Prospect for a GBS vaccine and the pathway to licensure, including considerations for LMICs

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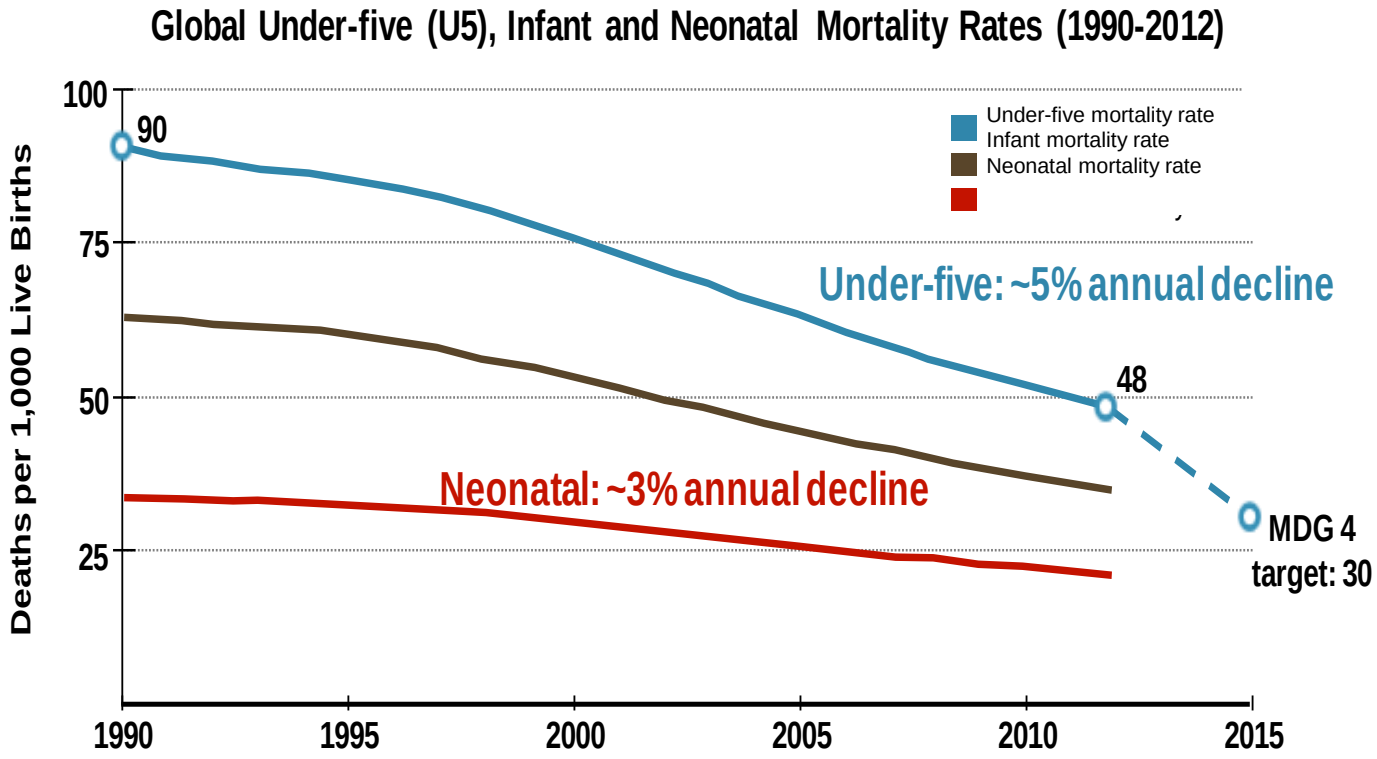
What problem are we trying to solve?

Slower progress in reducing neonatal mortality



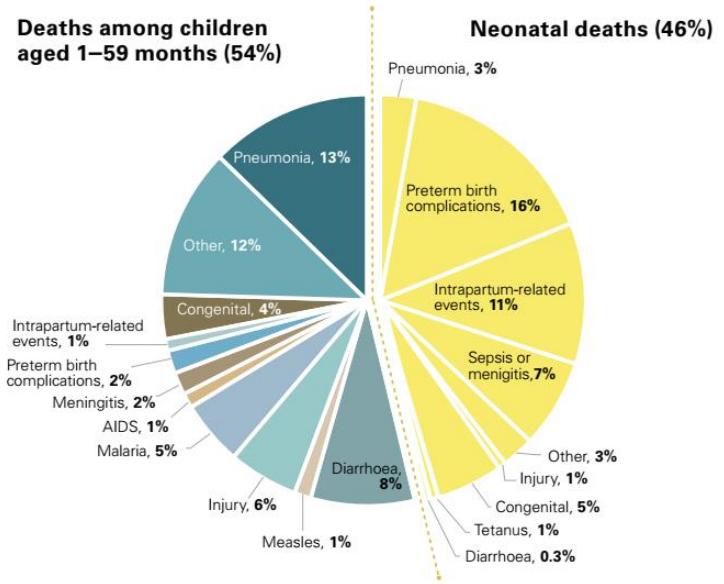
In 2016, of the **5.6 million** deaths of children under the age of five, **2.6million** (46%) occurred in the neonatal period. **2.2 million** survivors had neurodevelopmental impairment

1. Millennium development goal; Source: http://www.childinfo.org/mortality_underfive.php
2. IGME child mortality report 2017

What problem are we trying to solve?

