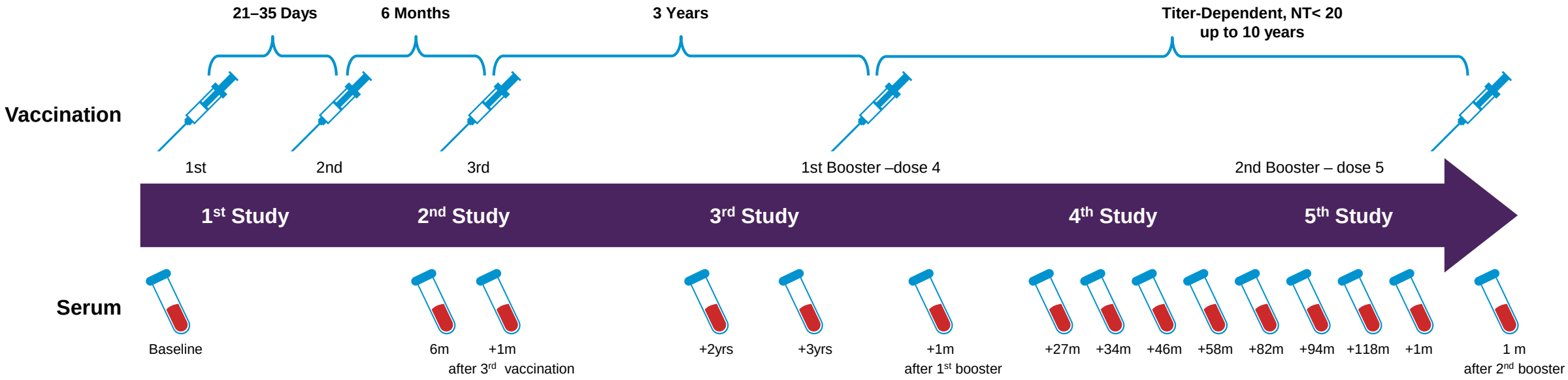
Neutralization assay (NT)

- Virus neutralization tests were performed in accordance with the method described by Adner et al (2001) (in house test; Nd seed virus strain).
- A neutralization value of **≥ 1:10** is considered **positive**

Adner N et al (2001) Pharmacokinetics of human tick-borne encephalitis virus antibody levels after injection with human tick-borne encephalitis immunoglobulin, solvent/detergent treated, FSME-BULIN S/D in healthy volunteers. *Scand J Infect Dis* 33(11):843-7

Clinical Studies Presented Here for Full Schedule

FSME-IMMUN, Adults 16–65 Years



	1st Study	2nd Study	3rd Study	4th + 5th Study
Study Period	10/2001 – 01/2002	05 – 08/ 2002	06/2004 – 07/2005	07/2007 – 07/2010, 05/2012 – 06/2015
Vaccine Dose #	1 + 2	3	1st Booster	2nd Booster

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Sources: Konior et al (2017) *Vaccine* 35:3607-3613; Pöllabauer et al. (2019) *Vaccine* 37:3241-3250

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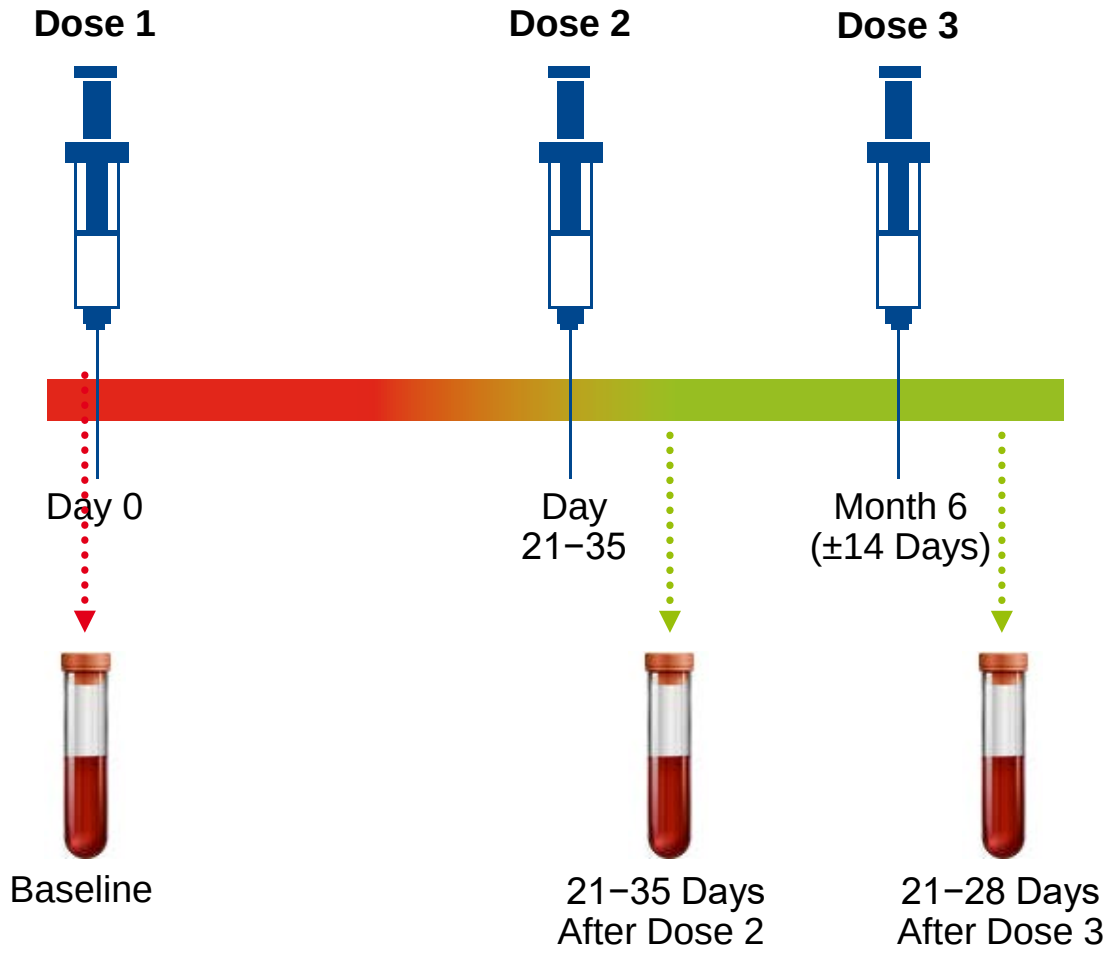
Dose Finding (Ehrlich et al 2003 - In adults aged 16-65yrs (N=405))

Schedule for Vaccination and Immunogenicity Testing

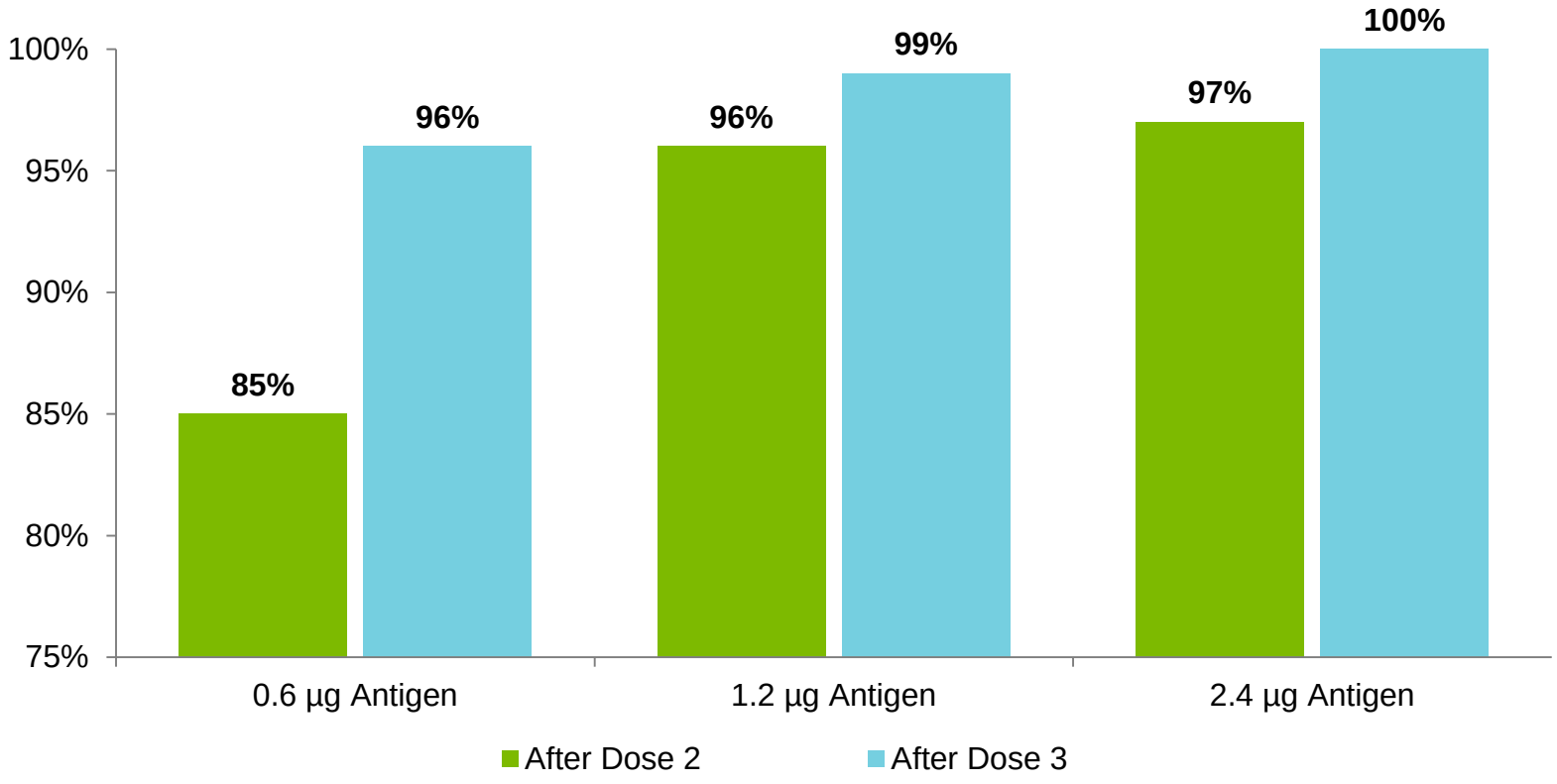


Ehrlich H et al (2003) Randomized, phase II dose-finding studies of a modified tick-bome encephalitis vaccine: evaluation of safety and immunogenicity. *Vaccine* 22:217−223.

Dose Finding (Ehrlich et al 2003 - In adults aged 16-65yrs (N=405))

Immunological Response

Seropositivity Rates (%) After Doses 2 and 3 [ELISA]



Serum IgG Levels >126 VIE U/ml Are Considered Positive

- The lower limit of the 95% CI of the seroconversion rate of the 0.6 µg dose was below the predefined 85% limit, eliminating this dose from further consideration
- **The two higher doses were compared with regards to the fever rates after dose 1**

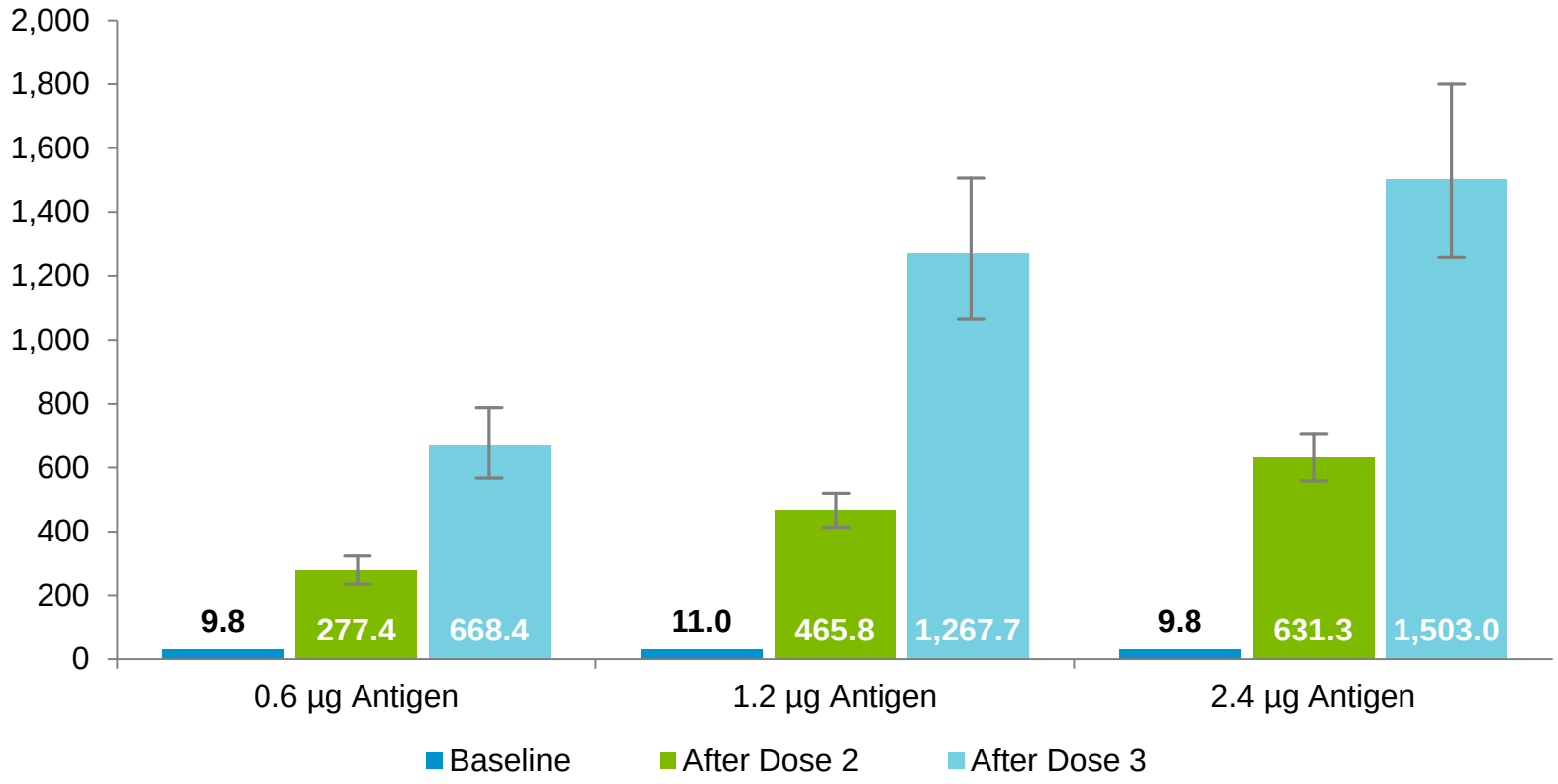
Pfizer Medical

Ehrlich H et al (2003) Randomized, phase II dose-finding studies of a modified tick-bome encephalitis vaccine: evaluation of safety and immunogenicity. *Vaccine* 22:217−223.

