FIGHTING PNEUMONIA: AN AGENDA FOR ACTION
WORLD PNEUMONIA DAY EVENT

Exciting New Vaccines to Save the Lives of Children – 14 November 2022

Keith P. Klugman, MD PhD
William H. Foege Emeritus Professor of Global Health, Emory University
Honorary Professor, University of the Witwatersrand
Director, Pneumonia Programs, Bill & Melinda Gates Foundation

REGIONAL UNDER 5 LOWER RESPIRATORY INFECTION MORTALITY AND INCIDENCE PLOTTED AGAINST SOCIODEMOGRAPHIC INDEX

- **Disease burden reflects lack of equity**

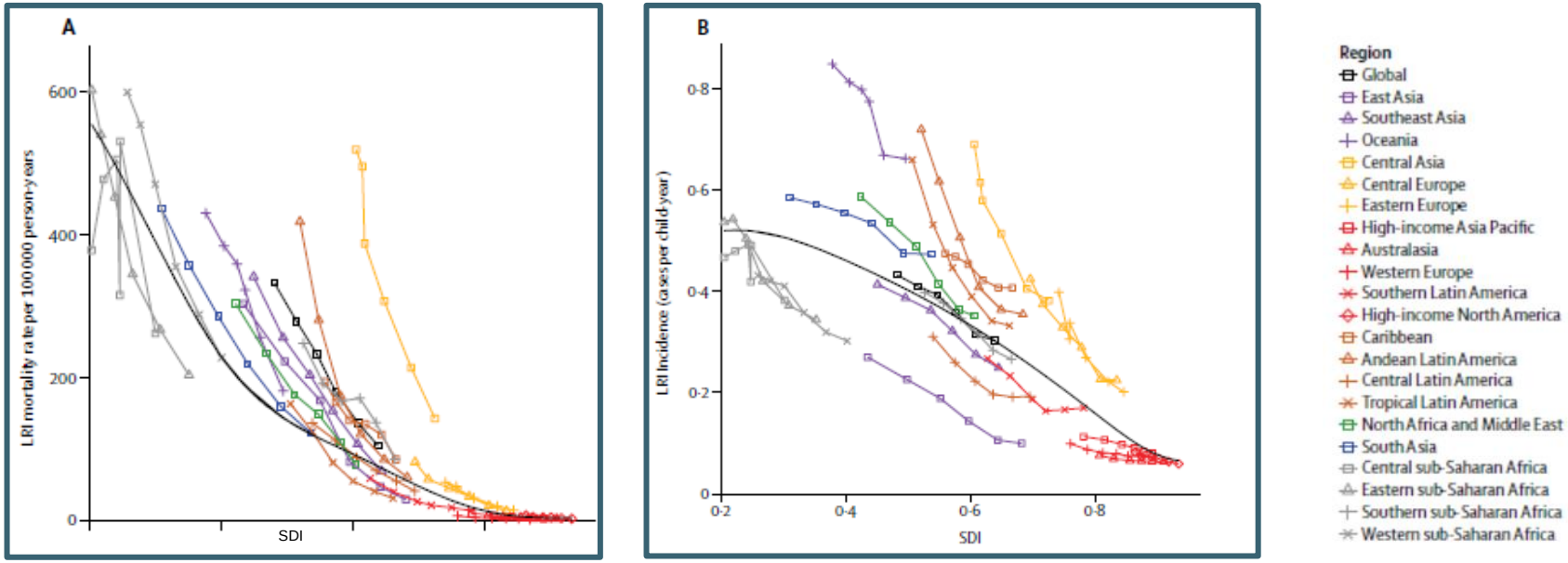
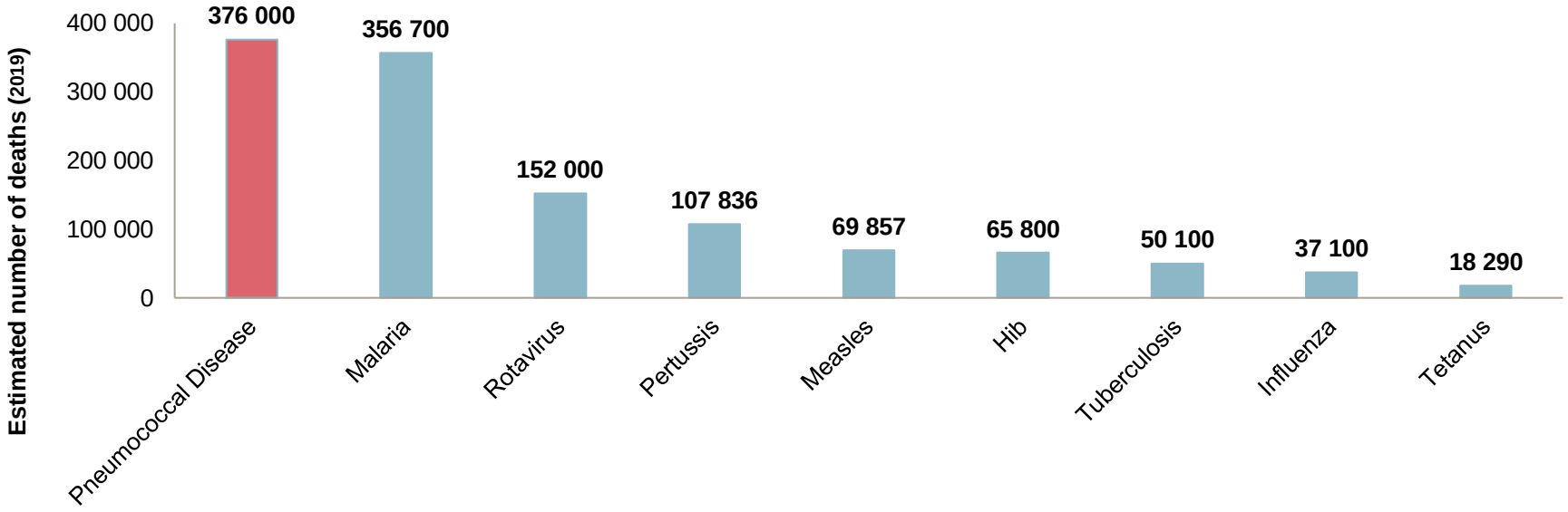