Nearly half of all deaths in children under the age of five occurred in the neonatal period in 2016. And one quarter of neonatal deaths are due to infectious causes.

Global distribution of deaths among children under age 5, by cause, 2016



WHO and Maternal and Child Epidemiology Estimation Group (MCEE) provisional estimates 2017

Why pursue a maternal Group B Streptococcus (GBS) vaccine?

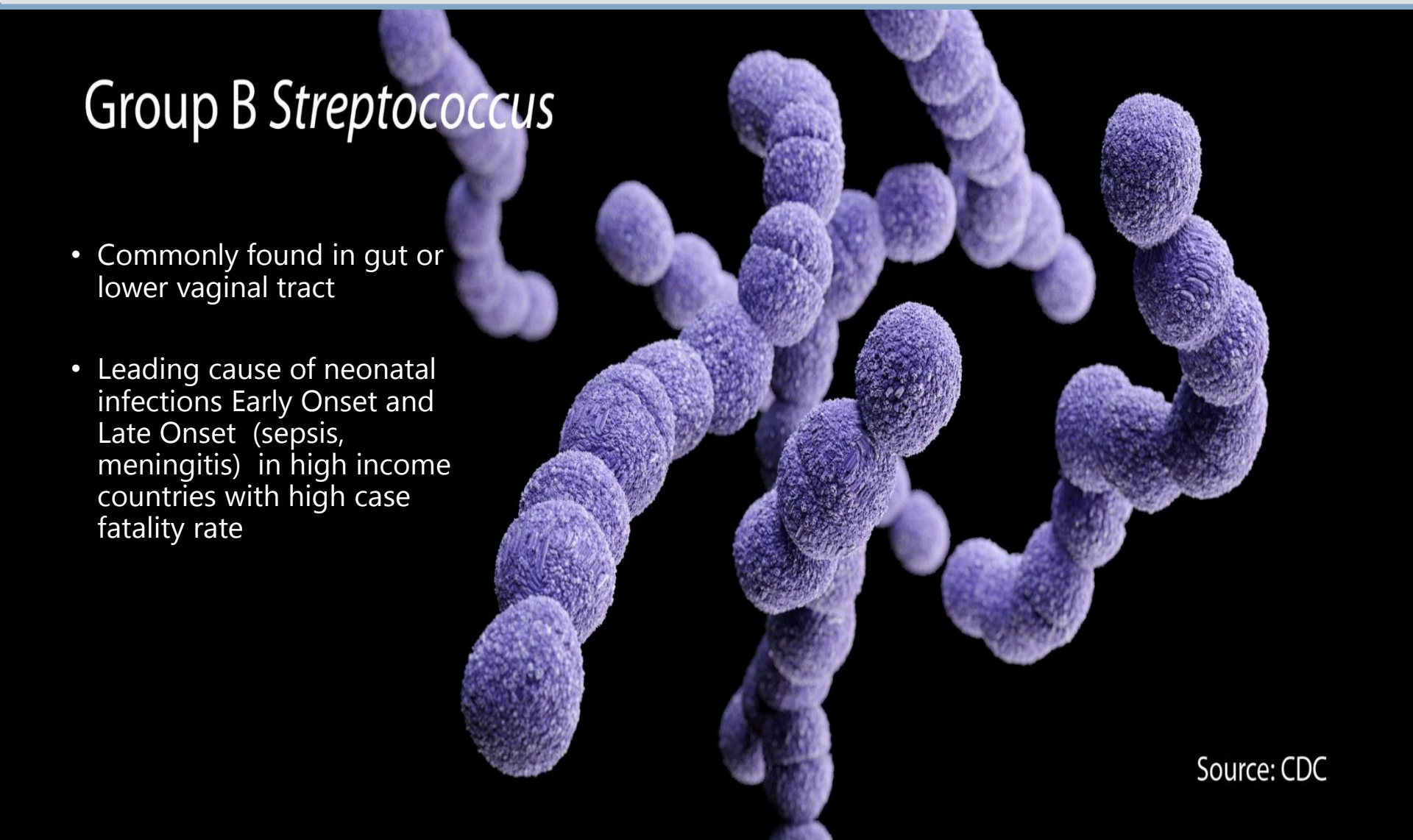
- Maternal Morbidity & Mortality
- Neonatal Morbidity & Mortality
- Stillbirths
- Pre-term births