Dose Finding (Ehrlich et al 2003 - In adults aged 16-65yrs (N=405))

Immunological Response

GMCs (95% CIs) at Baseline and After Doses 2 and 3 (VIE U/ml)



- High geometric mean concentrations (GMCs) were seen for the 1.2 and 2.4 µg doses after doses 2 and 3
- After dose 2, the GMC was significantly higher following vaccination with the 2.4 µg dose
- After dose 3, the GMC was higher following vaccination with the 2.4 µg dose, but the CIs of the 1.2 and 2.4 µg doses overlapped

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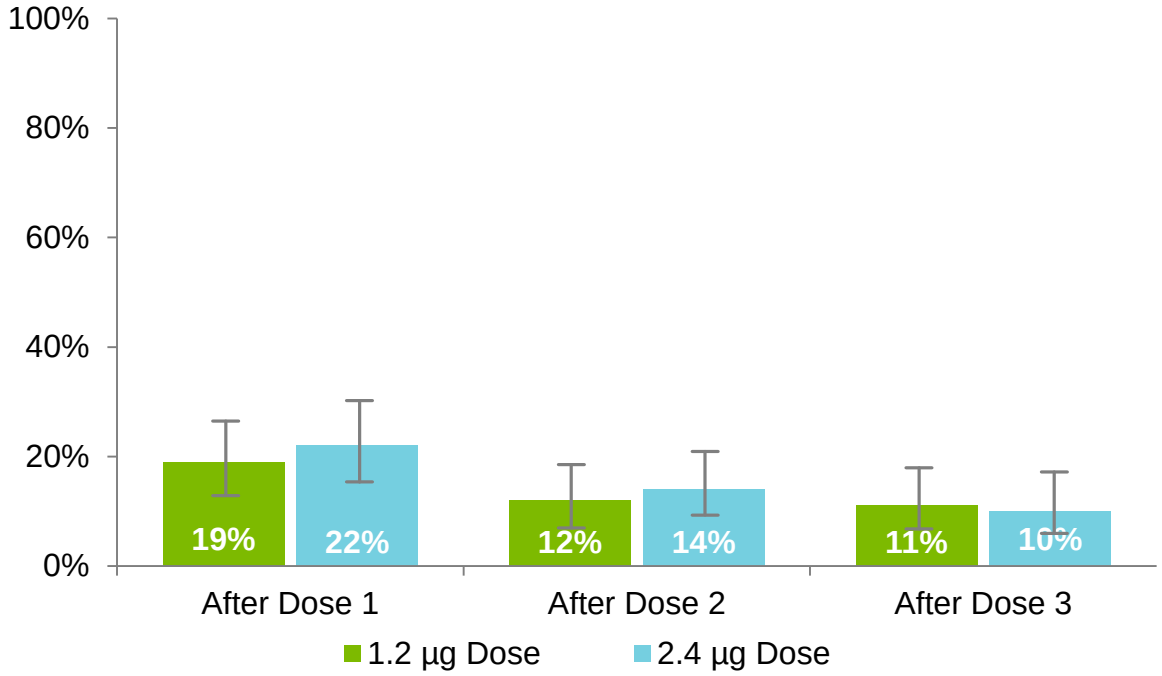
Ehrlich H et al (2003) Randomized, phase II dose-finding studies of a modified tick-bome encephalitis vaccine: evaluation of safety and immunogenicity. *Vaccine* 22:217−223.

Dose Finding (Ehrlich et al 2003 - In adults aged 16-65yrs (N=405))

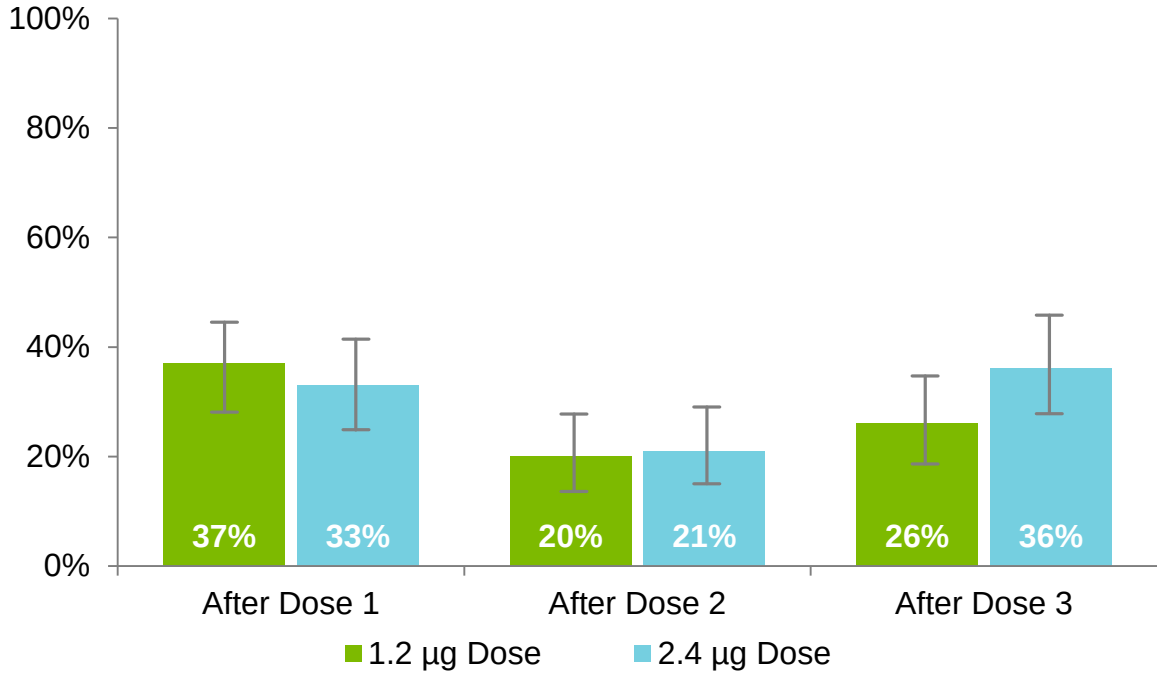
Safety

Systemic Reactions (Excluding Fever)



Systemic Reactions Were Mainly Mild, and Their Frequency Decreased With Later Doses

Local Reactions



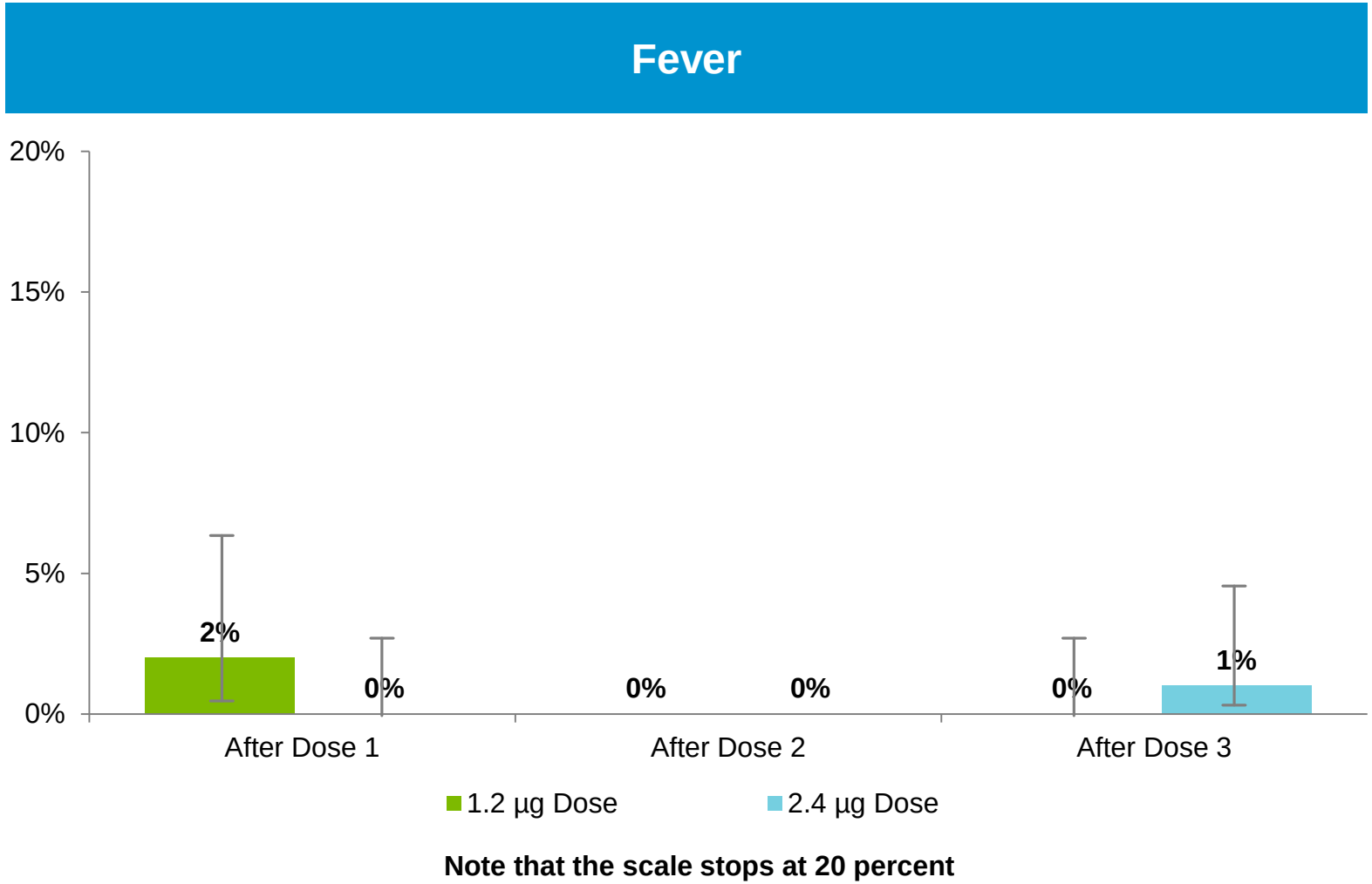
The Occurrence of Local Reactions Was Not Dose-dependent, and Their Frequency Was Lowest After Dose 2

Pfizer Medical

Ehrlich H et al (2003) Randomized, phase II dose-finding studies of a modified tick-bome encephalitis vaccine: evaluation of safety and immunogenicity. *Vaccine* 22:217−223.

Dose Finding (Ehrlich et al 2003 - In adults aged 16-65yrs (N=405))

Safety

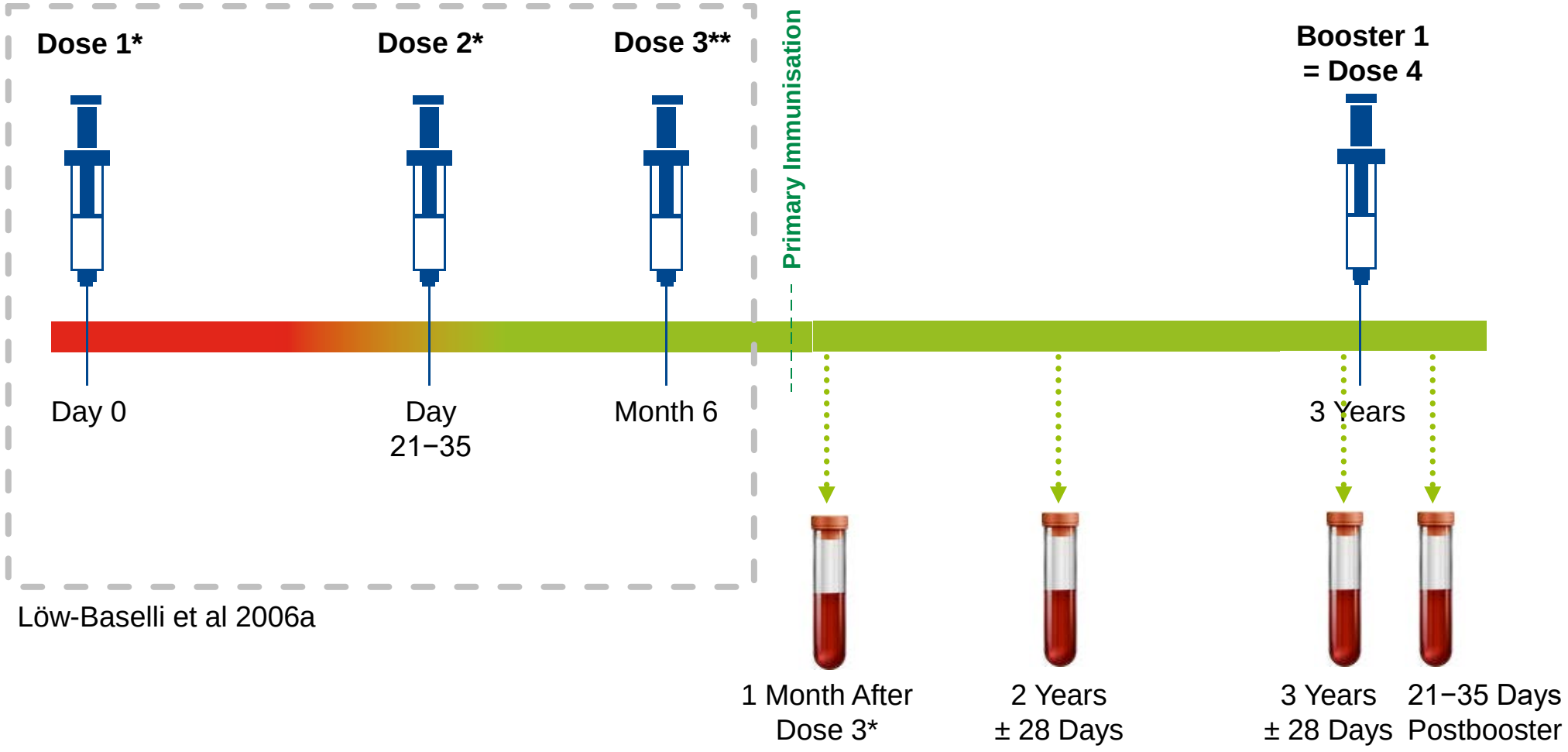


- Fever ≥38°C was observed at a very low rate
- **Only 1 case of fever reported in the 2.4 µg dose group**
- **No unexpected adverse events or vaccine-related serious adverse events were observed during the study**

Ehrlich H et al (2003) Randomized, phase II dose-finding studies of a modified tick-bome encephalitis vaccine: evaluation of safety and immunogenicity. *Vaccine* 22:217−223.
Marth E, Kleinhappl B. Albumin is a necessary stabilizer of TBE-vaccine to avoid fever in children after vaccination. Vaccine. 2001;20(3-4):532-537.

Antibody Persistence 2 and 3 Years After 3 Doses FSME-IMMUN and Booster (4th Dose) (Löw-Baselli et al 2009 – In Adults 18-67yrs (N=347))

Schedule for Vaccination and Immunogenicity Testing



Löw-Baselli et al 2006a

* FSME-IMMUN Adults or Encepur

** FSME-IMMUN

Löw-Baselli A et al (2009) Seropersistence of tick-borne encephalitis antibodies, safety and booster response to FSME-IMMUN 0.5 ml in adults aged 18-67 years. *Human Vaccines* 5:551-6.

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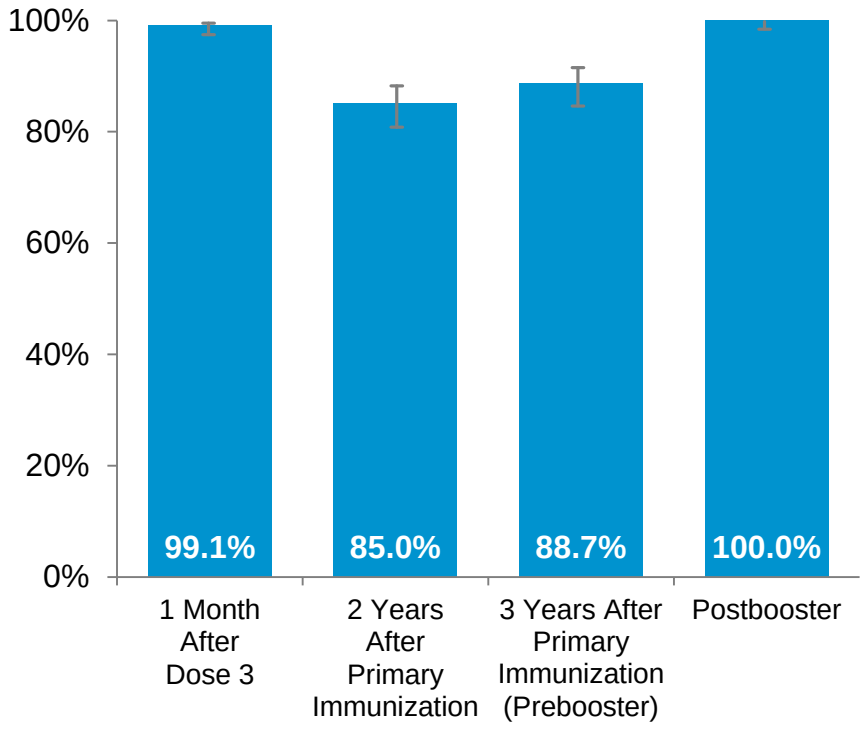
Antibody Persistence 2 and 3 Years After 3 Doses FSME-IMMUN and Booster (4th Dose) (Löw-Baselli et al 2009 – In Adults 18-67yrs (N=347))