***Figure 2*: LRI burden by Global Burden of Diseases Study region plotted against SDI**
Under-5 LRI mortality rate per 100 000 (A) and incidence per child-year (B) is shown. Data points show 5-year increments from 1990 to 2015. The black line is a least-squares cubic spline regression, with knots at 0·4, 0·6, and 0·8, using the under-5 LRI mortality rate or incidence for each geographic location, and represents the expected rate based on SDI alone (estimates above the black line are higher than expected and those below are lower than expected). More information on the formulation and theory of the SDI can be found in the Cause of Death GBD 2015 capstone paper.[5] LRI=lower respiratory tract infection. SDI=Sociodemographic Index.

GBD 2015 LRI Collaborators. *Lancet ID* 2017; DOI: 10.1016/S1473-3099(17)30396-1

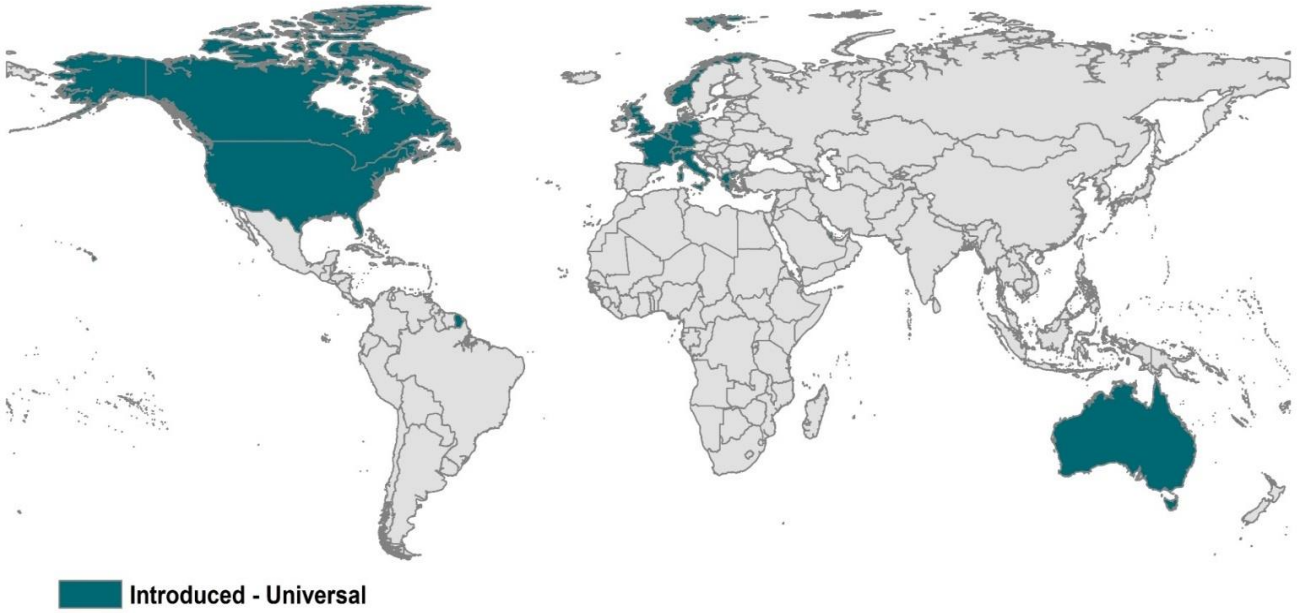
NUMBER OF CHILDREN <5 YEARS OLD WHO DIE ANNUALLY FROM VACCINE-PREVENTABLE DISEASE



