Group B Streptococcus Maternal Immunization Program

Vaccines and Related Biological Products Advisory Committee

May 17, 2018

CC-1

Presentation Agenda

Annaliesa S Anderson Ph.D. FAAM Vice President, Chief Scientific Officer Pfizer Vaccine Research and Development	**The Burden of GBS Disease and Pfizer's GBS Vaccine**
Judith Absalon, MD, MPH Senior Medical Director Pfizer Vaccine Research and Development	**Potential GBS Vaccine Clinical Development Pathways**

CC-2

Guidance on Approaches to Demonstrating Effectiveness of a Group B Streptococcal Conjugate Vaccine

- Pfizer is developing a six valent polysaccharide CRM_{197} conjugate vaccine (GBS6) for the prevention of infant GBS invasive disease by maternal immunization
- No regulatory precedent for the licensure of maternal vaccines and the development pathway for a GBS maternal vaccine will be complex
- Pfizer is looking for guidance from CBER and the VRBPAC for acceptable approaches to demonstrate effectiveness to support future licensure of maternal GBS vaccines

CC-3

GBS Colonization Is a Risk Factor for GBS Disease

GBS Recto-Vaginal Colonization

	United States
Rates (%)	24.7

- Maternal GBS infections
- Stillbirth
- Preterm birth
- Infant invasive disease

Russell et al 2017 Maternal Colonization With Group B Streptococcus and Serotype Distribution Worldwide: Systematic Review and Meta-analyses. *Clinical Infectious Diseases* 65(S2):S100–11.

CC-4

The Majority of Infant Invasive GBS Disease Occurs Within the First 90 Days of Life

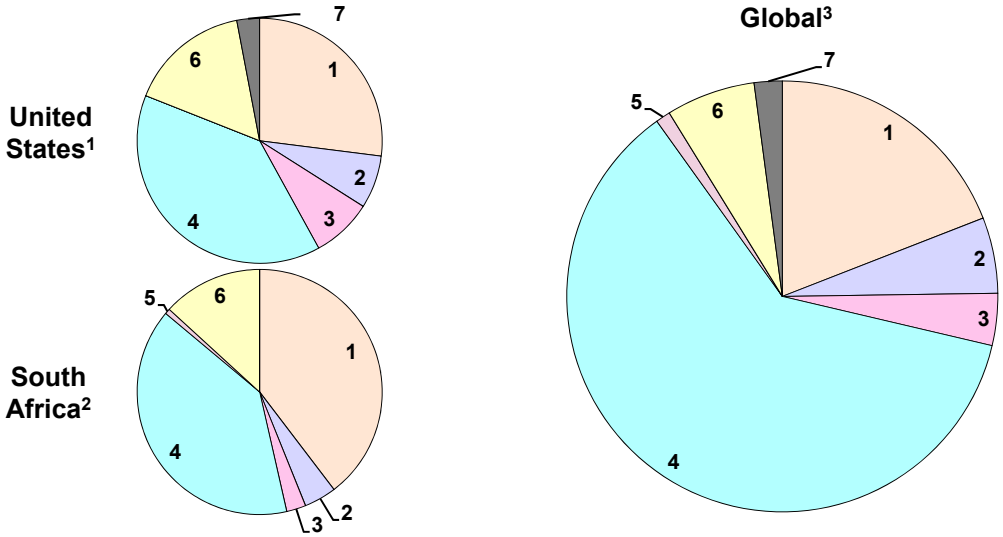
	Rates per 1000 Live Births		
	Pre-IAP in US (1990)	Post-IAP in US[1]	South Africa[4]
EOD (<7 days)	1.8[2]	0.21	1.41
LOD (≥7 days)	0.41[3]	0.32	1.18
Total		0.53	2.59

EOD: early onset disease; LOD: late onset disease; IAP: Intrapartum Antibiotic Prophylaxis

1. Centers for Disease Control and Prevention. 2015. Active Bacterial Core Surveillance Report, Emerging Infections Program Network, Group B *Streptococcus*, 2015.
2. Schrag & Verani 2013 *Vaccine* 31S, D20.
3. Jordan et al 2008 *Pediatr Inf Dis* J 27, 1057.
4. Dangor Z, Cutland CL, Izu A, Kwatra G, Trenor S, Lala SG, et al. (2016) Temporal Changes in Invasive Group B *Streptococcus* Serotypes: Implications for Vaccine Development. *PLoS ONE* 11(12): e0169101. https://doi.org/10.1371/journal.pone.0169101.