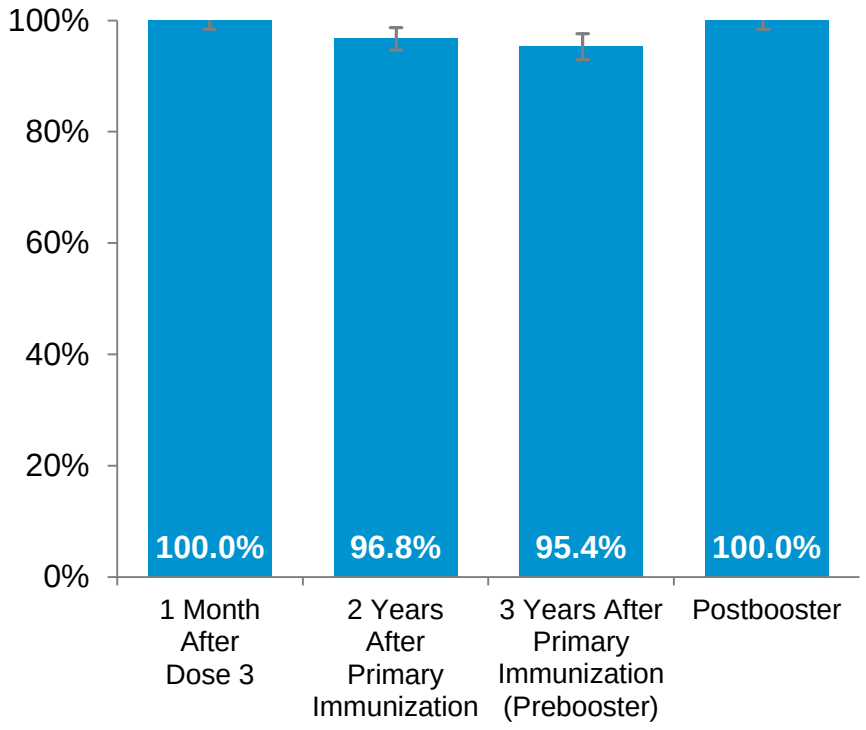
Seropositivity Rates

Seropositivity Rates (%) and 95% CIs Before and After the Booster Dose [ELISA]



Serum IgG Levels >126 VIE U/ml Are Considered Positive

Seropositivity Rates (%) and 95% CIs Before and After the Booster Dose [NT]



A Neutralization Value of ≥ 1:10 Is Considered Positive

- One month after primary immunization, seropositivity rates were close to 100% using ELISA and 100% using NT
- By 2 and 3 years after primary immunization, seropositivity rates had decreased
- **After the first booster, seropositivity rates increased to 100%,** regardless of the test method

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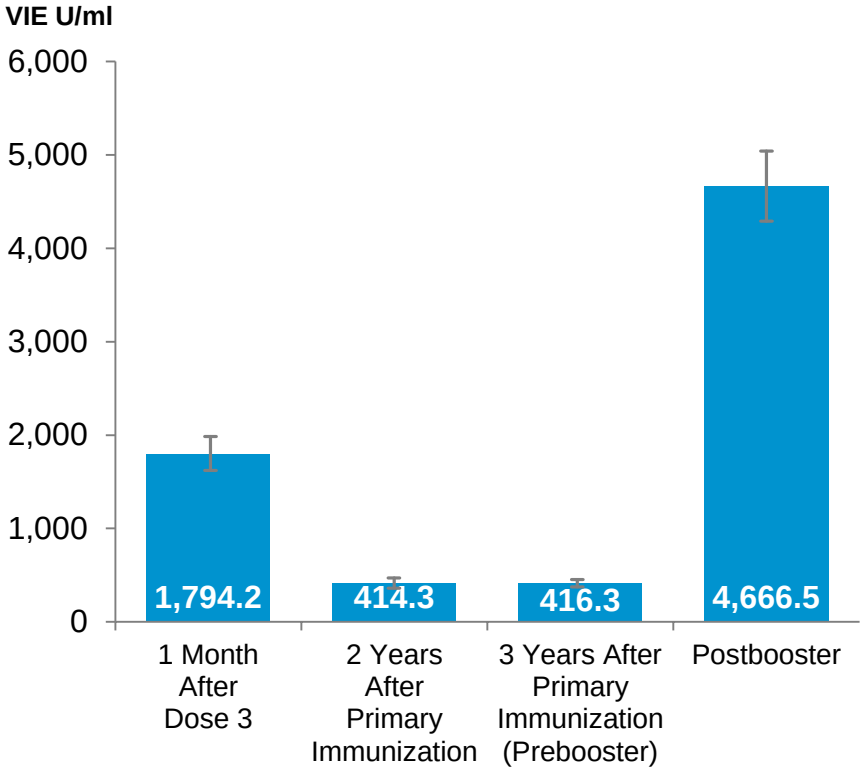
Löw-Baselli A et al (2009) Seropersistence of tick-borne encephalitis antibodies, safety and booster response to FSME-IMMUN 0.5 ml in adults aged 18-67 years. *Human Vaccines* 5:551-6.

Antibody Persistence 2 and 3 Years After 3 Doses FSME-IMMUN and Booster (4th Dose) (Löw-Baselli et al 2009 – In Adults 18-67yrs (N=347))

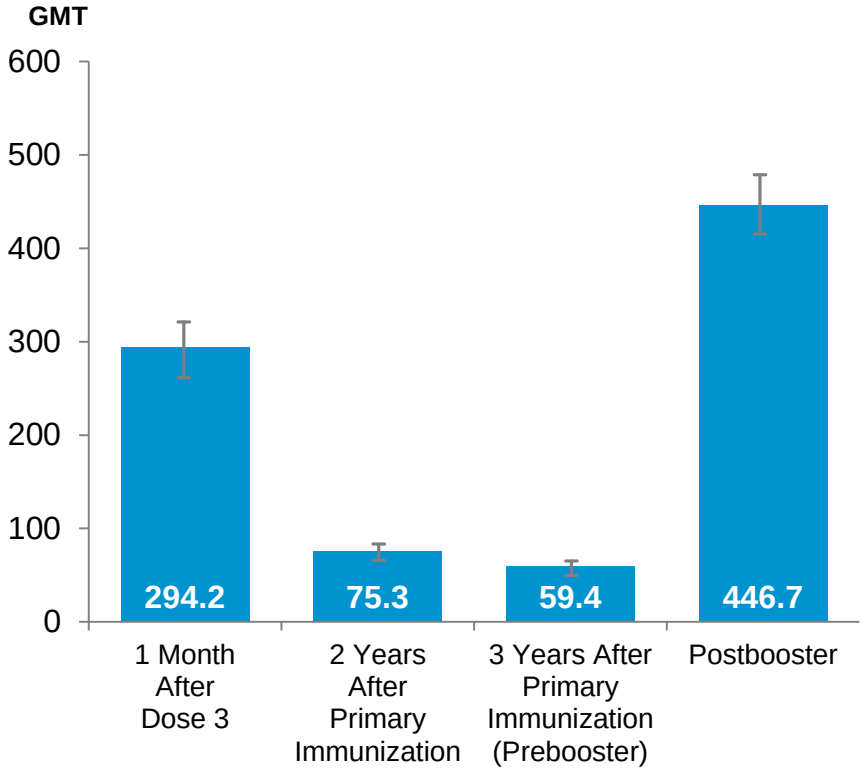
GMC and GMTs

Geometric Mean Concentrations (GMCs) and 95% CIs Before and After the Booster Dose [ELISA]



Serum IgG Levels >126 VIE U/ml Are Considered Positive

Geometric Mean Titers (GMTs) and 95% CIs Before and After the Booster Dose [NT]



A Neutralization Value of ≥ 1:10 Is Considered Positive

- Between 1 month and 2 years after primary immunization, GMCs/GMTs **decreased about 4-fold**
- After the booster vaccination, GMCs/GMTs **increased above 1-month levels. The geometric mean of the fold increase** between prebooster and postbooster antibody levels was **11.2** (95% CI, 10.2 to 12.3) using ELISA and **7.5** (95% CI, 6.7 to 8.4) using NT

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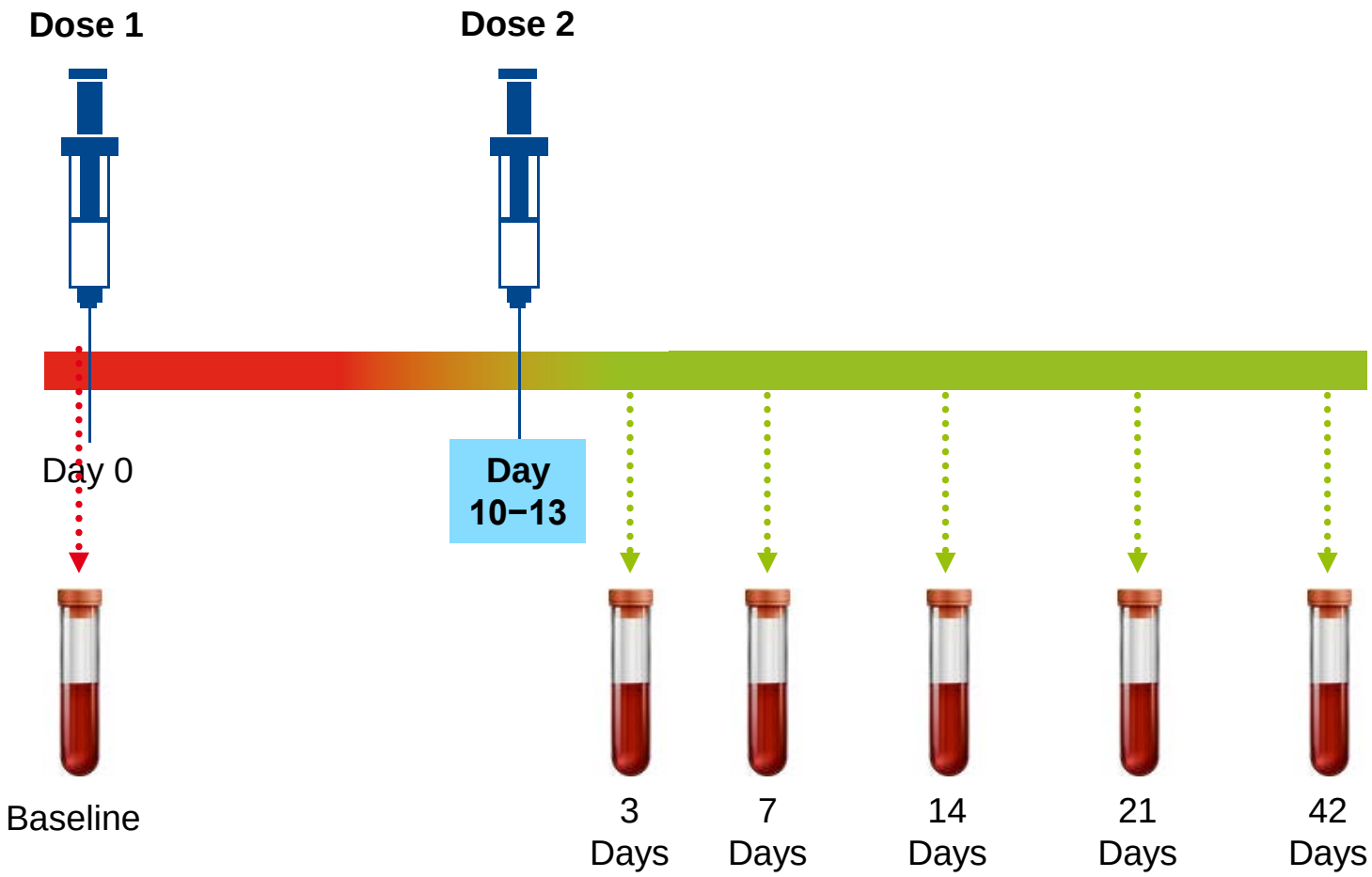
Löw-Baselli A et al (2009) Seropersistence of tick-borne encephalitis antibodies, safety and booster response to FSME-IMMUN 0.5 ml in adults aged 18-67 years. *Human Vaccines* 5:551-6.

FSME-IMMUN: Rapid Schedule (First 2 Doses 2 Weeks Apart)

(Löw-Baselli et al 2006b - In adults aged 16-65yrs (N=60))

Schedule for Vaccination and Immunogenicity Testing



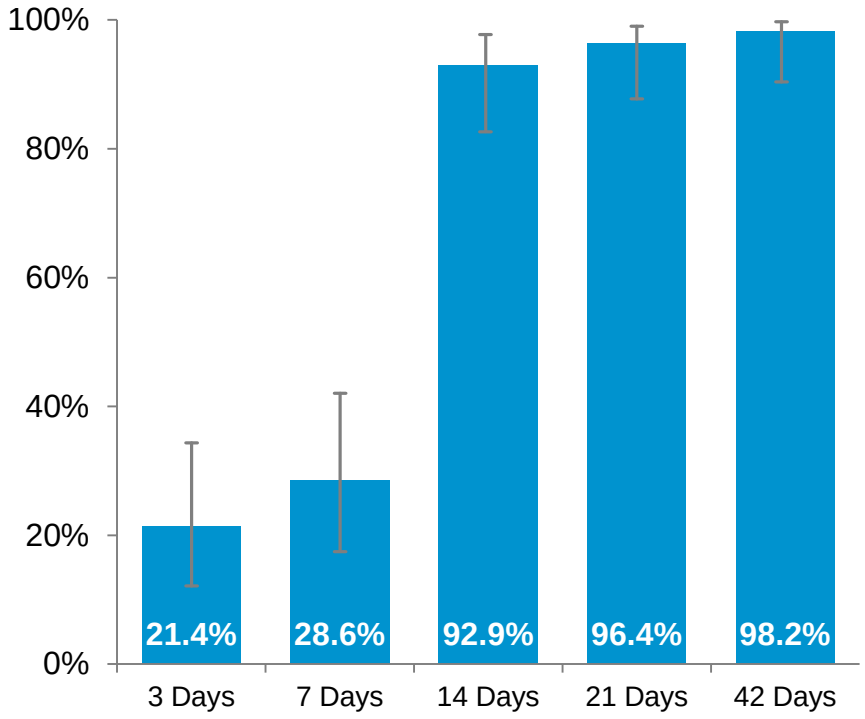
Loew-Baselli A et al (2006) Immunogenicity and safety of FSME-IMMUN 0.5 ml using a rapid immunization schedule. *IJMM* 296:213−4.

FSME-IMMUN: Rapid Schedule (First 2 Doses 2 Weeks Apart)

(Löw-Baselli et al 2006b - In adults aged 16-65yrs (N=60))

Immunogenicity After Dose 2

Seropositivity Rates (%) and 95% CIs After Dose 2 [ELISA]



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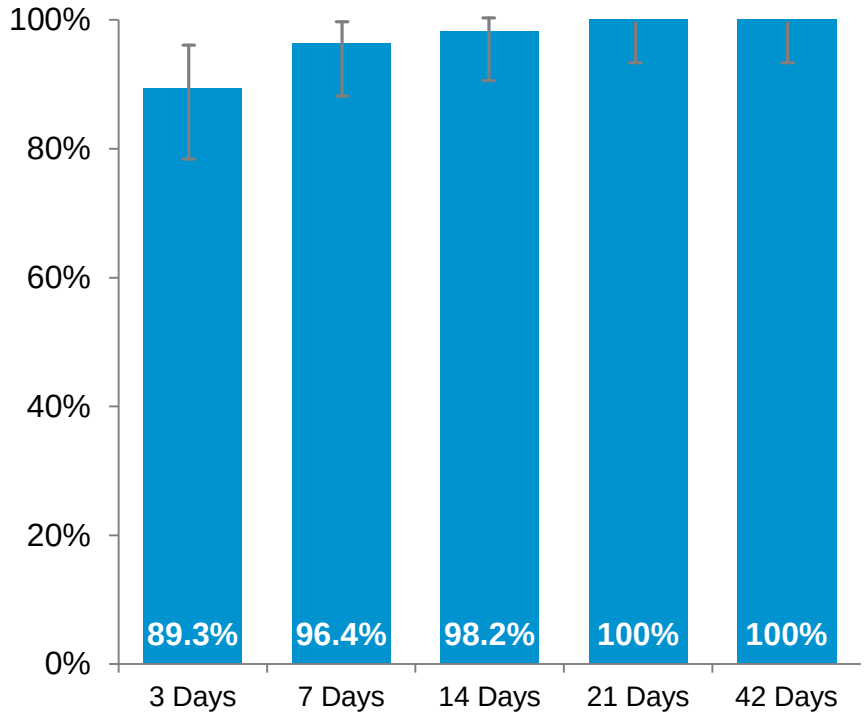
Seropositivity Rates (%) and 95% CIs After Dose 2 [NT]



A Neutralization Value of ≥ 1:10 Is Considered Positive

- Similar developments were seen in terms of GMCs and GMTs, with peaks reached 21 days after dose 2