***Streptococcus pneumoniae* is the leading cause of vaccine-preventable deaths globally**

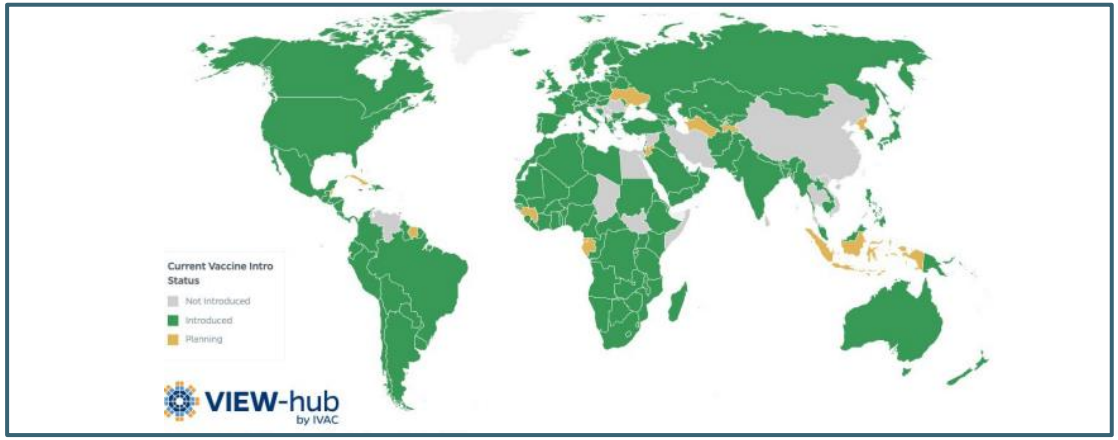
GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020; 396: 1204–22. Supplementary Appendix 2.

2006 GLOBAL PCV INTRODUCTION STATUS – A PICTURE OF GLOBAL INEQUITY

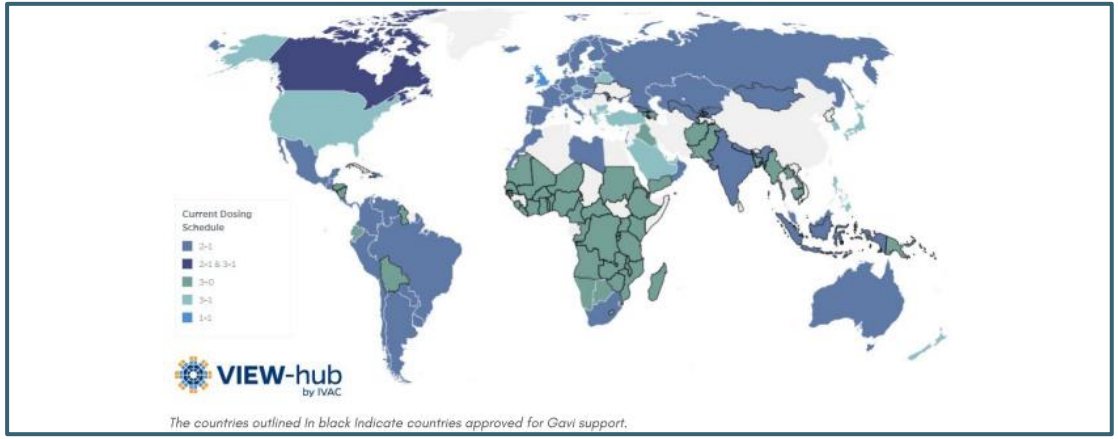


IVAC/JHSPH – VIMS Report Dec. 2013

2022 GLOBAL PCV INTRODUCTION STATUS[1]



2022 PCV CURRENT DOSING SCHEDULE[1]



Gavi	Global
National Introductions[1]	
60/73 (82%)	**148/194 (76%)**
Surviving Infants have access to PCV[2]	
51.5M (64%)	**80.7M (60%)**
Surviving Infants immunized with PCV[2]	
37M (46%)	**61.7M (45%)**
Countries with more than 1M unimmunized or underimmunized infants[2]	
Indonesia, India	China, Egypt, Iran, Philippines, Algeria