CC-5

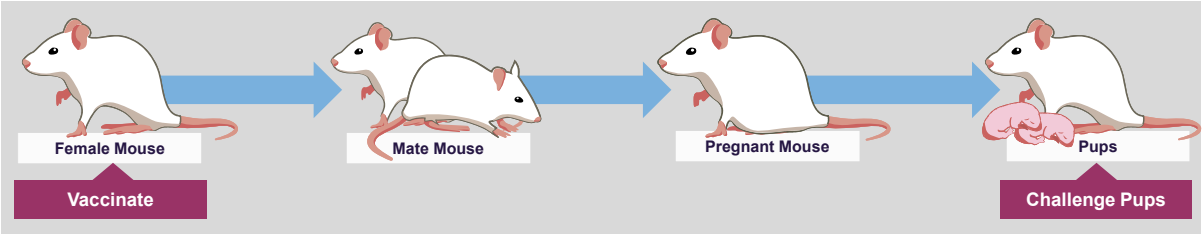
Six Serotypes Cause >95% of Infant GBS Disease Globally

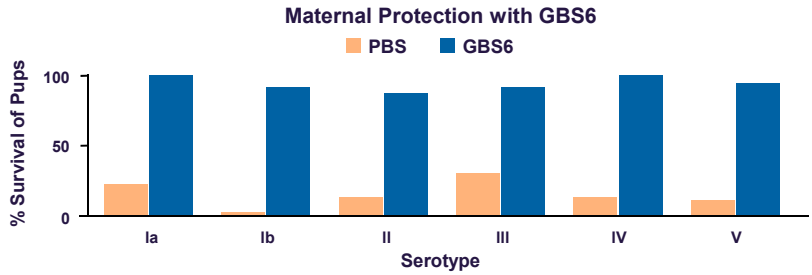


1. Phares et al 2008 *JAMA* 299, 2056; 2. Dangor et al 2015 *PLoS One* e0123014; 3. Madrid et al 2017 Infant Group B Streptococcal Disease Incidence and Serotypes Worldwide: Systematic Review and Meta-analyses. *Clinical Infectious Diseases* 65(S2):S160–72

CC-6

Pre-clinical Proof of Principle: GBS6 Induced Maternal Antibodies Are Transferred and Protective



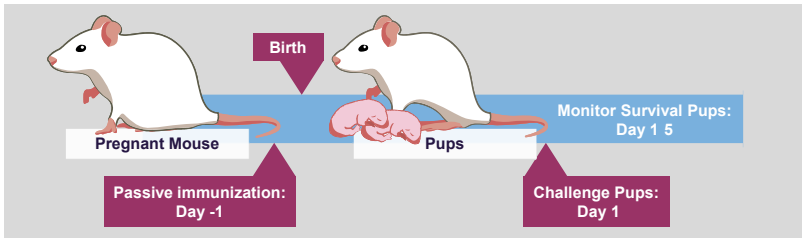


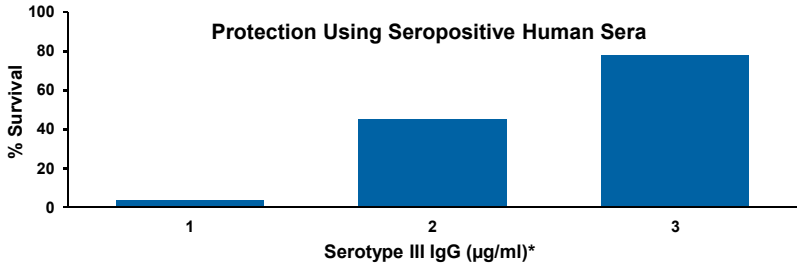
PBS: Phosphate buffered saline; GBS6: Six valent polysaccharide CRM_{197} conjugate vaccine

All procedures performed on animals were in accordance with regulations and established guidelines, and were reviewed and approved by an Institutional Animal Care and Use Committee.