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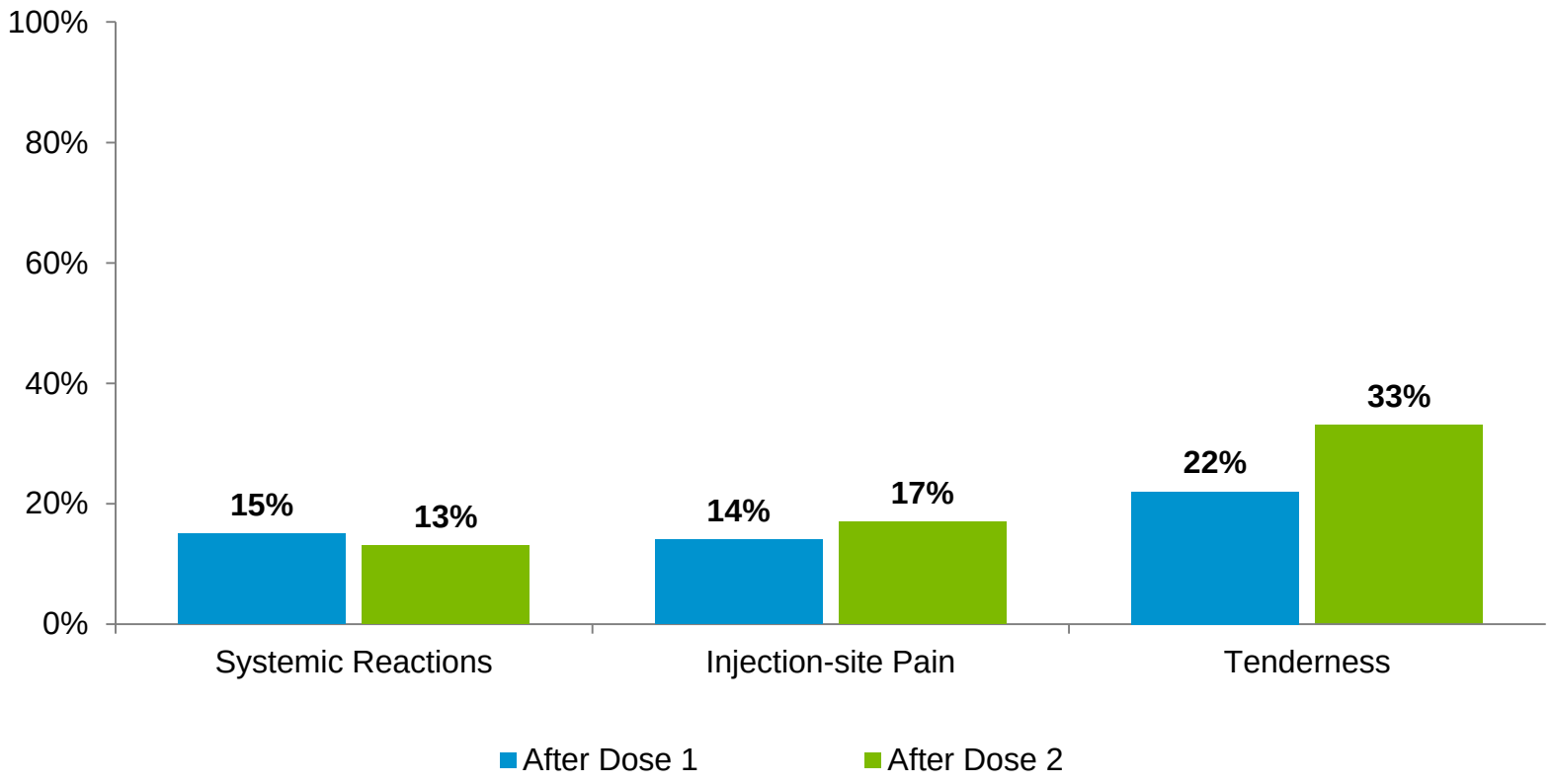
Loew-Baselli A et al (2006) Immunogenicity and safety of FSME-IMMUN 0.5 ml using a rapid immunization schedule. *IJMM* 296:213−4.

FSME-IMMUN: Rapid Schedule (First 2 Doses 2 Weeks Apart)

(Löw-Baselli et al 2006b - In adults aged 16-65yrs (N=60))

Safety After Doses 1 and 2

Systemic and Most Frequent Local Reactions After Doses 1 and 2



- Most systemic and all local reactions were mild
- The most frequently reported systemic reactions were myalgia, headache, and fatigue
- Injections-site pain and tenderness were by far the most frequent local reactions
- **No serious adverse experiences were reported**

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Loew-Baselli A et al (2006) Immunogenicity and safety of FSME-IMMUN 0.5 ml using a rapid immunization schedule. *IJMM* 296:213−4.

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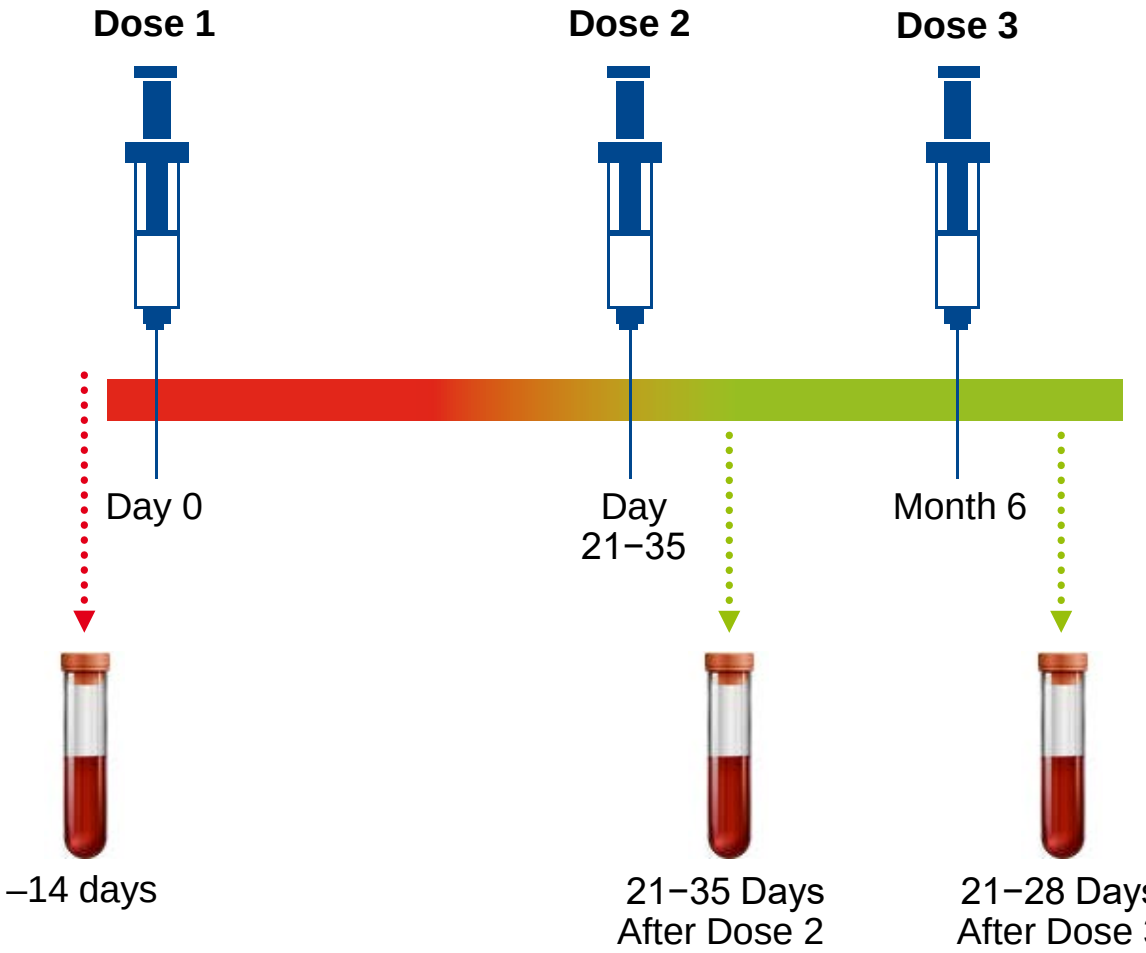
Pediatric Dose Finding + Safety Study
(Pöllabauer et al 2010a – In children age 1-15yrs)

Schedule for Vaccination and Immunogenicity Testing



- **Design**: Two dose-finding studies (**N = 1278**) AND one open label safety study (**N = 2417**) with the pediatric formulation in children / adolescents 1–15 years
- **Conclusions:** FSME-IMMUN pediatric vaccine formulation is safe and highly immunogenic, not only for children <12 years, but also for adolescents <16 years.

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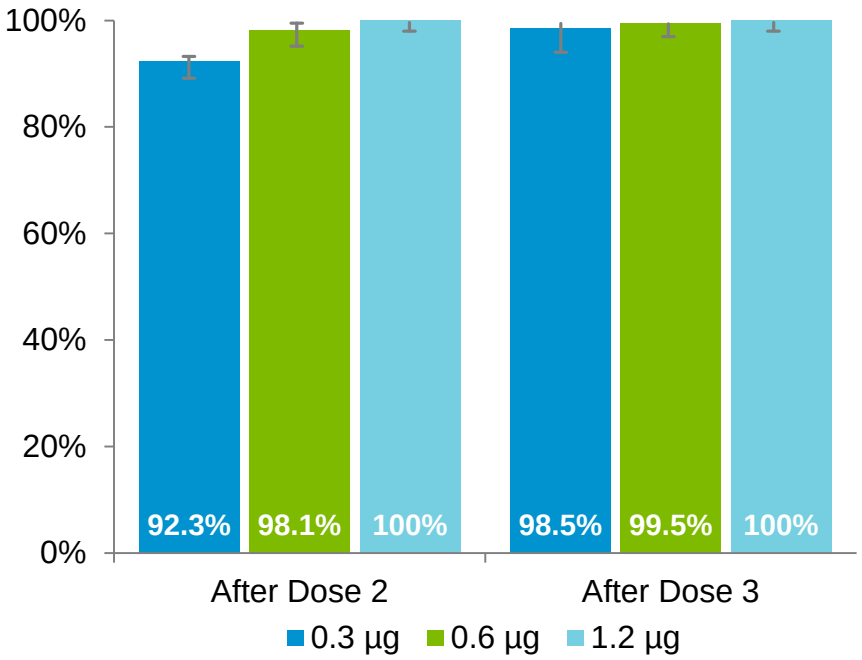
Pöllabauer EM et al (2010a) Clinical evaluation to determine the appropriate paediatric formulation of a tick-borne encephalitis vaccine. *Vaccine* 28:4558−65

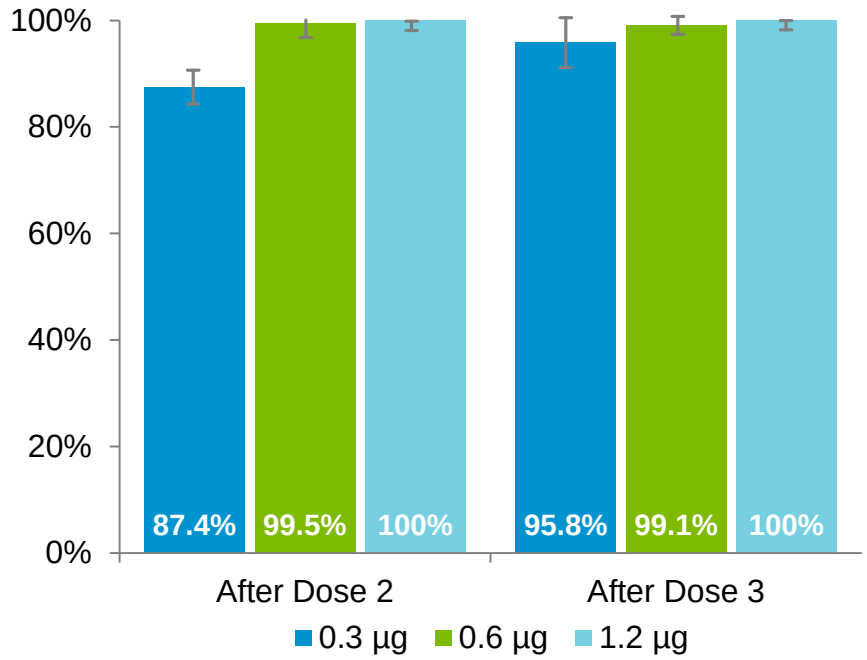
Pediatric Dose Finding Study (Pöllabauer et al 2010a - In children aged 1-15yrs (N=1278))

Seroconversion Rates After Doses 2 and 3

Seroconversion Rates Determined by ELISA After Doses 2 and 3 in Children Aged 1−5 Yrs.



Seroconversion Rates Determined by ELISA After Doses 2 and 3 in Children Aged 6−15 Yrs.



- Both the 0.6 and 1.2 µg doses were highly immunogenic in both age groups. The 0.3 µg dose induced slightly lower seroconversion rates, with the lower level of the 95% CI after dose 2 in the older age group below 85%, the predefined lower limit for the optimal vaccine dose

Based on the Results of These Dose-finding Studies, 1.2 µg Was Considered the Preferred Dose for Children Aged 1–15 years

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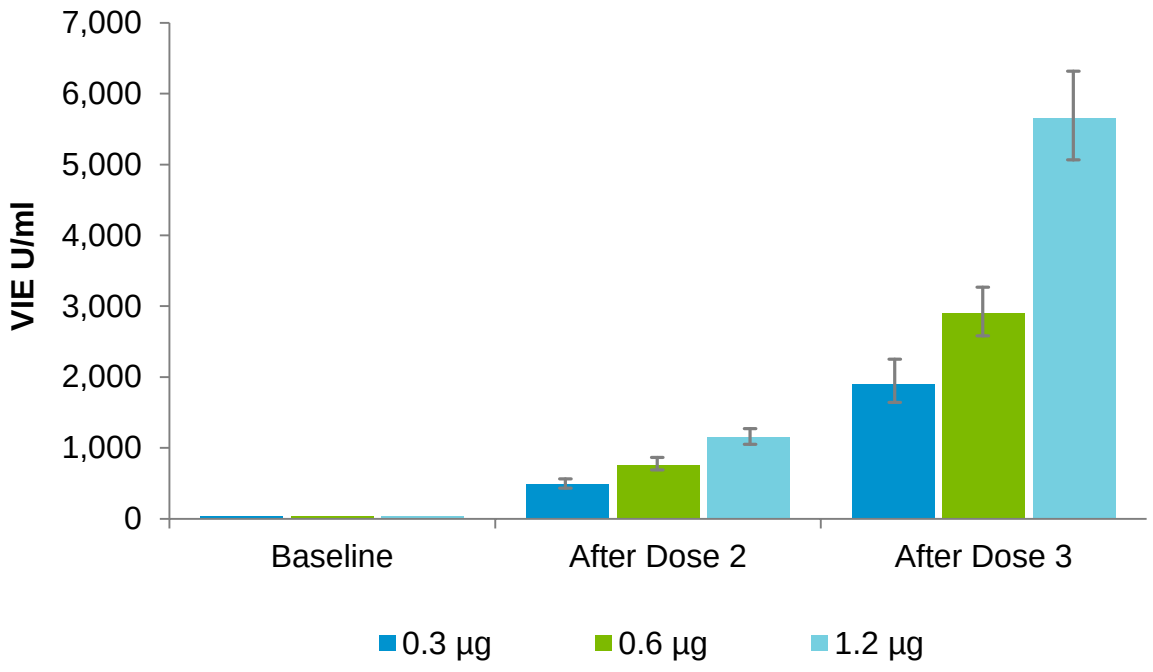
Pöllabauer EM et al (2010a) Clinical evaluation to determine the appropriate paediatric formulation of a tick-borne encephalitis vaccine. *Vaccine* 28:4558−65