[1]IVAC VIEW-Hub Report March 2022
[2]IVAC VIEW-Hub Report March 2020

PCV VACCINE LANDSCAPE

Current Investigational 15+ PCVs in Human Clinical Trials *

No. of Serotypes	Manufacturer	Serotypes	Clinical Study Phase
15- valent	Merck	Prevenar 13 + **22F**, **33F**	Licensed
20- valent	Pfizer	Prevenar 13 + **8**, **10A**, **11A**, **12F, 15B**, 22F, 33F	Licensed / Phase III
24- valent	Affinivax	Prevenar 13 + **2**, 8, **9N**, 10A, 11A, 12F, 15B, **17F**, **20B**, 22F, 33F	Phase II
24- valent	Vaxcyte	Prevenar 13 + **2**, 8, **9N**, 10A, 11A, 12F, 15B, **17F**, **20**, 22F, 33F	Phase I
25- valent	Inventprise	Prevenar 13 + **2**, 8, **9N**, 10A, 12F, **15A**, 15B, **16F**, 22F, **24F**, 33F, **35B**	Phase I

*Pfizer's 20-valent PCV and Merck's 15V have been approved for adult use in the US; and PCV15 in children.

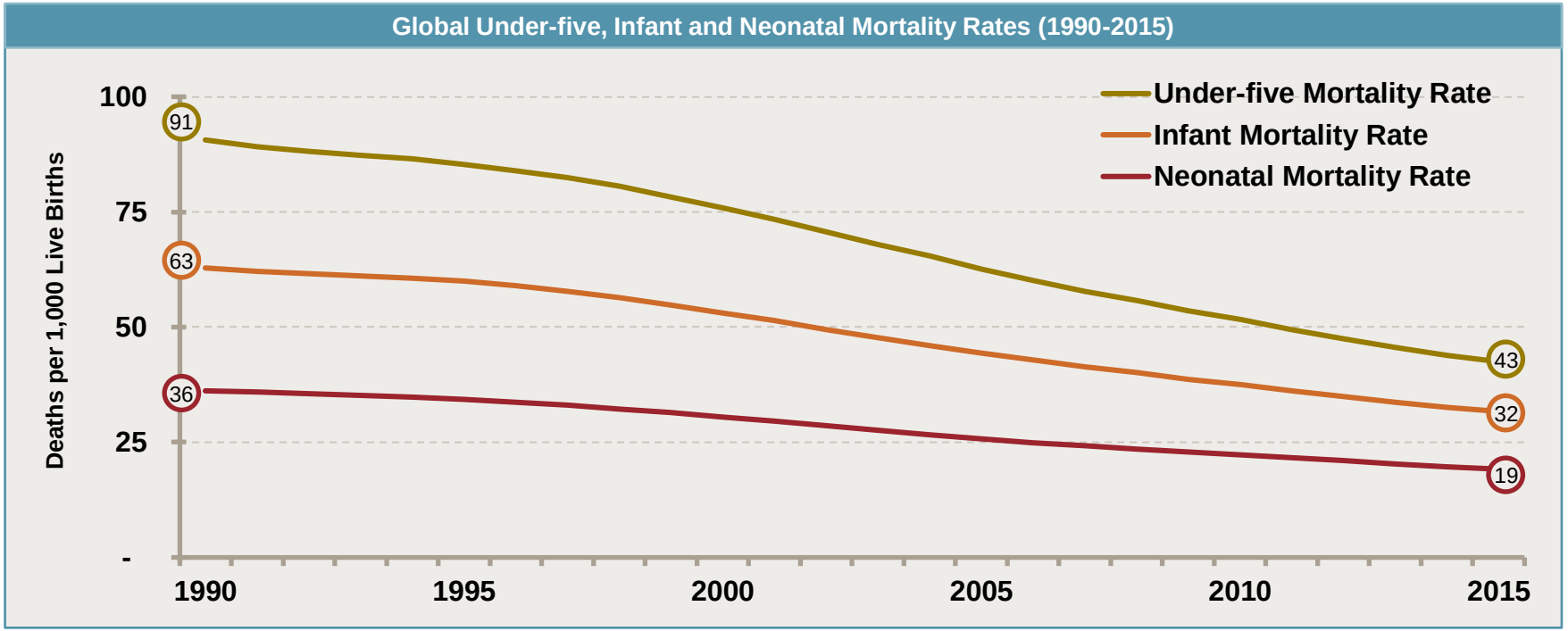
How were these serotypes selected ?