CC-7

Pre-clinical Studies Confirm the Correlation Between Increased Maternal Antibody Levels and Protection





* Estimated maternal mouse concentration

All procedures performed on animals were in accordance with regulations and established guidelines, and were reviewed and approved by an Institutional Animal Care and Use Committee.

CC-8

Anticapsular GBS IgG Antibody Concentrations are Linked to Protection

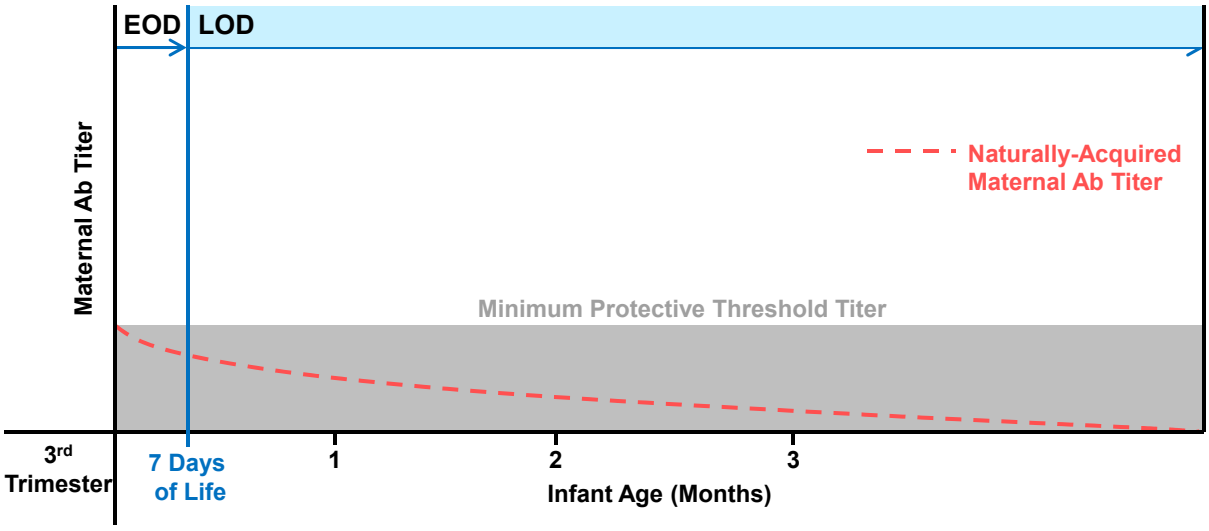
Study[1]	Time period	Region	Study Size	Ia		III	
				Cases	Threshold (Reduced Disease Risk Based on Bayesian Model)	Cases	Threshold (Reduced Disease Risk Based on Bayesian Model)
Baker 2014	EOD	US	132,000	17	2 µg/mL (51%)	9	1 µg/mL (100%)
Dangor 2015	30 Days	S. Africa	45,000	27	5 µg/mL (85%)	29	3 µg/mL (98%)
Fabbrini 2016	EOD	Europe	25,000	8	1 µg/mL (81%)	23	1 µg/mL (78%)

- **Differences between these studies prevent absolute comparison**
- **Standardized assays are being developed to provide a link between sero-epidemiology studies and vaccines in development**

1. Baker et al 2014 JID 209, 781; Dangor et al 2015 Vaccine 33, 6793; Fabbrini et al 2016 CID 63, 746

CC-9

With Maternal Immunization, Higher GBS CPS Antibody Titers Increase the Proportion of Infants Protected