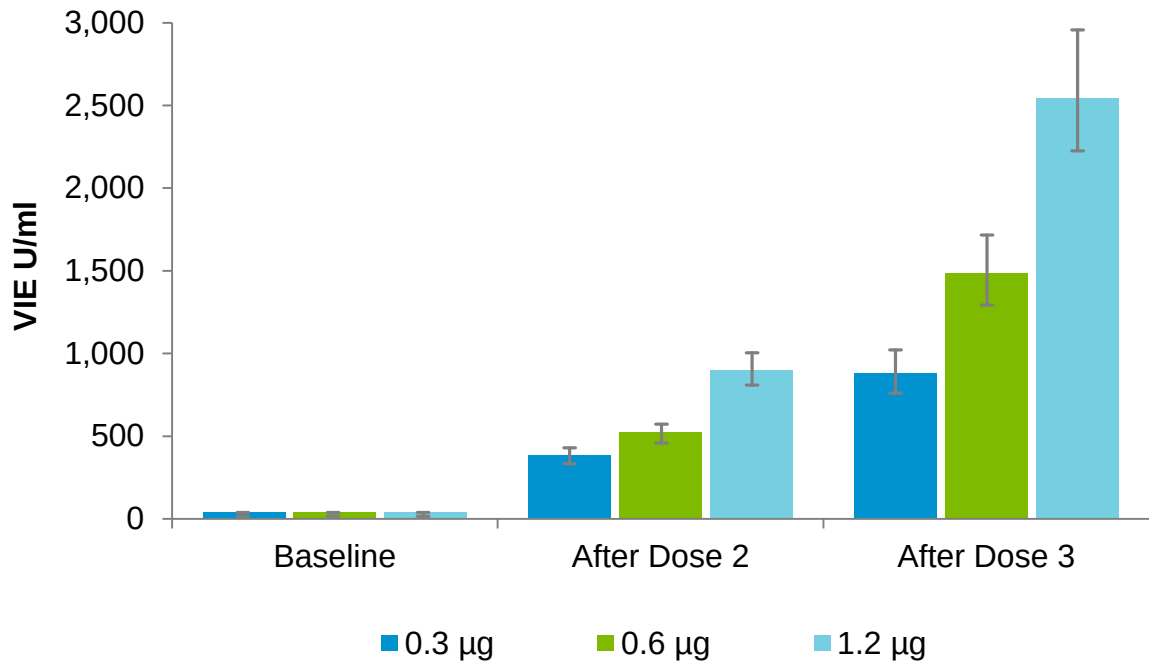
Pediatric Dose Finding Study (Pöllabauer et al 2010a - In children aged 1-15yrs (N=1278))

Geometric Mean Concentrations (GMCs)

GMCs Determined by ELISA in Children Aged 1−5 Years



GMCs Determined by ELISA in Children Aged 6−15 Years



In Both Age Groups, a Clear Dose-dependent Immunogenic Response Was Seen for GMCs After Doses 2 and 3

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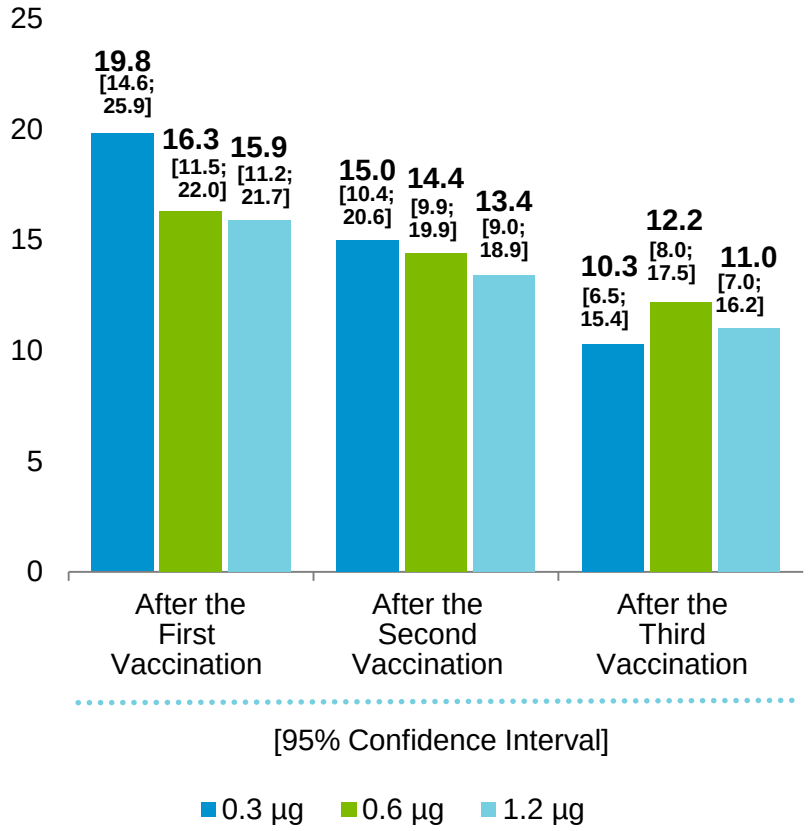
Pöllabauer EM et al (2010a) Clinical evaluation to determine the appropriate paediatric formulation of a tick-borne encephalitis vaccine. *Vaccine* 28:4558−65

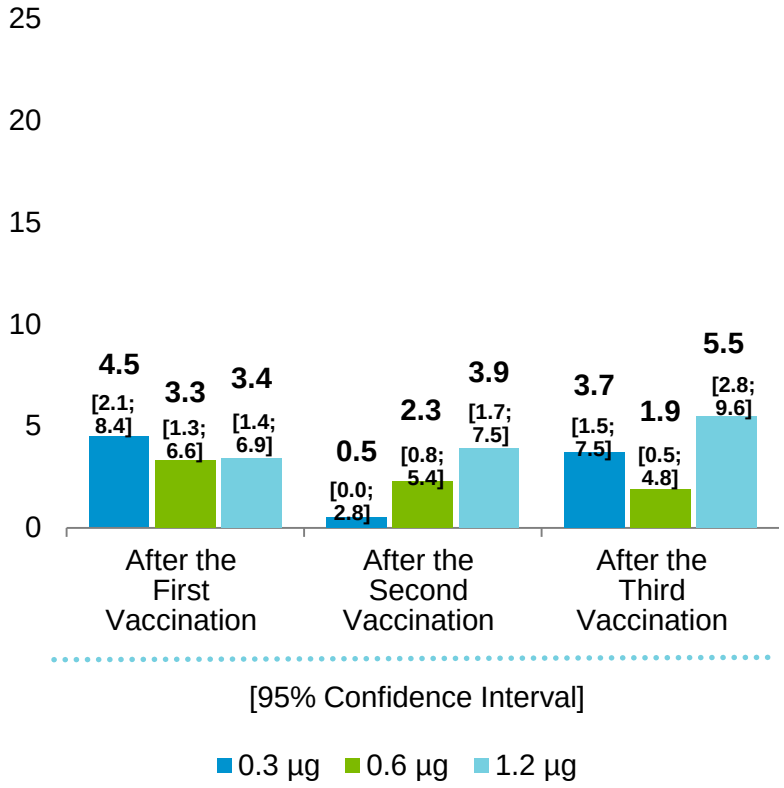
Pediatric Dose Finding Study (Pöllabauer et al 2010a - In children aged 1-15yrs (N=1278))

Safety

Fever (%) Among Children Aged 1−5 Years



Fever (%) Among Children Aged 6−15 Years



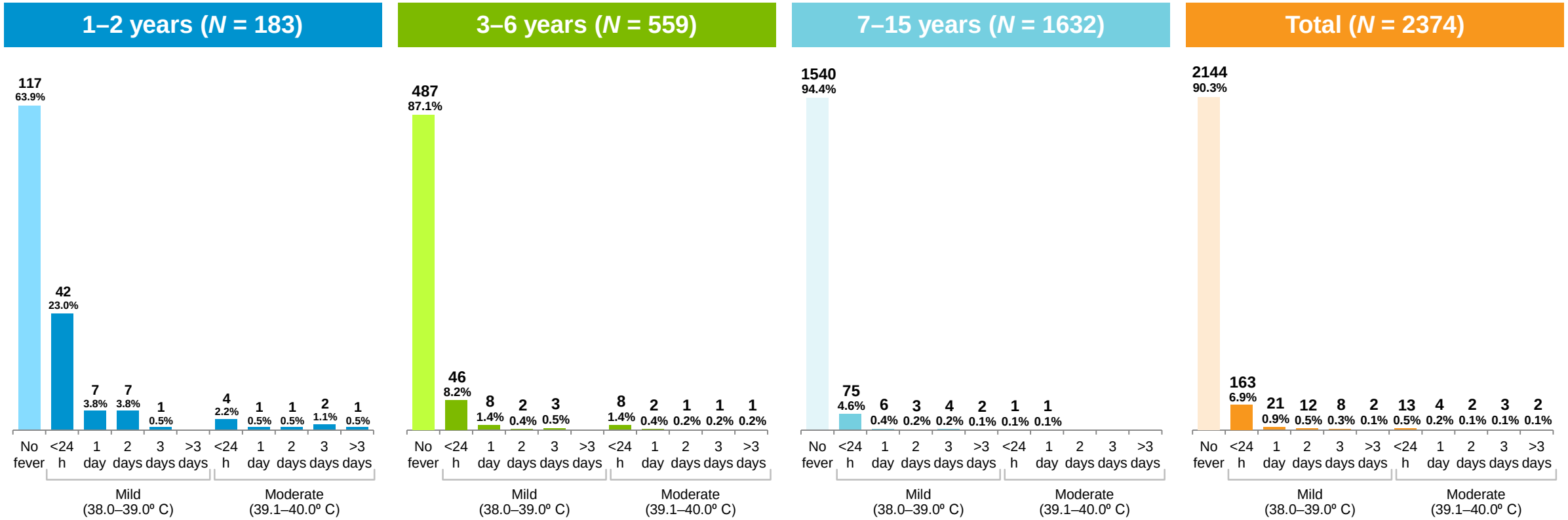
- FSME-IMMUN was found to be safe in children aged 1–15 years at all 3 doses
- Fever and other adverse reactions were not dose-dependent
- Fever was more frequent in the younger age group, with most cases of fever mild in severity
- Total systemic reactions (excluding fever) occurred at a relatively low frequency (<13%) after dose 1 and were comparable between the three dose groups (data not shown)
- Local and systemic adverse reactions occurred at a much lower frequency after doses 2 and 3 (data not shown)
- **No serious adverse reactions were reported in either age group**

Pfizer Medical

Pöllabauer EM et al (2010a) Clinical evaluation to determine the appropriate paediatric formulation of a tick-borne encephalitis vaccine. *Vaccine* 28:4558−65

Pediatric Open Label Safety Study
(Pöllabauer et al 2010a - In children aged 1-15yrs (N=2417))

Frequency (%) and Duration of Fever After Dose 1 by Age Class and Severity



- Fever rates after dose 1 were low (9.7%) and decreased after doses 2 and 3 (2.4% and 2.4%, respectively)
- Fever was more frequent in the youngest age class, with most cases of fever being mild in severity

Pfizer Medical

Pöllabauer EM et al (2010a) Clinical evaluation to determine the appropriate paediatric formulation of a tick-borne encephalitis vaccine. *Vaccine* 28:4558−65

Pediatric Open Label Safety Study
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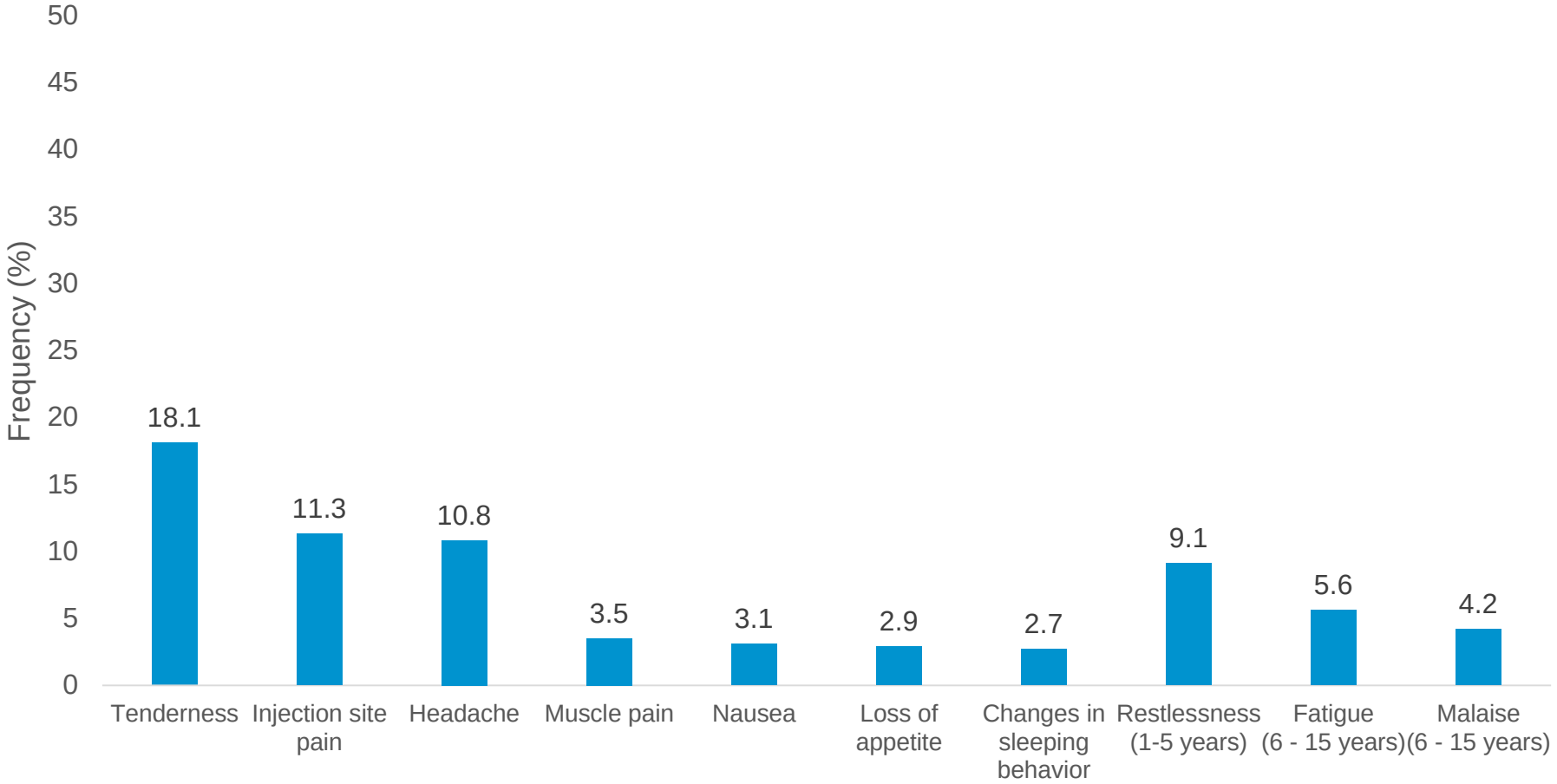
Safety

Most frequent local and systemic reactions after the first vaccination



- The most common systemic reaction (excluding fever) was headache
- The most common local reactions were injection-site pain and tenderness
- **No vaccine-related serious adverse events were observed during the studies**