Seale AC et al Clinical Infectious Diseases. 2017;65(S2):S200-19

Reducing neonatal deaths is a focus of SGD targets

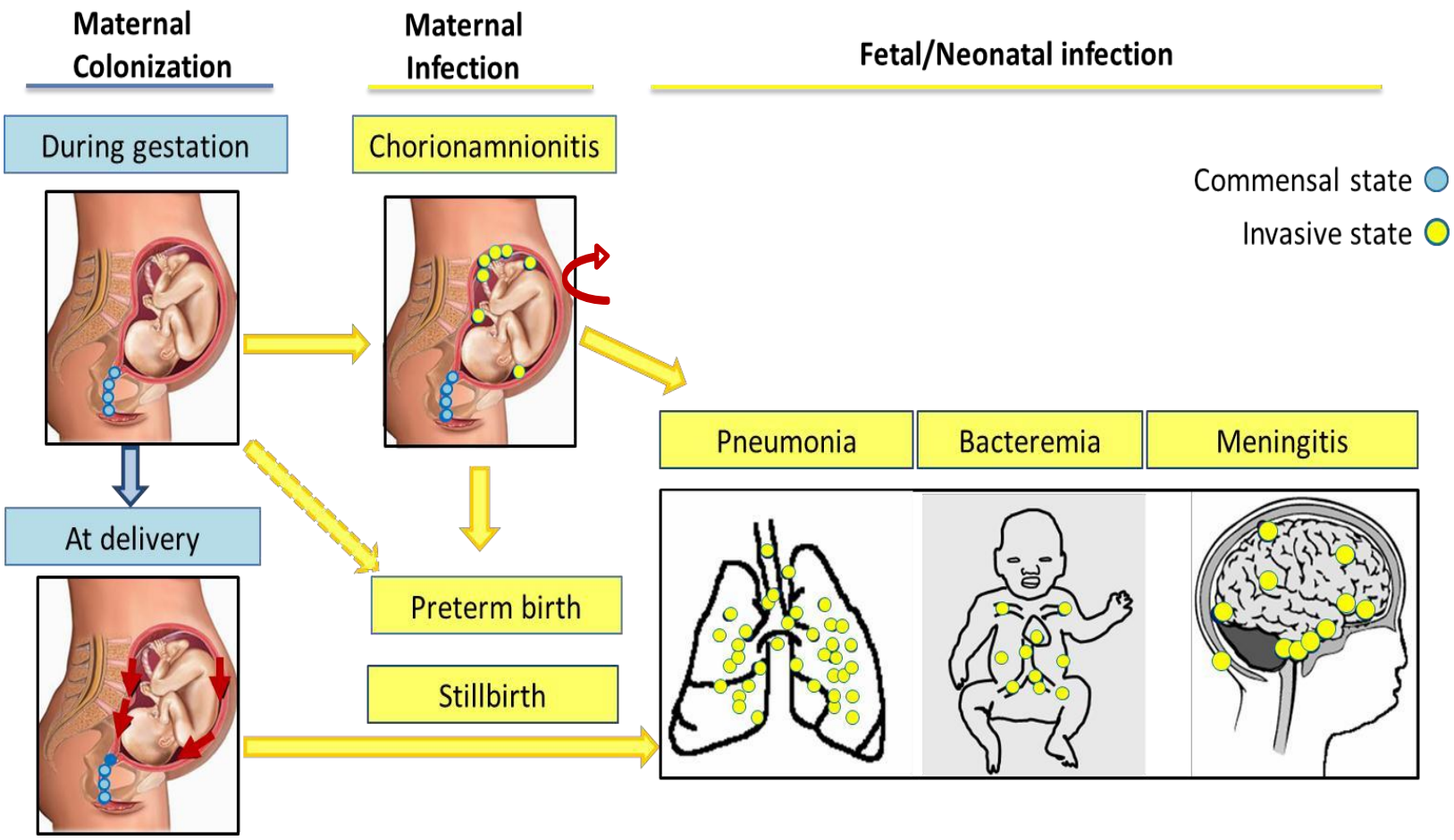
By 2030 neonatal mortality reduction in ALL countries to <12:1000 livebirths

Group B Streptococcus



- Commonly found in gut or lower vaginal tract
- Leading cause of neonatal infections Early Onset and Late Onset (sepsis, meningitis) in high income countries with high case fatality rate

Stages of GBS maternal and neonatal infection



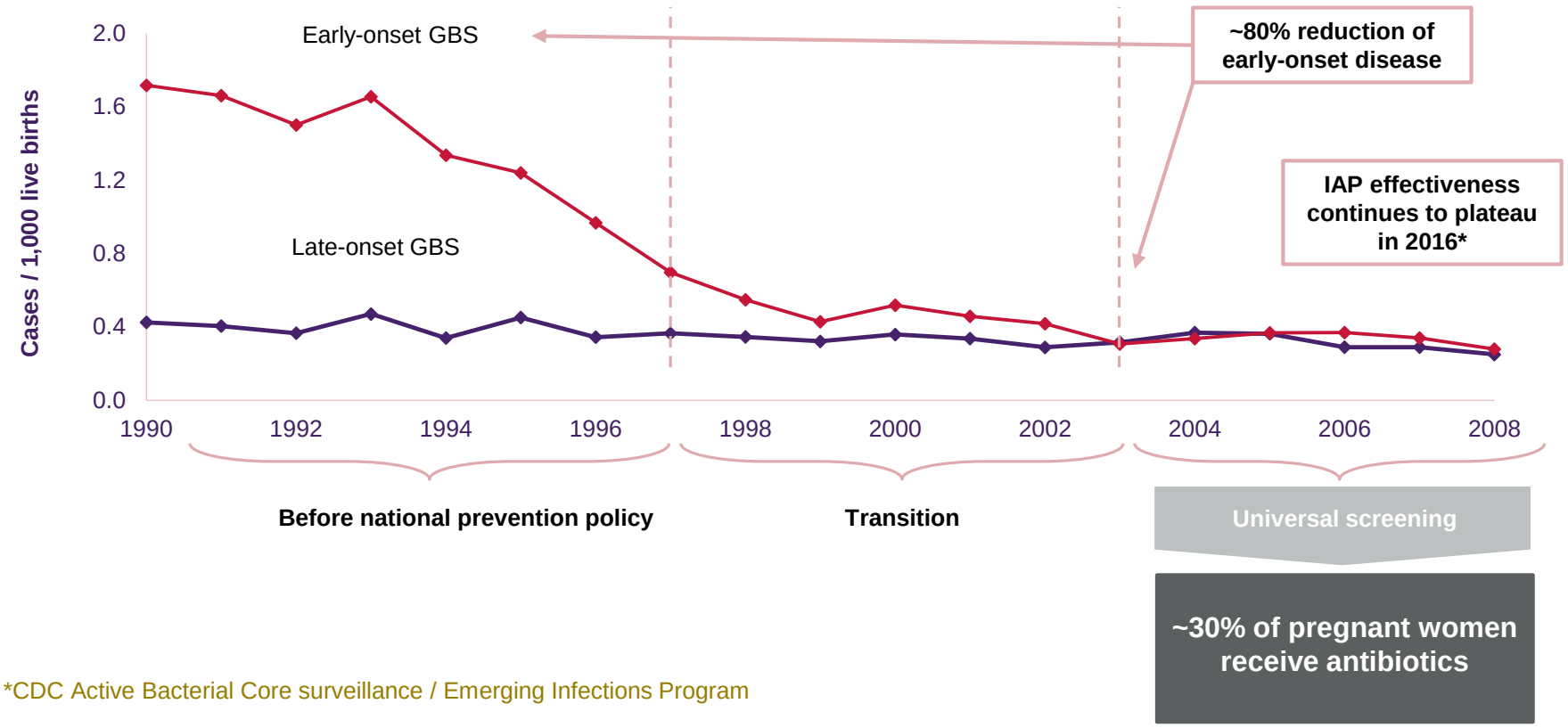
Pathogenesis of late-onset disease (>72 hours) possibly through maternal transmission (including breast milk) or other environmental acquisition.