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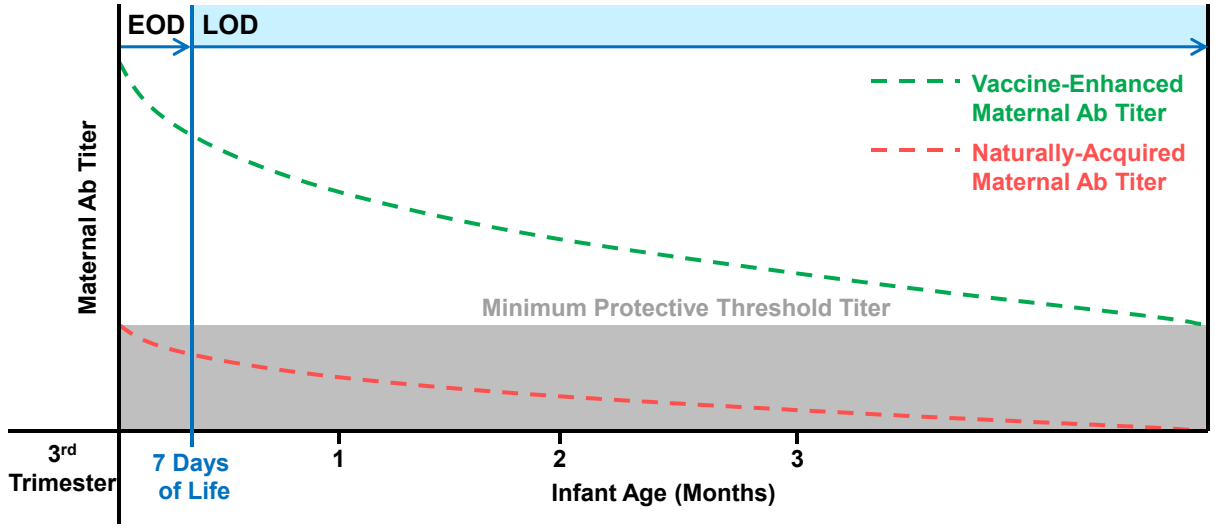
With Maternal Immunization, Higher GBS CPS Antibody Titers Increase the Proportion of Infants Protected



CC-11

Potential GBS Vaccine Clinical Development Pathways

Judith Absalon, MD, MPH

Senior Medical Director
Pfizer Vaccine Research and Development

CC-12

Clinical Development of a Group B Streptococcal Conjugate Vaccine

- **Pfizer is developing a 6-valent polysaccharide CRM_{197} conjugate vaccine (GBS6) for the prevention of infant invasive GBS disease by maternal immunization**
  - First in human clinical studies initiated June 2017
  - Studies in pregnant women planned in late 2018
- **Different clinical development pathways can be pursued to demonstrate effectiveness to support vaccine licensure**

CC-13

Potential GBS Clinical Development Pathways: Traditional or Accelerated Approval

Initial Basis for Licensure	Endpoint(s)	Regulatory Pathway
Effectiveness established with a disease endpoint study	Incidence of infant invasive GBS disease	Traditional approval
Effectiveness demonstrated using an established correlate of protection[1]	Proportion of infants achieving protective antibody levels	Traditional approval
Effectiveness demonstrated initially with a surrogate of protection[2]	Proportion of infants achieving protective antibody levels	Accelerated approval

1. Correlate of protection is generally a laboratory parameter that has been shown from adequate and well-controlled trials to be associated with protection from clinical disease. FDA Guidance on Combination Vaccines 1997.
2. A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Drug companies are still required to conduct studies to confirm the anticipated clinical benefit. FDA 1992 Accelerated Approval Program.

CC-14

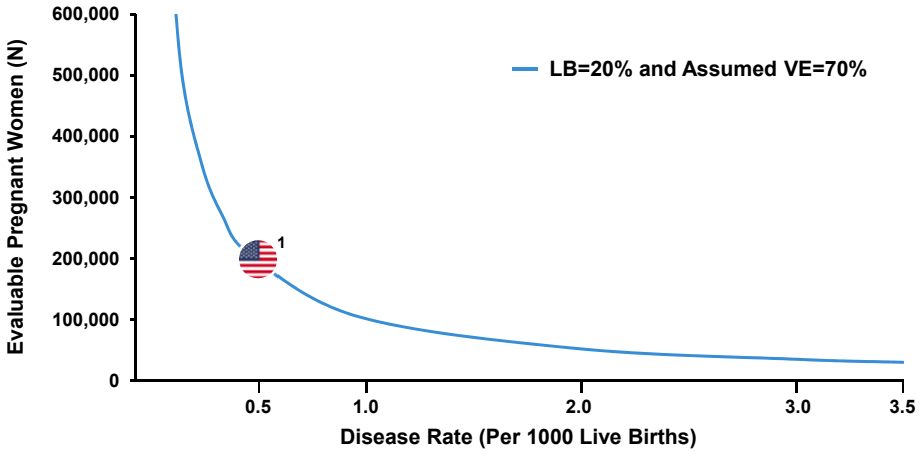
Clinical Development Pathways to Demonstrate Vaccine Effectiveness