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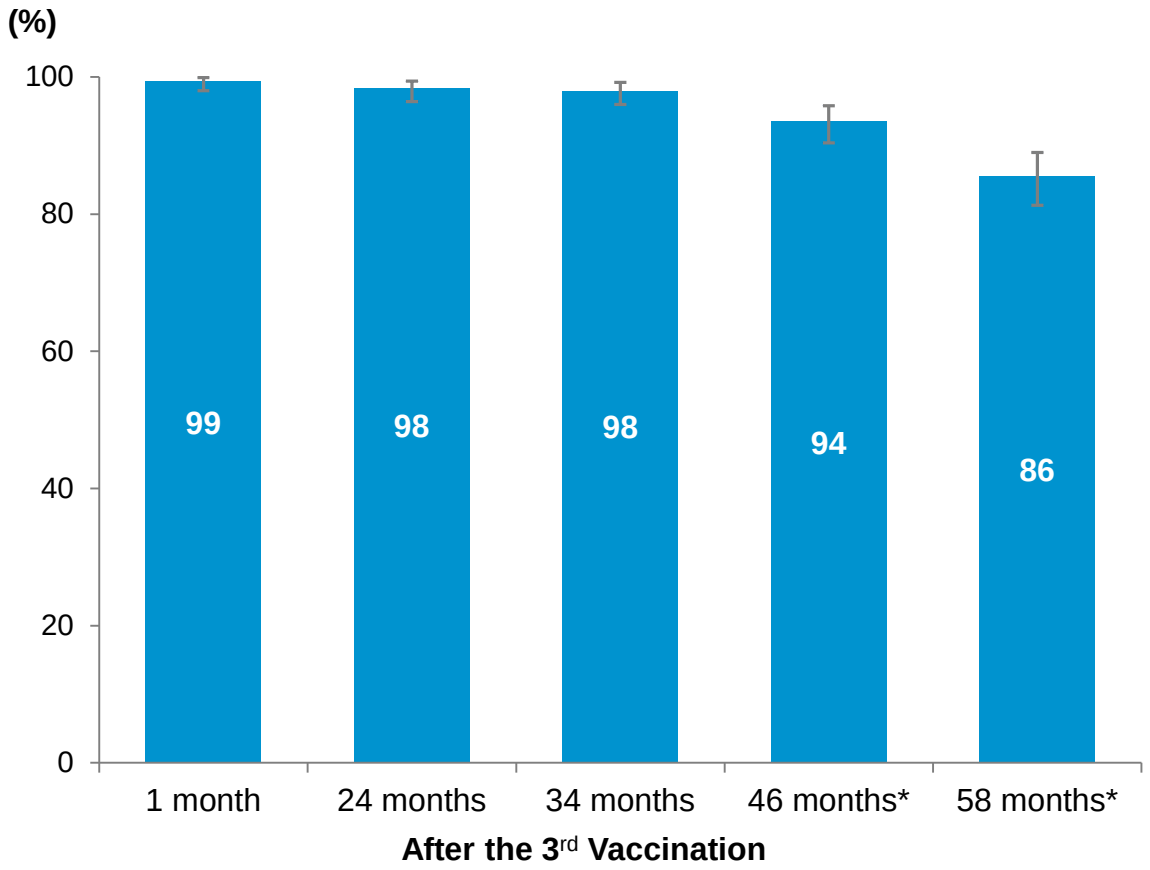
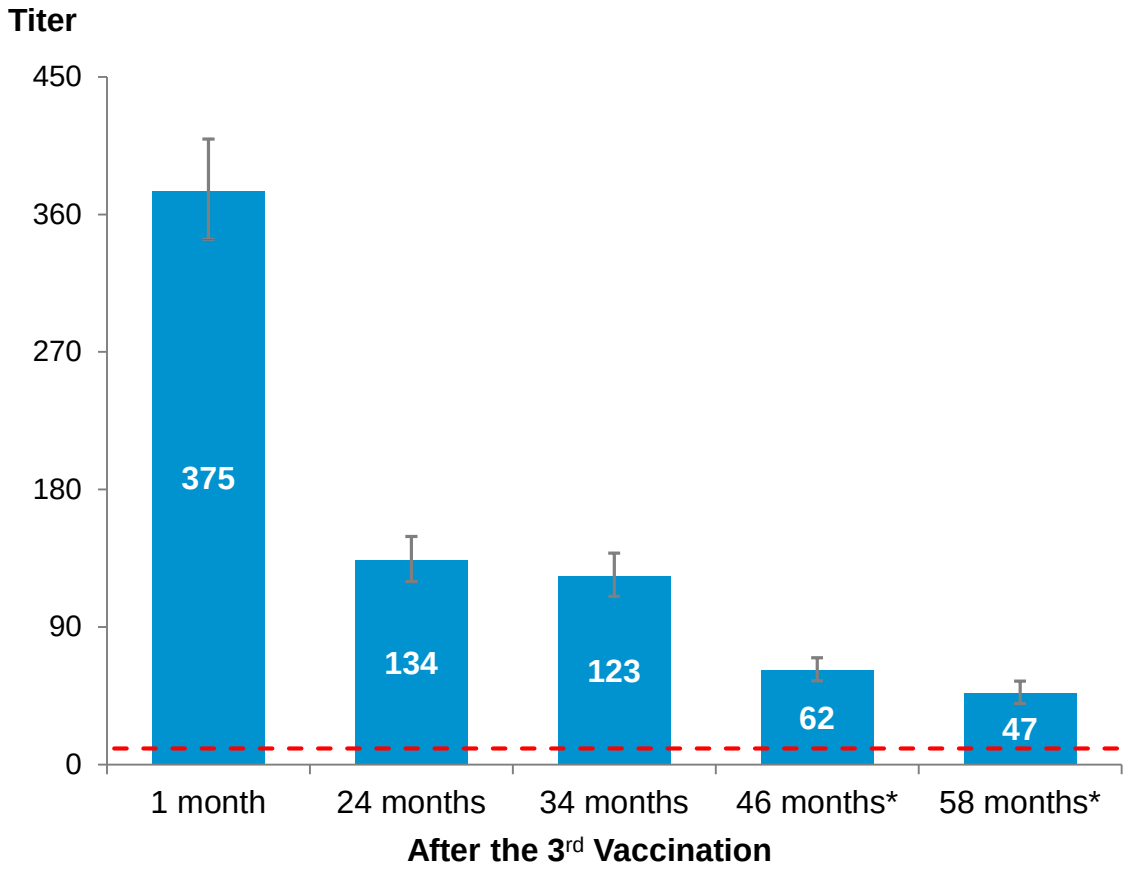
Seropersistence in Children and Adolescents After 3-Dose Primary Immunization

Seropositivity Rate (NT)



GMT (NT)



* Data partially extrapolated based on annual decline rates; Seropositivity in NT (Adner N et al (2001) *Scand J Infect Dis* 33(11):843-7): Titer ≥10.
Loew-Baselli, A., et al. (2011) Vaccine **29**: 7307-7319.

Pfizer Medical

Safety:
Vaccination Safety Data from Pivotal Clinical Studies

TICO-VAC 0.5ml		
Symptom	**n/N**	**(%)**
Local pain	392/2977	13.2%
Tenderness	890/2977	29.9%
Headache	171/2977	5.7%
Fever	23/2947	0.8%
Muscle pain	144/2977	4.8%
Nausea	59/2977	2.0%
Joint pain	38/2977	1.3%
Fatigue	186/2977	6.2%
Malaise	133/2977	4.5%
Lymphadenopathy	17/2977	0.6%

TICO-VAC 0.25ml Junior		
Symptom	**n/N**	**(%)**
Local pain	272/2417	11.3%
Tenderness	438/2417	18.1%
Headache	261/2417	10.8%
Fever	230/2374	9.7%
Muscle pain	85/2417	3.5%
Nausea	76/2417	3.1%
Loss of appetite	71/2417	2.9%
Changes in sleeping behaviour	66/2417	2.7%
Restlessness (only age 1–5 years)	53/584	9.1%
Fatigue (only age 6–15 years)	102/1833	5.6%
Malaise (only age 6–15 years)	76/1833	4.2%

Summary: Based on almost 20 years of experience and >47mio doses distributed, it is concluded that TICO-VAC is well tolerated and has an excellent safety profile

Pfizer Medical

Source: Pöllabauer et al. *Vaccine* 28, 2010; Löw-Baselli et al., *Vaccine* 24, 2006.

Agenda

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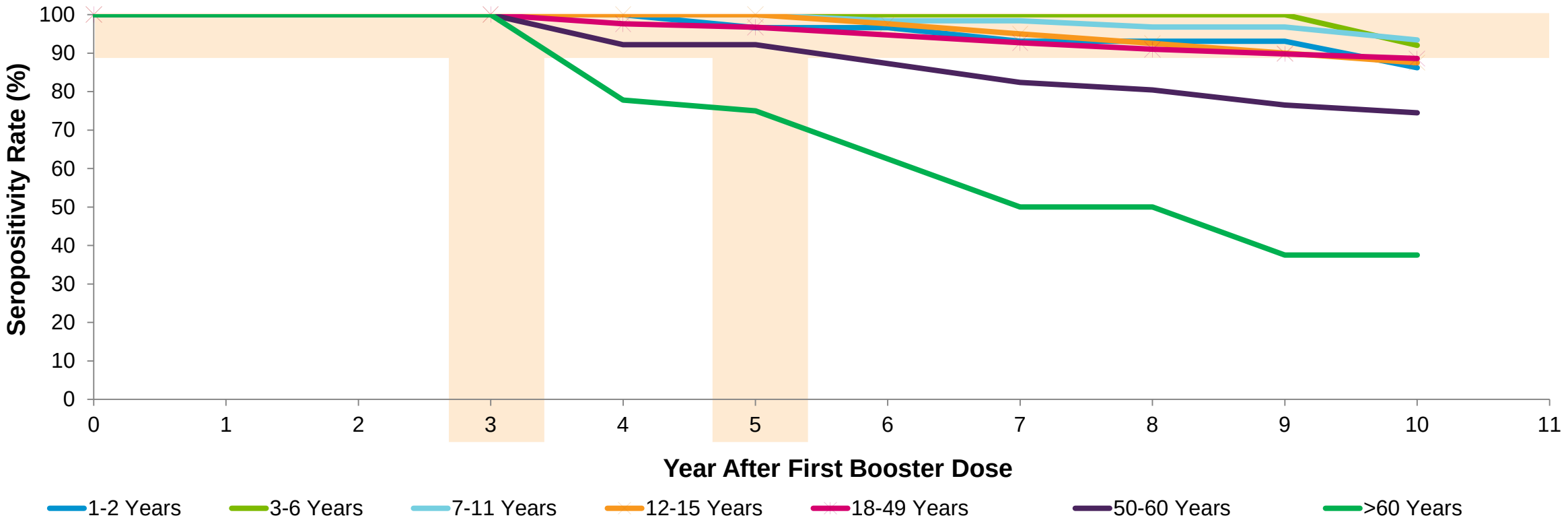
Seropersistence-rate Through 10 Years After the First Booster (After Dose 4) Across All Age Groups

As Measured by the Neutralization Test (NT) (According to Adner et al., 2001)

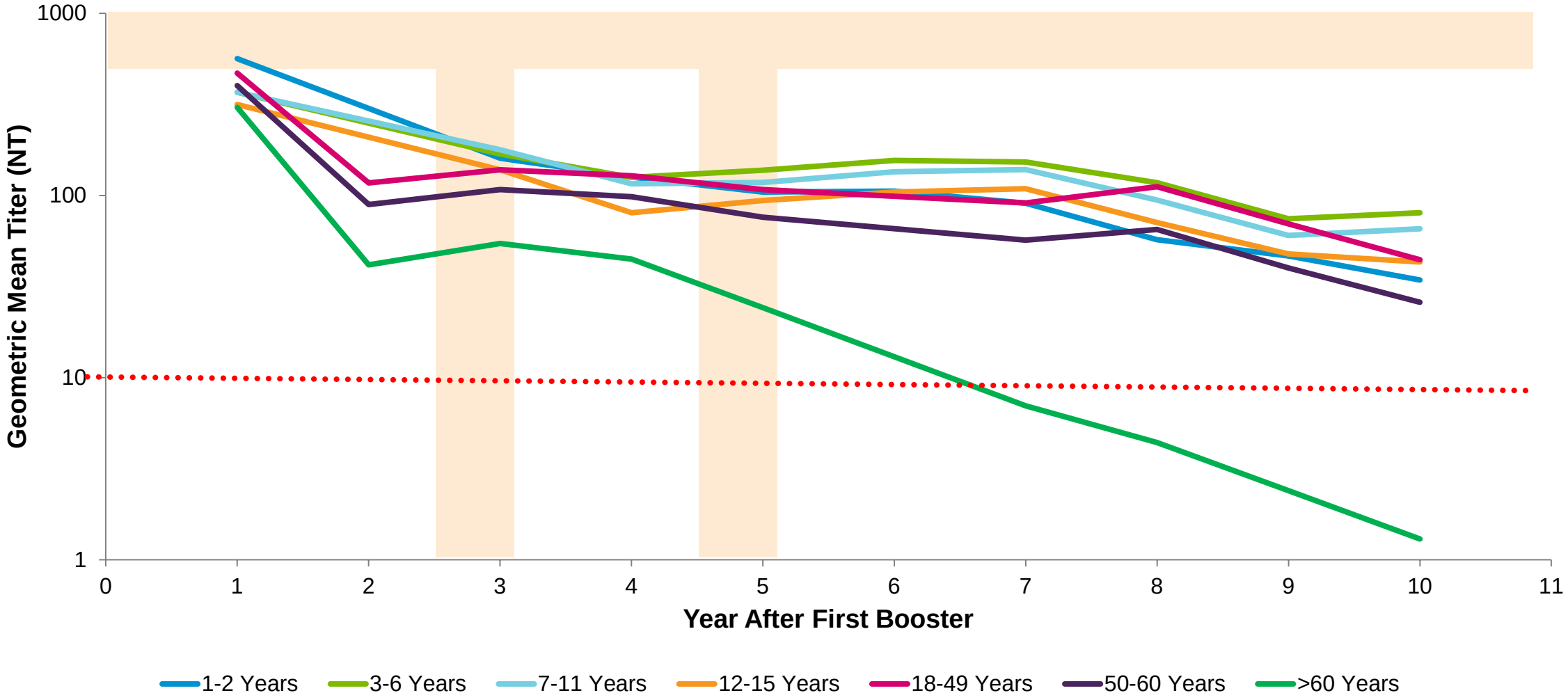


Results as Measured by ELISA Were Consistent with the Results as Measured by NT

Pfizer Medical

Sources: Konior et al. (2017) *Vaccine* 35:3607-3613; Pöllabauer et al. (2019) *Vaccine* 37:3241-3250

Seropersistence GMTs Through 10 Years After First Booster (Dose 4) Across All Age Groups



Pfizer Medical

Sources: Konior et al (2017) *Vaccine* 35:3607-3613; Pöllabauer et al. (2019) *Vaccine* 37:3241-3250

Booster Doses: Reactogenicity and Safety

- **Konior et al. (TICO-VAC 0.5mL):** After doses 4 and 5
  - Safety was not evaluated as an endpoint; however, any adverse event (AE) or serious adverse event (SAE) that occurred after a booster vaccination in the 2– 5 year follow-up and any SAE that occurred after the booster vaccination in the 7–10 year follow-up were to be reported.
  - 2 subjects who reported 3 mild AEs after a booster vaccination in the 2–5 year follow-up; fatigue and injection site pain for one subject and malaise for the other.
  - No vaccine-related SAE were reported and no deaths occurred during the study.

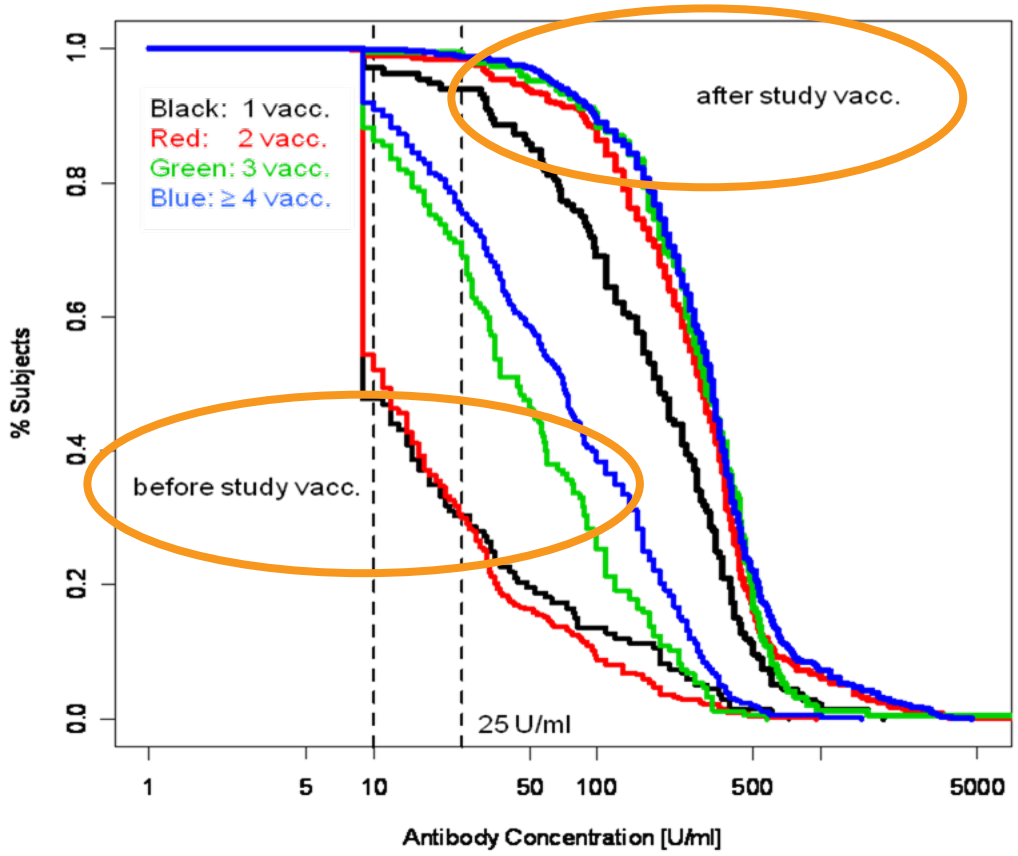
- **Poellabauer et al. (TICO-VAC 0.25 mL):** After dose 5
  - No deaths occurred
  - No vaccine-related SAE were reported
  - No subjects were withdrawn due to an unrelated SAE