Adapted from: Doran & Nizet Molecular Microbiology 2004 54 (1), 23–31

Slide: courtesy S. Madhi

Universal intrapartum antibiotic prophylaxis (IAP) reduces early-onset disease (EOD), but does not prevent late-onset-disease (LOD)

Rate of Early- and Late-Onset GBS, US 1990-2008*



*CDC Active Bacterial Core surveillance / Emerging Infections Program

Risk-based IAP is associated with increase in GBS in High income countries and difficult to implement in LMIC

Group B streptococcal disease in UK and Irish infants younger than 90 days, 2014–15: a prospective surveillance study

Catherine P O'Sullivan, Theresa Lamagni, Darshana Patel, Androulla Efstratiou, Robert Cunney, Mary Meehan, Shamez Ladhani, Arlene J Reynolds, Ruth Campbell, Lorraine Doherty, Margaret Boyle, Georgia Kapatai, Victoria Chalker, Diane Lindsay, Andrew Smith, Eleri Davies, Christine E Jones, Paul T Heath

Summary

Background Group B streptococcus is a leading cause of serious infection in young infants in many countries worldwide. We aimed to define the burden and clinical features of invasive group B streptococcal disease in infants younger than 90 days in the UK and Ireland, together with the characteristics of disease-causing isolates.

Methods Prospective, active national surveillance of invasive group B streptococcal disease in infants younger than

Lancet Infect Dis 2019; 19: 83-90

Published Online November 26, 2018 http://dx.doi.org/10.1016/S1473-3099(18)30555-3

GBS incidence rate per 1000 live births (n=cases) UK		
	2014-15	2000-01
EOD	0.57 (517)	0.48 (377)
LOD	0.37 (339)	0.24 (191)

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Cost-effectiveness analysis of maternal immunisation against group B *Streptococcus* (GBS) disease: A modelling study

Kyriaki Giorgakoudi [a,*], Catherine O'Sullivan [b], Paul T. Heath [b], Shamez Ladhani [b,c], Theresa Lamagni [d], Mary Ramsay [c], Hareth Al-Janabi [e], Caroline Trotter [a]