- **Demonstrate effectiveness in clinical efficacy trial with disease endpoint**
- Demonstrate effectiveness using an established immunological correlate of protection
- Demonstrate effectiveness using a surrogate of protection and clinical disease endpoint

CC-15

An Efficacy Study In the US is Not Feasible

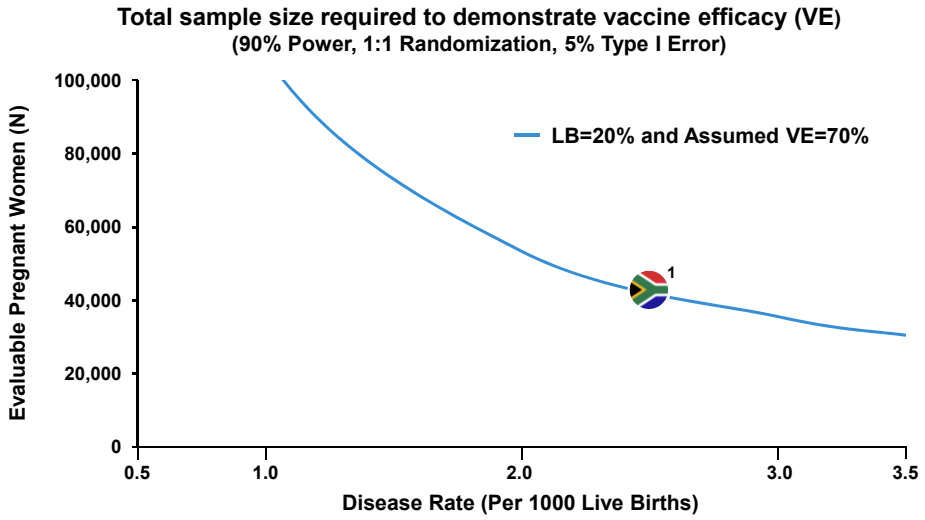
Total sample size required to demonstrate vaccine efficacy (VE)
(90% Power, 1:1 Randomization, 5% Type I Error)



LB: 95% lower bound confidence level.
1. Centers for Disease Control and Prevention. 2015. Active Bacterial Core Surveillance Report, Emerging Infections Program Network, Group B Streptococcus, 2015.

CC-16

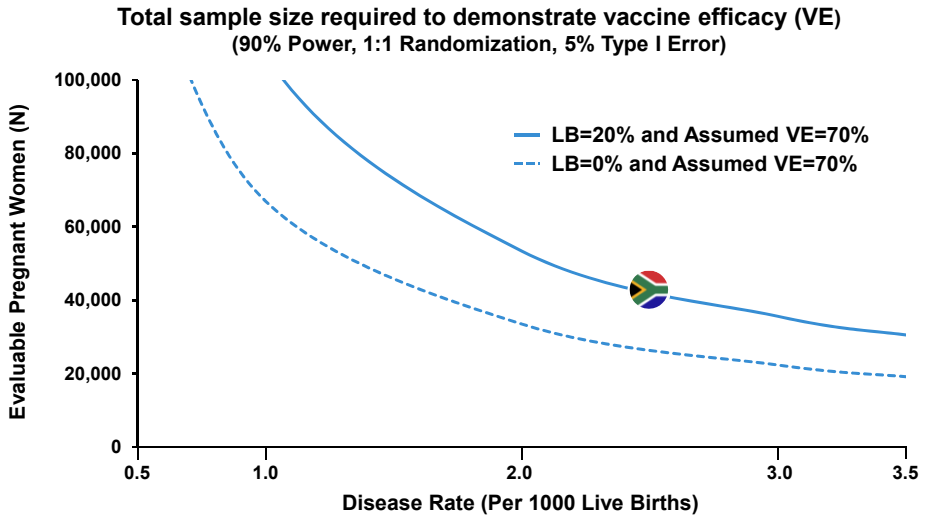
Efficacy Trial Size Could Be Reduced if Conducted in Higher Incidence Countries



LB: 95% lower bound confidence level.
1. Dangor, et al. Temporal Changes in Invasive Group B Streptococcus Serotypes: Implications for Vaccine Development; PLOS 2016.