(Konior, Brzostek et al. 2017) (Poellabauer, Angermayr et al. 2019)

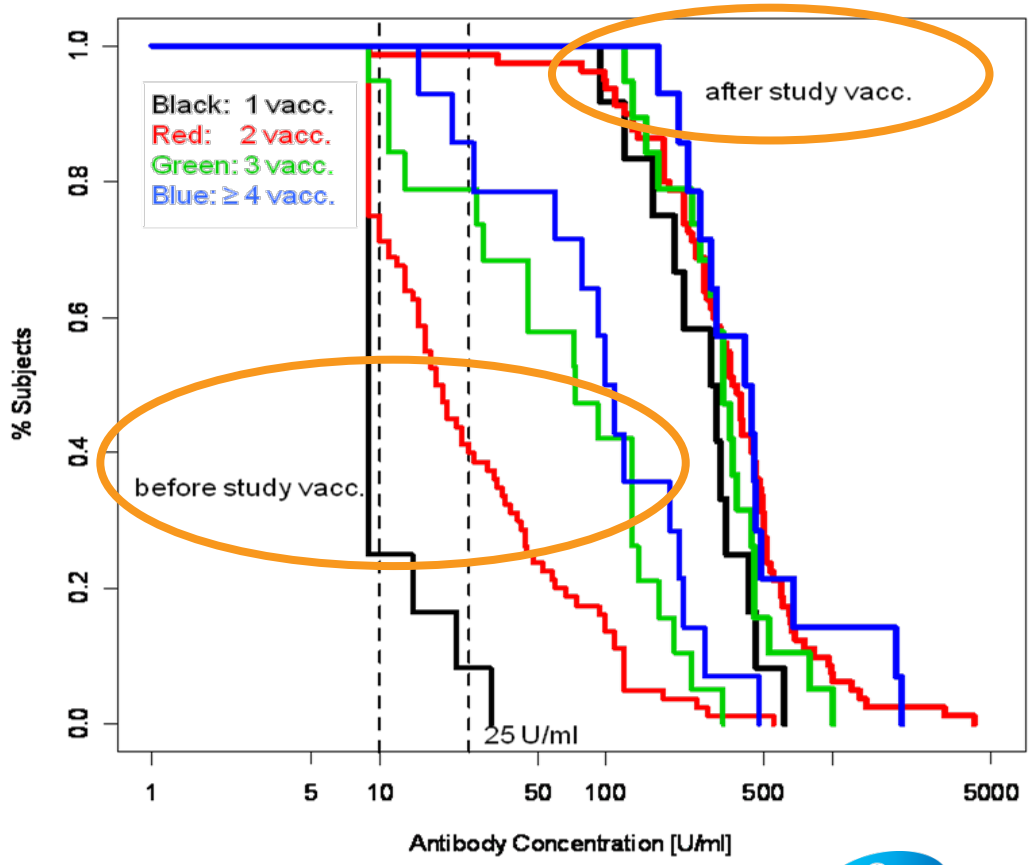
TBE Antibody Response by ELISA Before and After the Catch-up Vaccination (Schosser, 2014 – In adults ≥16 years (N=1115) and children 6–15 years (N=135))

Reverse Cumulative Distributions of 1 Vaccine Dose: Stratified by Number of Previous Vaccinations in Adults and Children

Subjects ≥ 16 Years



Subjects < 16 Years



Number of previous vaccine doses Adults/Children: 1: 132/12; 2: 346/80; 3: 145/19; ≥4: 492/14

Schosser et al. (2014) *Vaccine* 32:2375-81

Catch-up Study: ELISA Responses

(Schosser, 2014 – In adults ≥16 years (N=1115) and children 6–15 years (N=135))

Adult Subjects with Putative Seroprotection (≥25 U/ml) After Study Vaccination by Each Irregular Interval Category (Sensitivity Analysis Irregular Interval Requirement)			
Age Group	**Time Interval from Last Vaccine to Catch-up Dose**	**n/N**	**%**
≥16–<60 years	**5–9 years (1827–3651 days)**	**797/802**	**99.4**
	≥10 years (≥2652 days)	**405/409**	**99.0**
	10–12 years (3652–4747 days)	257/259	99.2
	13–15 years (4748–5843 days)	81/83	97.6
	16–18 years (5844–6939 days)	51/51	100.0
	19–20 years (6940–7670)	10/10	100.0
	≥21 years (≥7671 days)	6/6	100.0
≥60 years	**5–9 years (1827–3651 days)**	**245/252**	**97.2**
	≥10 years (≥2652 days)	**74/76**	**97.4**
	10–12 years (3652–4747 days)	43/44	97.7
	13–15 years (4748–5843 days)	15/15	100.0
	16–18 years (5844–6939 days)	10/11	90.9
	19–20 years (6940–7670)	4/4	100.0
	≥21 years (≥7671 days)	2/2	100.0

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Pfizer – data on file Schosser et al. (2014) *Vaccine* 32:2375-81.

Catch-up Study: Safety

(Schosser, 2014 – In adults ≥16 years (N=1115) and children 6–15 years (N=135))

- **Six adverse reactions**, 5 in adults and 1 in children/adolescents, reported in temporal relationship with the catch-up vaccination during the study.
  - All 6 adverse reactions classified as non-serious and labeled in the summary of product characteristics

- **Adults-** Any AE – 0.45%
  - 3 local reactions at the injection site,
  - 1 systemic reaction with flu-like symptoms with onset 2–3 days after immunization,
  - 1 combination of a local reaction and flu-like symptoms 12 h after immunization

- **Children-** Any AE – 0.80%
  - 1 local reaction at the injection site.

Schosser et al. (2014) *Vaccine* 32:2375-81

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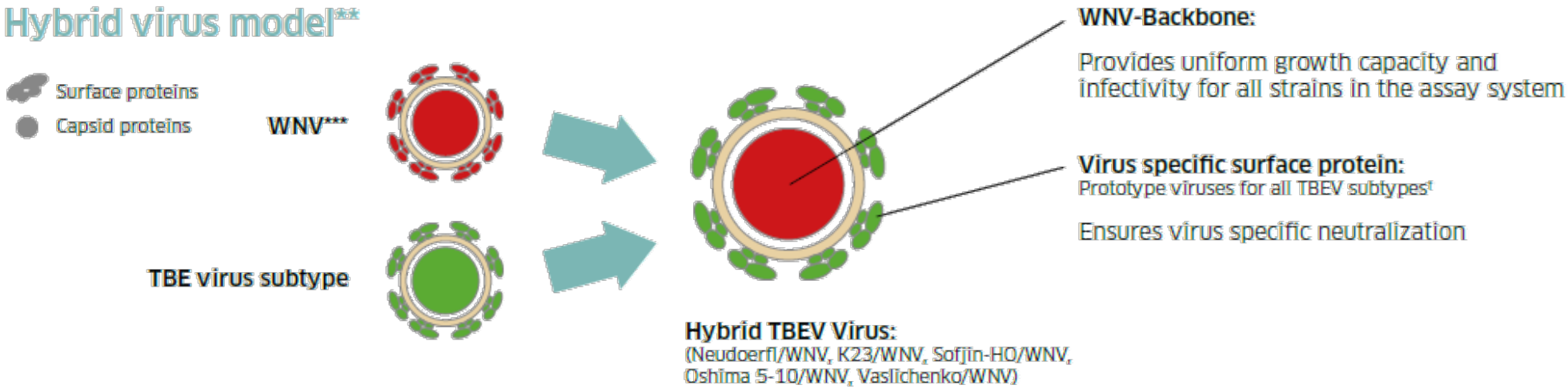
Hybrid Virus Model Assay: *Broad-* and *Cross-Immunity*

Construction of Hybrid Viruses Enables Unbiased Quantitative Analysis



The cell-based assay system with hybrid viruses enables unbiased quantitative analysis of cross-neutralization capacity against all TBEV subtypes.

Hybrids	TBEV subtype	(%) Protein E homology to TBEV Nd
Neudoerfl	European	100
K23	European	99
Sofjin	Far Eastern	96
Vasilchenko	Siberian	96
Oshima 5–10	Far Eastern	96
Omsk HF	N/A	93

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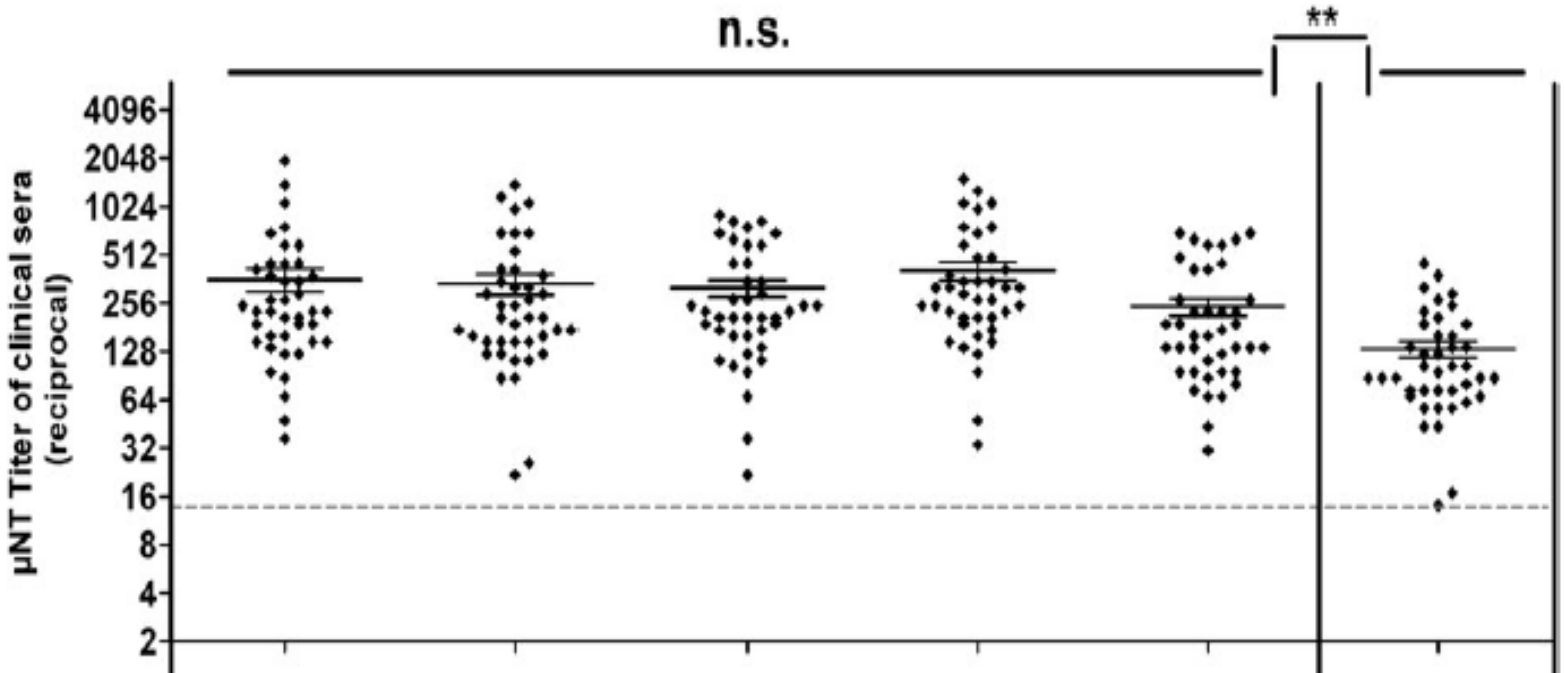
Source: Orlinger K. et al., *J Infect Dis*. (2011) 203(11): 1556-1564.

Vaccination with FSME-IMMUN Cross-NT Data in Label



Hybrids:	Neudoerfl	K23	Sofjin-HO	Oshima 5-10	Vaslichenko	Omsk HF
mean:	360	338	319	409	224	133
SEM:	58,7	50,5	37,8	54,1	31,0	15,3
N:	41	41	41	41	41	41

Immunization with **TICO-VAC** induces **equivalent NT** titers against the **European**, **Far Eastern** and the **Siberian** (Vasilchenko) TBEV subtypes and somewhat lower, but likely protective NT titers against Omsk HFV

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Source: Orlinger et al. (2011), *J Inf Dis* 203(11):1556-64.

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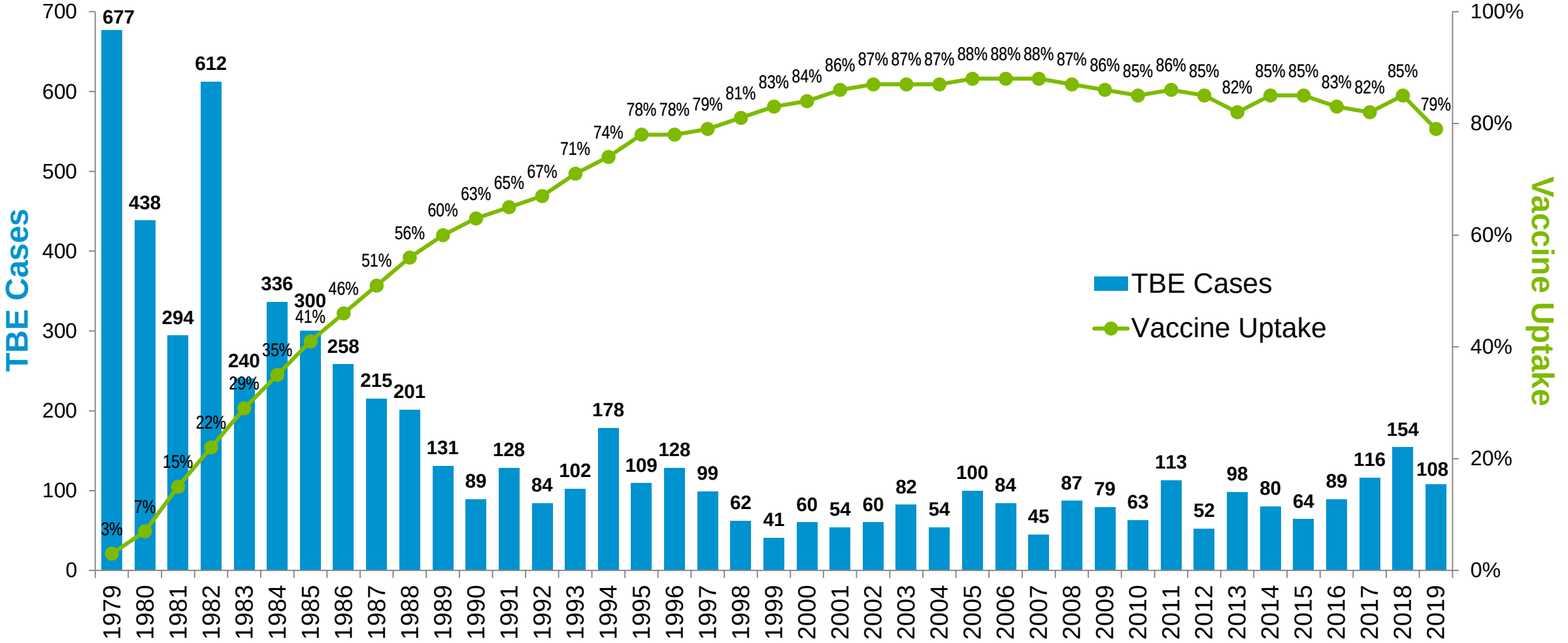
TBE Cases and Vaccine Uptake, Austria 1979–2019



Kunze M et al. TBE as a matter of public health. Chapter 13. In: Dobler G, Erber W, Bröker M, Schmitt HJ, eds. *The TBE Book*. 3rd ed. Global Health Press, Singapore, 2020. doi: 10.33442/26613980_13-3

Field Effectiveness of TBE Vaccination

About 4,000 Cases Prevented 2000–2011 in Austria

FSME-IMMUN market share: 96% (in 2000) and 90% (in 2006)