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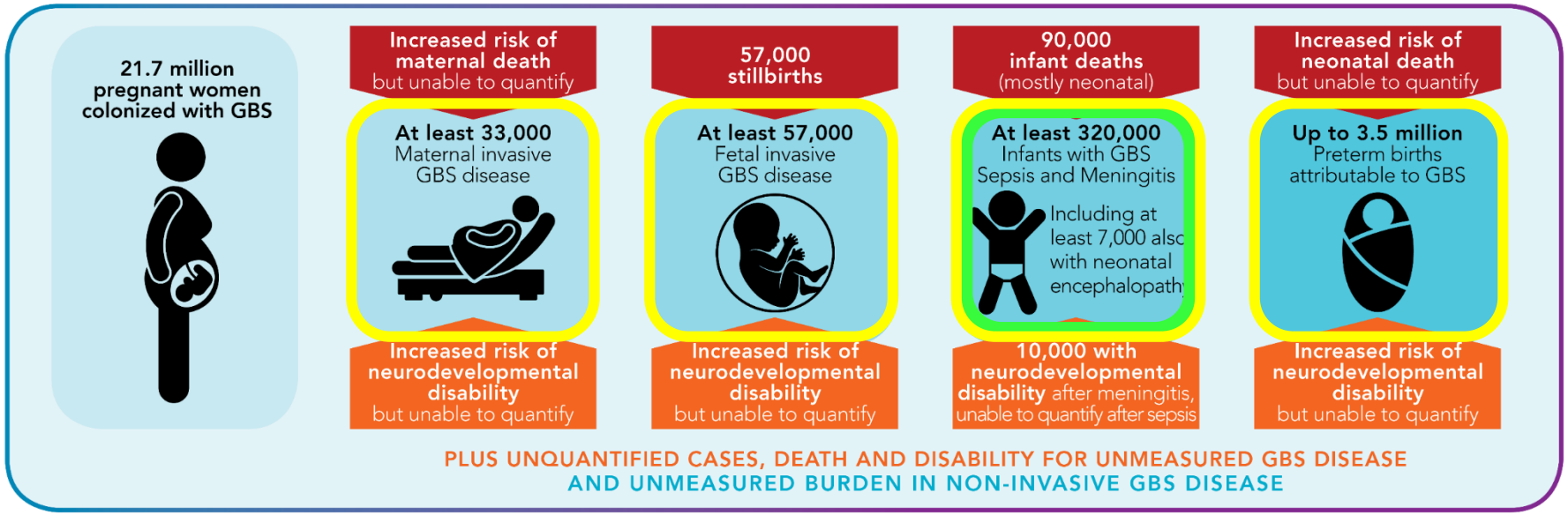
[b] Vaccine Institute, Institute of Infection and Immunity, St George's University of London, London, UK
[c] Immunisation, Hepatitis and Blood Safety Department, National Infection Service, Public Health England, London UK
[d] Healthcare-Associated Infection & Antimicrobial Resistance Department, National Infection Service, Public Health England, London UK
[e] Institute of Applied Health Research, University of Birmingham, Birmingham, UK

GBS vaccine may prevent 90,000 infant deaths and 57,000 stillbirths



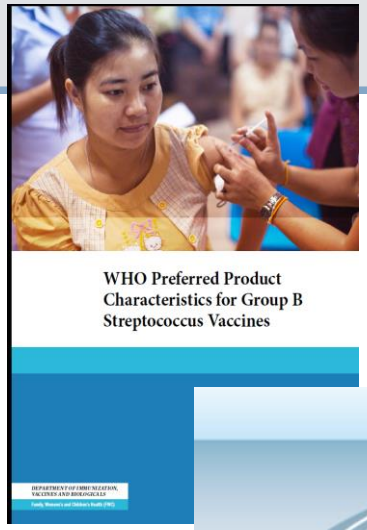
1. **Higher impact than Intrapartum antibiotic prophylaxis (IAP) as affects more outcomes**
2. **Higher coverage especially in challenging settings → more equitable than IAP**
3. **Leverage existing programmatic platforms (e.g. antenatal care)**
4. **Reduce antibiotic exposure (21.7 million women)**

Could be prevented by IAP

Could be prevented by maternal GBS vaccine

GBS vaccine development pipeline, guidelines, and norms

Vaccines			Phase				Program status
Candidate	Manufacturer	Vaccine construct	Discovery	Pre-clinical	Phase 1	Phase 2	
NA	Pfizer	Multivalent CPS conjugate		X			Clinical program start in 2017
GBS vaccine	Novartis/GSK	Trivalent CPS (serotypes Ia, IIb, III) conjugated to CRM_{197} unadjuvanted				X	Completed safety and immunogenicity in pregnant women. Study completed
NA	GSK	Pentavalent (Ia, Ib, II, III, V) CPS-CRM_{197}		X			
NA	GSK	Pilus proteins		X			
NA	Biovac	Polyvalent CPS conjugate	X				Program start in 2017
GBS-NN vaccine/MVX13211	Minervax	N-domains of Rib + Alpha C surface proteins, unadjuvanted or Alhydrogel-adjuvanted			X		Safety and immunogenicity in non-pregnant women. Study completed



http://www.who.int/immunization/research/development/ppc_groupb_strepvaccines/en/

Early-onset disease Incidence requires large Vaccine efficacy trial

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Considerations for a phase-III trial to evaluate a group B *Streptococcus* polysaccharide-protein conjugate vaccine in pregnant women for the prevention of early- and late-onset invasive disease in young-infants

Shabir A. Madhi[a,b,c,*], Ziyaad Dangor[b,c], Paul T. Heath[d], Stephanie Schrag[e], Alaine Izu[b,c], Ajoke Sobanjo-ter Meulen[f], Peter M. Dull[f]

Assumptions for a 1:1 randomized controlled GBS clinical vaccine efficacy trial in a high disease incidence area

Population disease incidence Per 1000 live births	Cases due to Vaccine serotypes	Cases eligible per protocol	Case incidence Per 1000 live births	Vaccine efficacy	Lower 95%CI bound	Sample size
2.0	75-85%	70-80%	1.05-1.35	75%	>20%	40,000 – 60,000

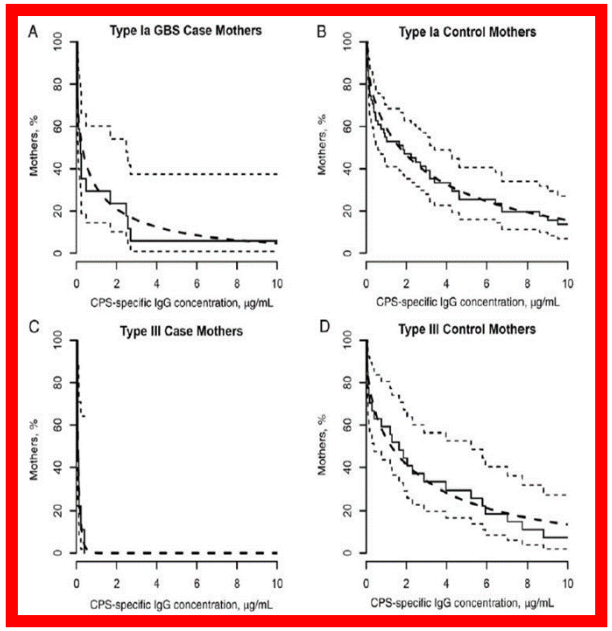
Why a vaccine could work: Maternal anti-GBS CPS Ab appears to confer protection