- Early data from the US suggested that serotypes 22F and 33F were important replacement serotypes in children – they are not key serotypes in Gavi countries
- Serotypes 8, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F are in the 23 valent adult pneumococcal polysaccharide vaccine (PPV23)
- Serotype 2 (in PPV23) and important in low income countries, particularly in children is in Affinivax, Vaxcyte & Inventprise 25 valent vaccines; 15A, 16F, 24F and 35B are important multi-resistant emerging serotypes in children in Gavi countries
- Vaxcyte 31, not yet in reported human trials, adds in the Inventprise 25 types 15A, 16F, 24F, 35B plus 7C, 23A, 23B, 31

Focus for selection has mainly been serotypes causing disease in adults in high income countries

PROGRESS IN REDUCTION OF CHILD & NEONATAL MORTALITY

- Despite significant declines, the global MDG target for under-five mortality rate of 30 per 1,000 live births was not achieved by 2015
- Neonatal mortality proved more challenging to address and declined at a lower rate than under-five mortality



Source: Data.unicef.org

MATERNAL IMMUNIZATION STRATEGY BUILDS ON THE PARADIGM SHIFT FROM AVOIDING RISK TO BENEFITING WOMEN & CHILDREN

Maternal immunization an unrecognized opportunity

Despite strong success in reducing neonatal tetanus, maternal vaccines are largely under-utilized and under-prioritized for product development

New urgency to vaccinate pregnant women in the wake of pandemics

H1N1, Ebola, and Zika elevate the need to vaccinate pregnant women and no longer exclude them from immunization programs

New tools needed to accelerate progress in saving newborn lives

The Foundation begins shaping a market for new vaccines specifically for use in pregnancy to reduce neonatal and maternal mortality

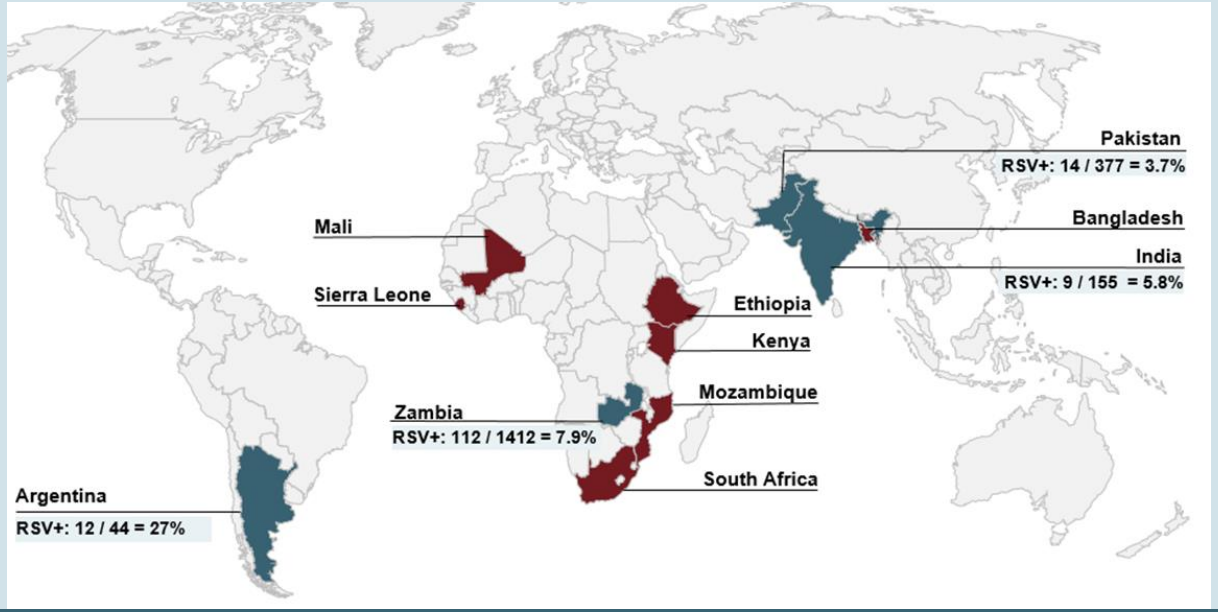
New era of maternal immunization & vaccine development