CC-17

Efficacy Trial Size Could Be Reduced if Conducted in Higher Incidence Countries or if a Smaller Lower Bound Confidence Interval Is Used



LB: 95% lower bound confidence level.

CC-18

Could a Composite Clinical Endpoint Facilitate a More Rapid Assessment of Vaccine Efficacy?

Infant Invasive GBS Disease

+ **Stillbirth**
+ **Preterm birth**

- Limited data
- Multifactorial etiology
- Early preterm births would not be evaluable

➢ **May dilute ability to detect vaccine effect due to lack of GBS specificity**

+ **Maternal Invasive GBS Disease**

- Burden of maternal invasive GBS disease not well established in LMICs

➢ **Impact on efficacy trial contingent on incidence and relationship to infant invasive GBS disease**

1. Estimates of the Burden of Group B Streptococcal Disease Worldwide for Pregnant Women, Stillbirths, and Children Searle et al., *Clin Infect Dis.* 2017;65(suppl_2):S200-S219. doi:10.1093/cid/cix664 Clin Infect Dis | © The Author 2017. Published by Oxford University Press for the Infectious Diseases Society of America. 2. Brandon & Dowzicky (2013) *J Clin Microbiol* 51, 2371; Tigecycline Evaluation and Surveillance Trial

CC-19

Vaccine Efficacy Trials Can Be Large

GBS Vaccine Efficacy (N~50,000)

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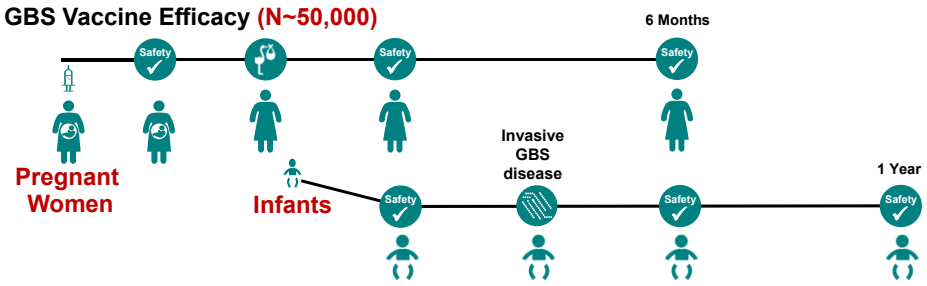
Maternal GBS Vaccine Efficacy Trials Will Be Both Large and Complex



- **This study would take more than 8 years to enroll with approximately 100 experienced sites in high GBS incidence regions**
  - A GBS vaccine would therefore not be available for at least 12 years from initiation of a clinical efficacy trial

CC-21

Clinical Development Pathways to Demonstrate Vaccine Effectiveness

- Demonstrate effectiveness in clinical efficacy trial with disease endpoint
- **Demonstrate effectiveness using an established immunological correlate of protection**
- Demonstrate effectiveness using a surrogate of protection and clinical disease endpoint