CORRELATION OF MATERNAL ANTIBODY DEFICIENCY WITH SUSCEPTIBILITY TO NEONATAL GROUP B STREPTOCOCCAL INFECTION

CAROL J. BAKER, M.D., AND DENNIS L. KASPER, M.D.

Abstract We investigated the role of maternal antibody in neonatal Group B streptococcal infection with a radioactive antigen-binding assay employing a purified polysaccharide antigen with both Type III and Group B determinants. Serums from seven women who gave birth to infants who had invasive Group B streptococcal infection with Type III strains were all deficient in antibody. In contrast, serums from 22 of 29 pregnant Type III vaginal carriers whose infants were healthy contained antibody with a prevalence significantly different from that in women delivering infants with Type III disease ($P < 0.01$). Three healthy neonates born to women with antibody in serums had demonstrable antibody in umbilical-cord serum. These data suggest that transplacental transfer of maternal antibody protects infants from invasive Group B streptococcal infection with Type III strains.
(N Engl J Med 294:753-756, 1976)

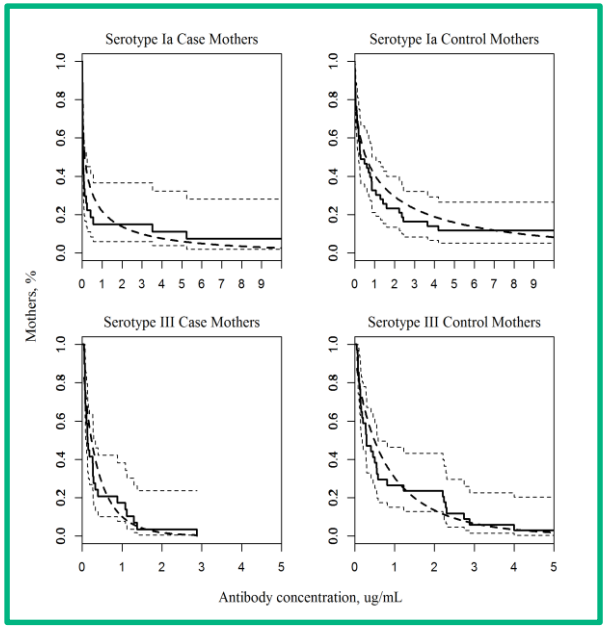
Need for Standardized Immunology Assays to Establish Correlate of Protection Against Invasive GBS disease



Serotype Ia: 89% reduced risk if ≥0.5 µg/mL.

Serotype III: 91% reduced in risk if ≥0.5 µg/mL.

Baker et al. (USA) J Infect Dis 2014



Serotype Ia: 90% reduced risk if ≥5 µg/mL.

Serotype III: 90% reduction in risk if ≥3 µg/mL.

Dangor Z et al. (South Africa) Vaccine 2015

GBS assay standardization consortium

CDC Centers for Disease Control and Prevention

World Health Organization

Bill & Melinda Gates foundation

St George's University of London

Objective 1: development of standard reagents and identification and review of assays for standardization

FDA

Public Health England

Objective 2: To standardized protocols for existing ELISA and functional GBS assays using standard reagents

London School of Hygiene & Tropical Medicine

Harvard University

Objective 3: To validate standard protocols and standard reagents across laboratories to establish a prediction of disease protection

RMPRU respiratory & meningeal pathogens research unit

UAB The University of Alabama at Birmingham
Knowledge that will change your world