Field Effectiveness of TBE Vaccination, Austria, 2000–2011*

Scenario by age group, y		Unvaccinated persons	Regularly vaccinated persons		Irregularly vaccinated persons	
		Incidence†	Incidence†	FE, % (95% CI)	Incidence†	FE, % (95% CI)
Best-case‡	0–14	1.62	0.10	94.0 (88.0–97.0)	0.18	88.6 (63.3–96.5)
	15–50	5.41	0.02	99.7 (99.3–99.9)	0.26	95.3 (92.9–96.9)
	51–60	7.60	0.13	98.2 (96.7–99.1)	0.31	96.0 (91.4–98.1)
	≥61	7.52	0.14	98.2 (97.0–98.9)	0.63	91.7 (87.9–94.3)
	TOTAL	5.01	0.07	**98.7 (98.2–99.0)**	0.37	**92.5 (90.3–94.3)**
Worst-case§	0–14	1.62	0.13	92.2 (87.4–97.0)	0.19	88.0 (62.3–96.2)
	15–50	5.41	0.11	98.1 (97.4–98.8)	0.30	94.5 (91.9–96.2)
	51–60	7.60	0.25	96.8 (95.3–98.4)	0.39	94.9 (89.9–97.4)
	≥61	7.52	0.44	94.4 (92.8–96.1)	0.71	90.5 (86.4–93.3)
	TOTAL	5.01	0.20	**96.3 (95.5–97.0)**	0.44	**91.3 (88.9–93.2)**

* TBE, tick-borne encephalitis; FE; field effectiveness.
† Cases/100,000 population.
‡ Persons with TBE but unknown vaccination status were excluded.
§ Persons with TBE but unknown vaccination status were considered regularly vaccinated.
Source: Heinz et al. (2013) *EID* 19: 69–76

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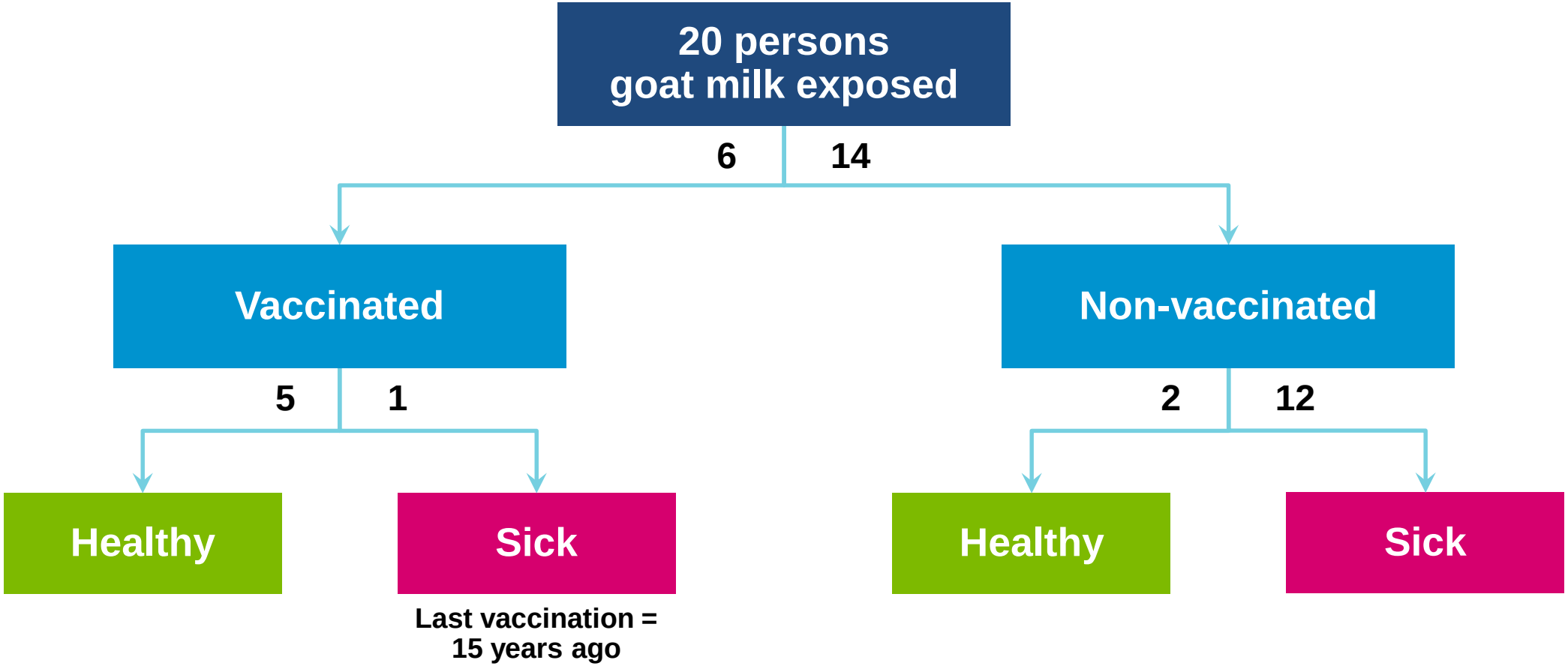
Alimentary TBE Outbreak, Germany 2017



Vaccine Effectiveness: 80%–100%

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Validated and provided by Prof. Dr. Gerhard Dobler, National Reference center for TBE, Germany, Presented at ESPID 2019, Slovenia

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Studies of FSME-IMMUN in Special Patient Populations

Study	Subject #	Population	Main Results
Panasiuk B et al (2003) Immunological response in HIV-positive patients vaccinated against tick-borne encephalitis. *Infection* 31:45−6	29	HIV-positive patients (Ages 19-23y)	Vaccination against TBE is safe in HIV-positive patients, but less effective than in healthy subjects, depending on CD4 counts.
Wolf HM et al (1992) Cellular and humoral immune responses in haemophiliacs after vaccination against tick-borne encephalitis. *Br J Haematol* 82:374−83	16	Patients with hemophilia; HIV + or – (Ages 7-50y)	Antibody titers comparable in HIV-negative hemophiliacs and controls but significantly lower in HIV-infected hemophiliacs after completion of the three-dose vaccination schedule.
Zielinski CC et al (1986) Impaired primary, but not secondary, immune response in breast cancer patients under adjuvant chemotherapy. *Cancer* 58:1648−52	24	Breast cancer patients (Mean Age: 47.3 ± 12.8y)	Patients with breast cancer undergoing adjuvant chemotherapy experience a serious and prolonged defect in primary antibody production, but secondary immune responses remain unimpaired.
Prelog M et al (2008) Diminished response to tick-borne encephalitis vaccination in thymectomized children. *Vaccine* 26:595−600	22	Thymectomized children (Mean Age 87 ± 51 months)	Thymectomized children showed significantly lower TBEV IgG after the second dose versus healthy age-matched controls (n = 30) (p = 0.03), but a normal response after the third vaccination
Hofmann H et al (1981), Haschke F, Popow C, Gotz M, Klabuschnigg A, Popow-Kraupp T. Shortening of interval between first and second TBE vaccination in asthmatic children. *WKW* 93:358−60	37	Children with asthma (Ages 8-14y)	**37 asthmatic children FSME-IMMUN vaccinated twice with a 10 day only interval showed no differences versus controls who had been vaccinated with the usual interval of 1 to 3 months.**
Baumhackl U et al (2003). A controlled trial of tick-borne encephalitis vaccination in patients with multiple sclerosis. *Vaccine* 21:s56−61	30	Patients with multiple sclerosis (Ages ≥19 and ≤60y)	**No association was seen between TBE vaccination and MRI detected disease activity, clinical relapse or disease progression of MS.**
Hapfelmaier, A (2019): A large case-control study on vaccination as risk factor for multiple sclerosis. *Neurology* 2019;93:e1-e9	Case control	MS vs. various controls from Claims database (Ages 26-60y)	**Data consistently suggest that vaccination (particularly including TBE vaccination) is associated with a lower likelihood of being diagnosed with MS within the next 5 years.**
Garner-Spitzer E et al. (2020) Obesity and Sex Affect the Immune Responses to Tick-Borne Encephalitis Booster Vaccination	73	Obese patients (n=36) [Ages 46.0 (43.2–48.8)]	**More frequent systemic but not local reaction in obese subjects. Booster vaccination was effective in obese individuals, yet the faster Ab decline could result in a reduced long-term protection.**

FSME-IMMUN Inadvertently Administered During Pregnancy

- Pfizer's safety database consists of AEs reported to Pfizer spontaneously, by health authorities, medical literature, Pfizer-sponsored marketing programs, non-interventional studies, cases of serious AEs reported from clinical studies regardless of causality.
- Database search for all subjects who had received FSME-IMMUN or FSME-IMMUN Junior with vaccine exposure during pregnancy any time from **1976 (Launch) - 31 August 2020** – >140 million doses distributed worldwide
- 138 cases with TBE vaccine exposure during pregnancy (mother/fetus) and 25 with exposure during breast-feeding (163 total reports)
  - 60 / 138 cases no associated AEs for either the mother or the baby (healthy mother/healthy infant delivered).
  - 48 cases, only exposure during pregnancy was reported (healthy mother) with no pregnancy outcome
  - 30 reports reporting AE(s) experienced by either the mother during pregnancy or the baby following birth.
    - In 7 cases, the mother experienced: gestational diabetes (2 reports); respiratory disorder; pre-eclampsia; vomiting; nausea and premature labor (1 each). In all 7 reports, the mother delivered a healthy baby.
    - In 6 reports, the mother experienced AE(s) without information on delivery status.
    - 10 reports of spontaneous abortion (9) / induced abortion (1) following TBE vaccination.
    - 3 other reports of fetal death (2) or ectopic pregnancy (1).
    - Remaining 4 reports, the baby experienced adverse events at the time of birth or shortly thereafter.
  - 25 remaining cases were "infant" cases that reported exposure via lactation.
    - In 19 of the 25 reports, there was either no adverse event information provided (exposure only = 8 cases) or the report specified that the baby did not experience any adverse event after exposure (n = 11 cases).
    - Remaining 6 cases, AEs were reported following TBE exposure via lactation

It is important to be aware that the spontaneous safety database is intended for hypothesis generation only and not for hypothesis testing. The safety database is not a pregnancy registry.

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Pfizer: data on file 2020

Simultaneous Administration

- No Study Data Are Available

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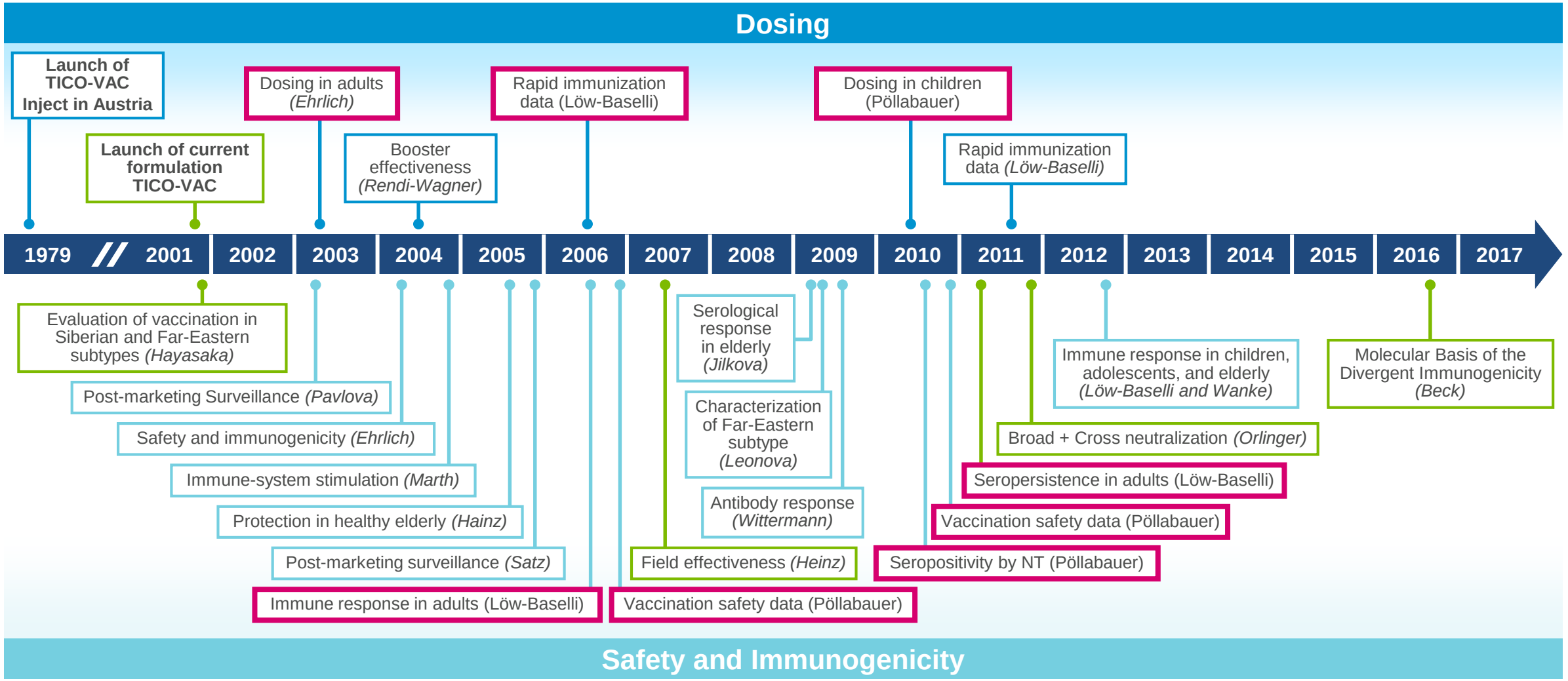
Over >40 Years FSME Accumulated a Large Body of Evidence and Extensive Experience



Studies Reviewed in Current Presentation

Pfizer Medical

Heinz et al. (2013) *Emerg Infect Dis.* 2013;19(1):69-76; Heinz et al. (2015) *Euro Surveill.* 2015;20(13):9-16.
Loew-Baselli et al. (2011) *Vaccine* 29: 7307–7319; Pfizer, data in file.

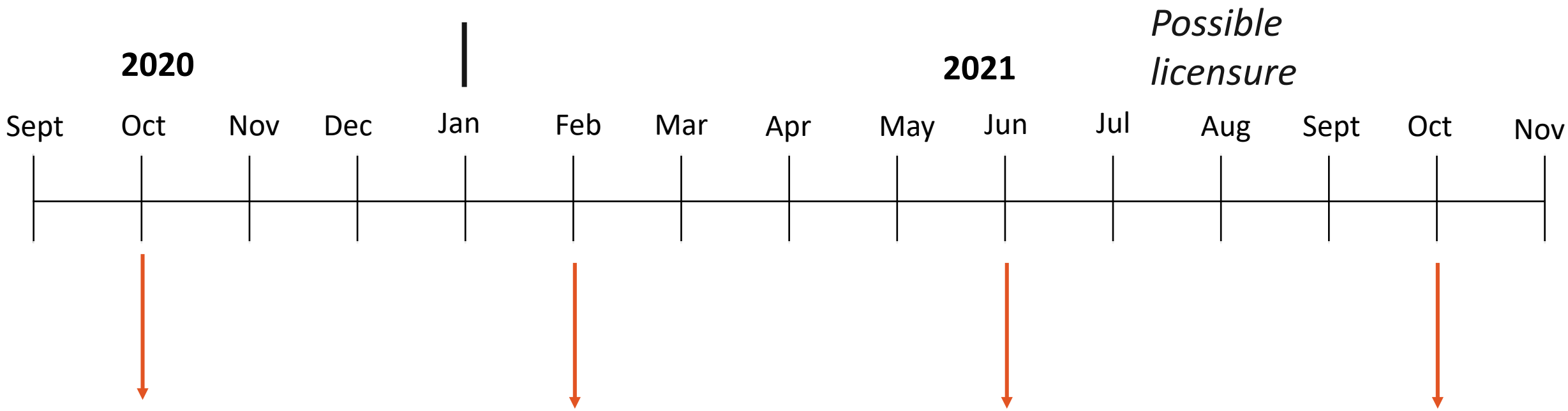
Thank you

Pfizer Medical

NEXT STEPS FOR TBE VACCINE WORK GROUP

Susan Hills, MBBS, MTH
Arboviral Diseases Branch
Division of Vector-Borne Diseases
Fort Collins, Colorado

Work Group timeline (planned), Oct 2020–Oct 2021



(Today)
Background information on TBE, and vaccine immunogenicity and safety data

Present to ACIP:
Traveler and laboratory worker risk data and additional data and considerations relevant to vaccine recommendations

Present to ACIP:
EtR and GRADE

ACIP vote on vaccine recommendations and finalize MMWR