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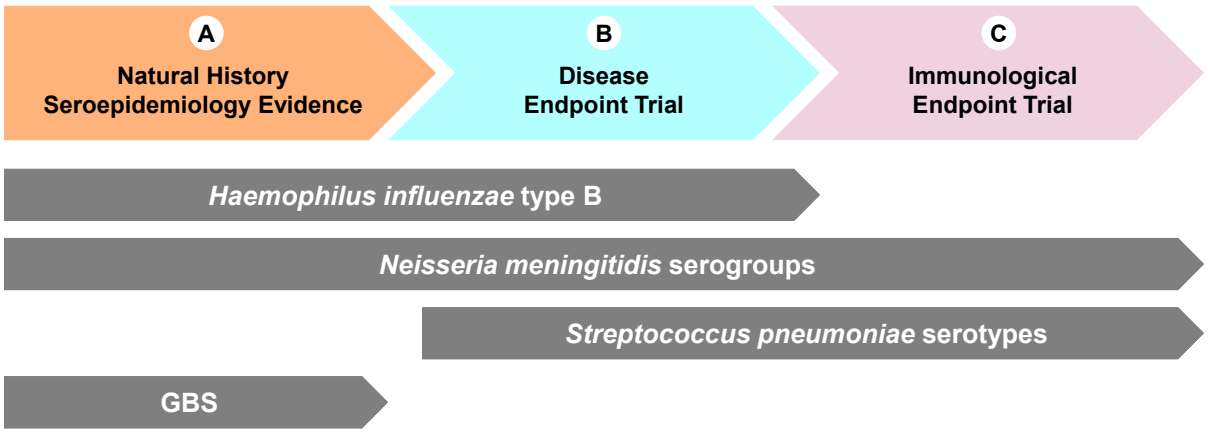
Precedent Established for Immunological Correlates of Protection for Encapsulated Pathogens



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Clinical Development Pathways to Demonstrate Vaccine Effectiveness

- Demonstrate effectiveness in clinical efficacy trial with disease endpoint
- Demonstrate effectiveness using an established immunological correlate of protection
- **Demonstrate effectiveness using a surrogate of protection and clinical disease endpoint**

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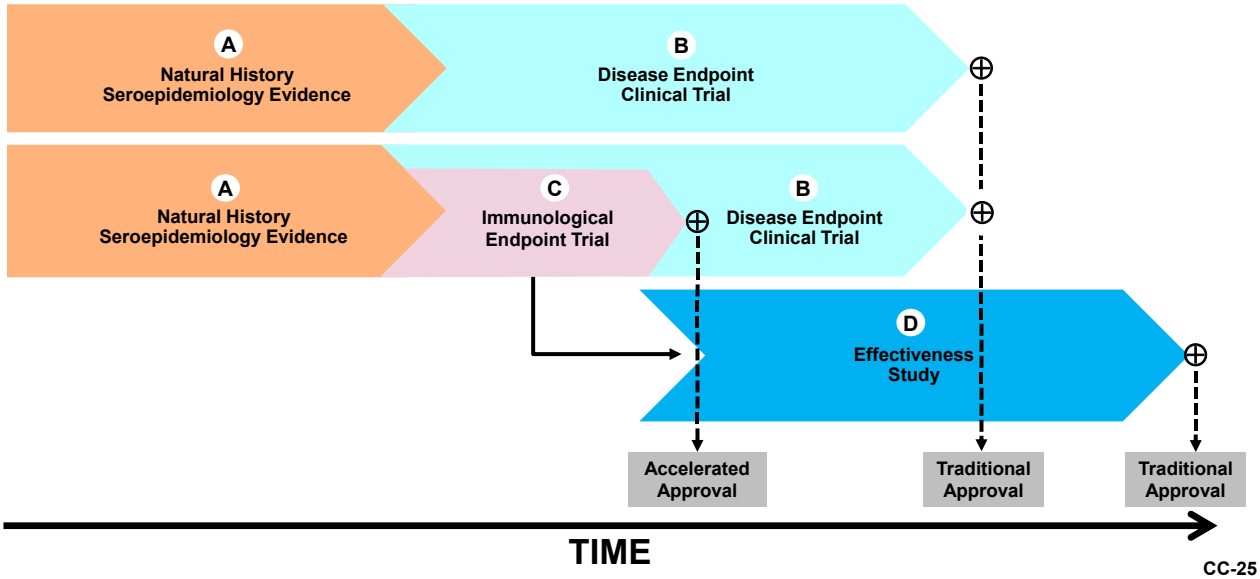
A Combined Immunological and Clinical Disease Endpoint Pathway Could Result in Earlier Licensure



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Potential GBS Vaccine Clinical Development Pathways to Demonstrate Vaccine Effectiveness

- There is an important unmet medical need for a vaccine to prevent GBS disease in infants
- The mechanism of action for immune protection is established
- Low incidence rates mean that clinical endpoint efficacy studies alone will take many years and may not be practical
- Pfizer is looking forward to working with the FDA to develop approaches that may bring a safe and effective vaccine to licensure

CC-26