UCL

NIBSC Confidence in Biological Medicines

MINERVAX

PATH A catalyst for global health

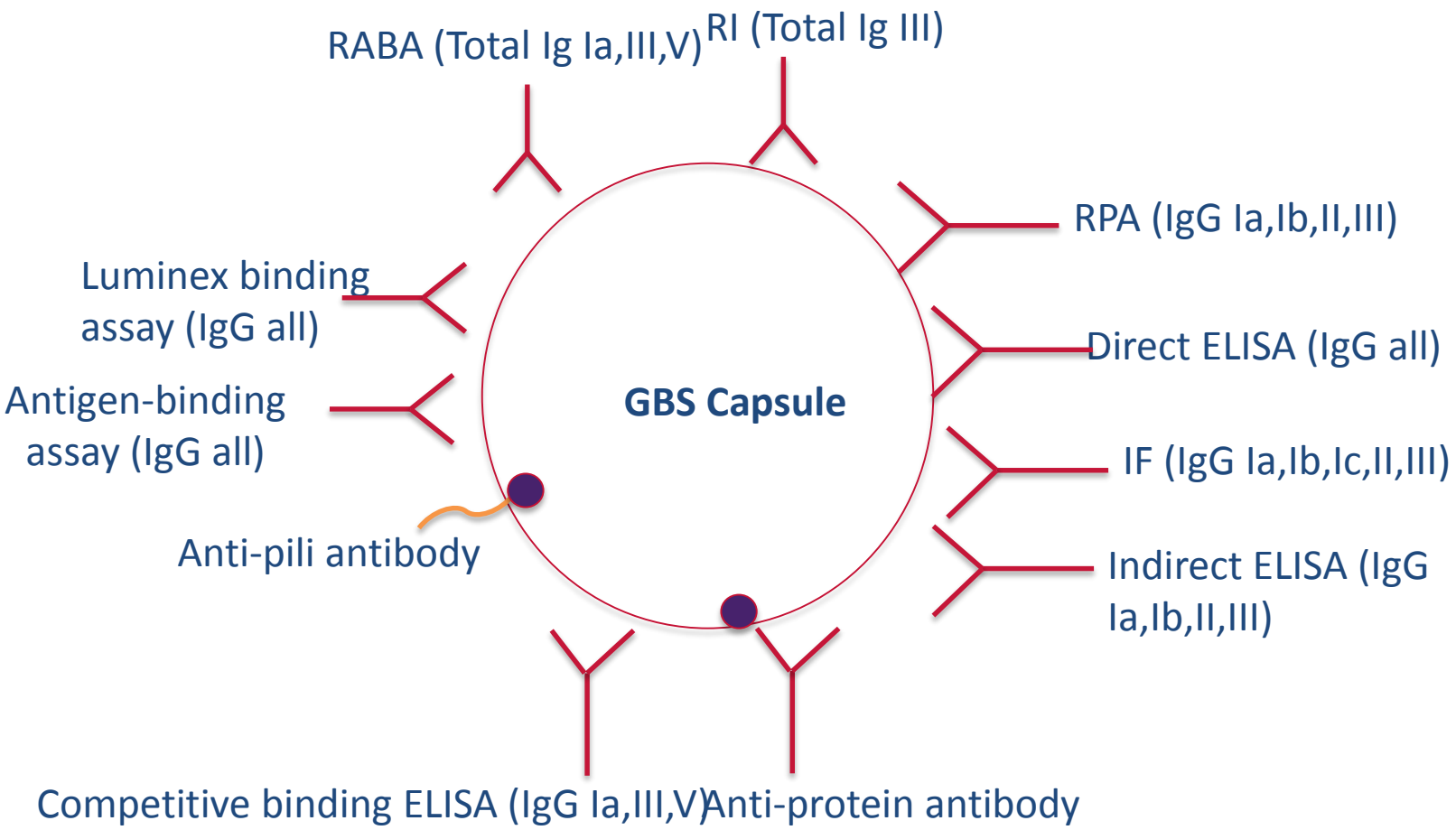
THE BIOVAC INSTITUTE The science of protecting life

PIDRG Paediatric Infectious Diseases Research Group

Industry expertise

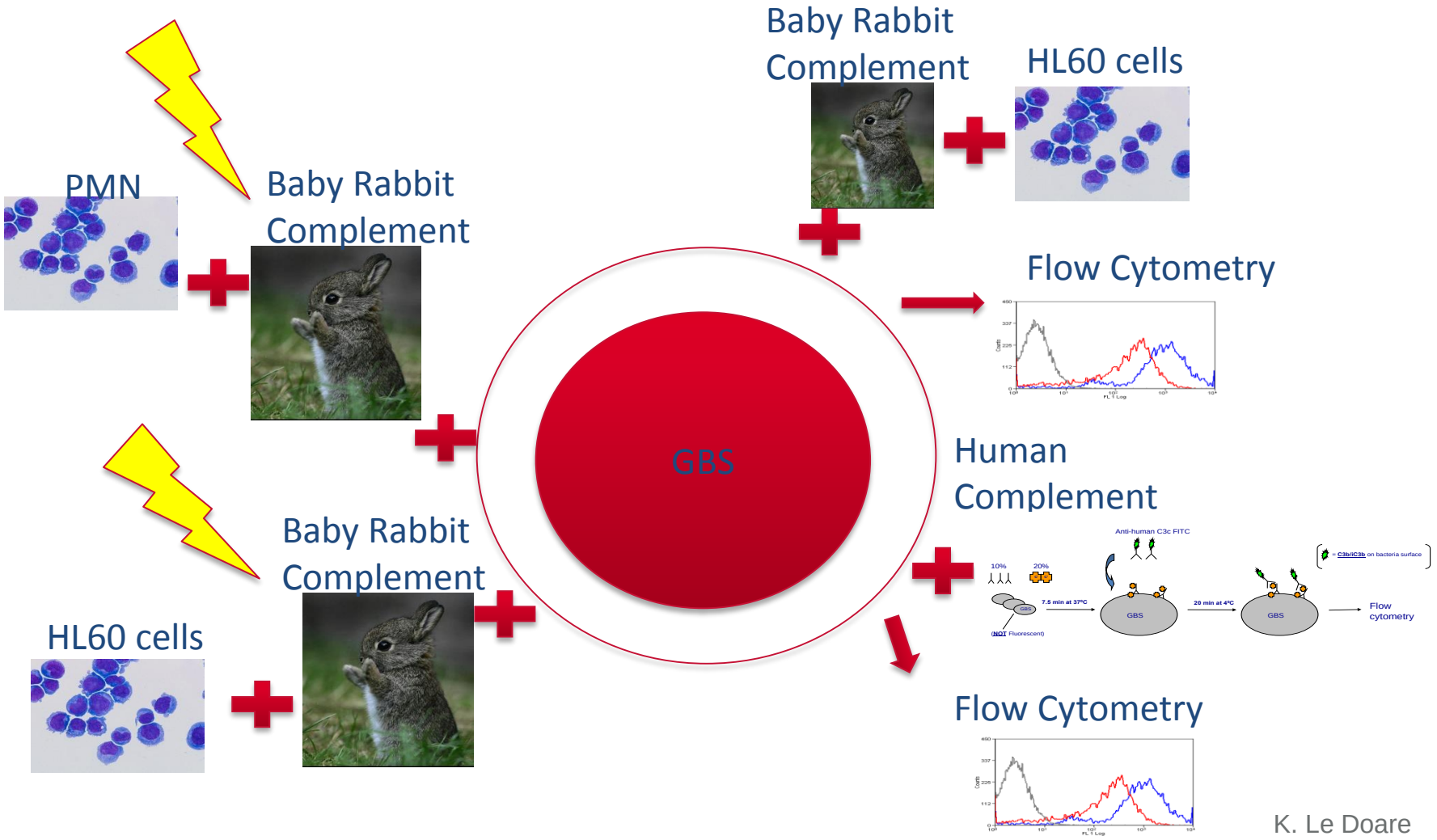
Anti-Capsular and anti-surface-protein assays

Mono-plex and multi-plex, approximately 34 different assays used



Functional and semi-functional antibody assays

Killing or uptake, with or without standards 9 different assays in circulation



K. Le Doare

Major regulatory authorities discuss Sero-correlate based path to GBS Vaccine licensure

European Medicines Agency (EMEA)

GBS Assay Standardization Group Meeting with the

Vaccine Working Party of EMEA on May 24th, 2017

US Food and Drug Administration (FDA)

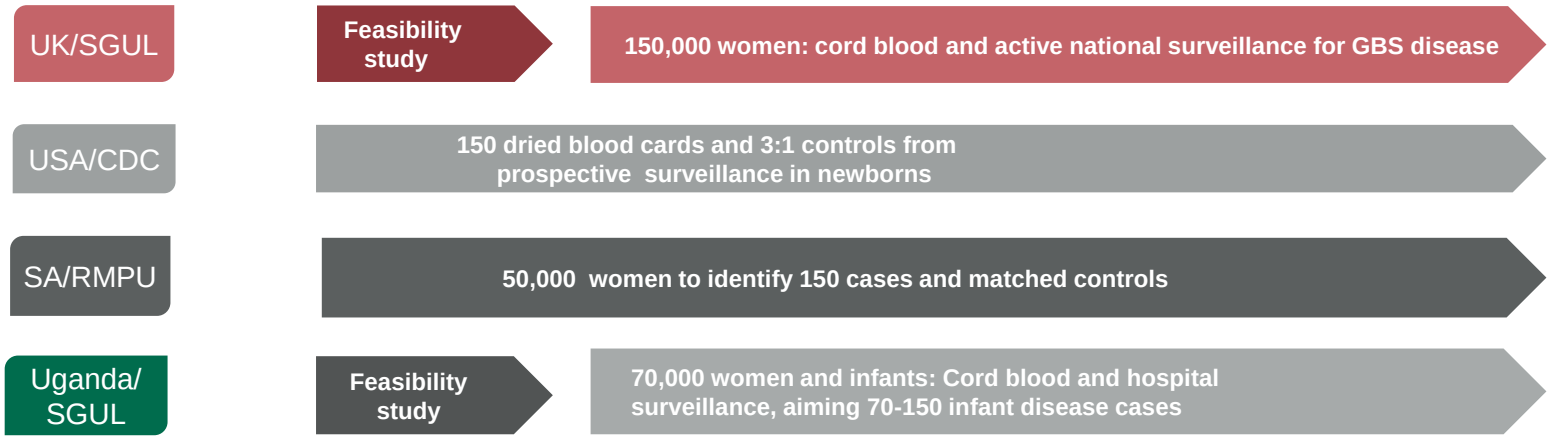
Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting on May 17th, 2018

Evaluation of the Effectiveness of Vaccine intended to

Prevent Group B Streptococcal Disease in Infants

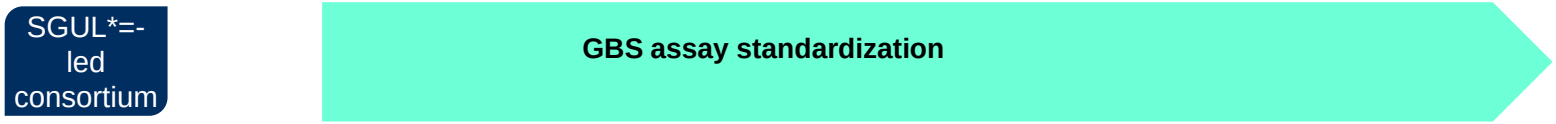
GBS vaccine path to licensure based on correlate-of-protection (CoP) – FDA opined supportively at VRBAC meeting May 2018

Sero-epidemiological CoP studies in pregnant women



Industry trials

Ph 1/2 GBS studies in South Africa and Uganda



*SGULSt. George's University

Questions?

St George's University of London

Bill & Melinda Gates foundation