Increasing global consensus on the value of vaccines for use during pregnancy driven by the covid pandemic

> *"NIH provided 10 years of funding clinical trials for maternal vaccines from 1992-2002 - with FDA oversight, to inspire manufacturers to take on GBS vaccine development - but this work had virtually no impact. Nothing happened until three key events led to recognition of the need for MI: (1) the flu pandemic of 2009; (2) the young infant pertussis deaths during epidemics in 2010 leading to the 2011 ACIP recommendation for routine maternal Tdap vaccination; and (3) support from the Gates Foundation."*
>
> *- Dr. Carol Baker, Professor of Pediatrics, McGovern Medical School at the University of Texas*

GLOBAL RSV MORTALITY BURDEN IN INFANTS <6M

- RSV is the **most common cause of severe lower respiratory tract infection (LRTI) in the first six months of life**
- **97% of mortality in low-and-middle income countries (LMICs)**
- BMGF-funded mortality surveillance studies reveal high unmeasured RSV mortality in community settings in LMICs
- RSV detected in 5-10% of all community deaths among infants less than 6 months in multiple countries



These data suggest that global RSV-associated mortality in infants <6m may be as high as 100,000 deaths annually

NOVAVAX RSV MATERNAL IMMUNIZATION TRIAL DATA

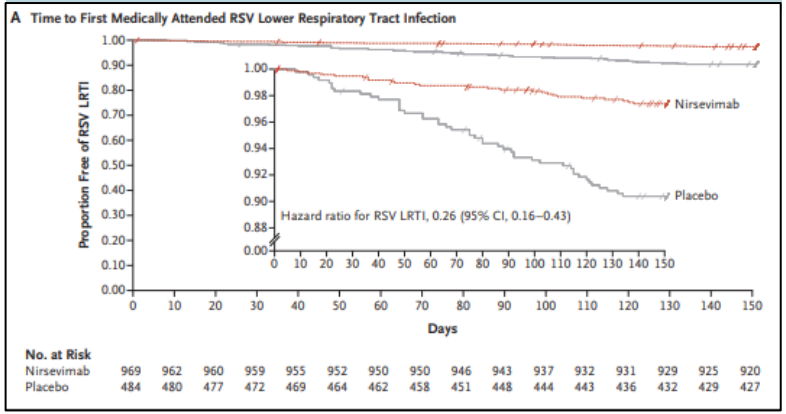
Table 2. Efficacy of Maternal Vaccination against Lower Respiratory Tract Infection in Infants.*

Efficacy End Point	Per-Protocol Analyses†			Exploratory Expanded-Data Intention-to-Treat Analyses‡		
	RSV F Vaccine	Placebo	Vaccine Efficacy (95% CI)	RSV F Vaccine	Placebo	Vaccine Efficacy (95% CI)
	% of infants (no./total no.)		%	*% of infants (no./total no.)*		%
Primary end point						
RSV-associated medically significant lower respiratory tract infection up to 90 days of life	1.5 (41/2765)	2.4 (35/1430)	39.4 (5.3 to 61.2)§	2.3 (70/2980)	4.0 (62/1547)	41.4 (18.0 to 58.1)¶
Secondary end points						
RSV-associated lower respiratory tract infection with severe hypoxemia up to 90 days of life	0.5 (14/2765)	1.0 (14/1430)	48.3 (–8.2 to 75.3)	0.9 (27/2980)	2.2 (34/1547)	58.8 (31.9 to 75.0)
Hospitalization for RSV-associated lower respiratory tract infection up to 90 days of life	2.1 (57/2765)	3.7 (53/1430)	44.4 (19.6 to 61.5)	2.2 (65/2980)	4.1 (63/1547)	46.4 (24.7 to 61.9)
	no. of events per 100 infants (no. of events/total no. of infants)			*no. of events per 100 infants (no. of events/total no. of infants)*		
Exploratory all-cause end points						
Medically significant lower respiratory tract infection from any cause up to 90 days of life	5.5 (153/2765)	7.2 (103/1430)	23.2 (1.4 to 40.2)	5.9 (175/2980)	7.5 (116/1547)	21.7 (1.0 to 38.1)
Lower respiratory tract infection from any cause with severe hypoxemia up to 90 days of life	1.7 (47/2765)	3.1 (45/1430)	46.0 (18.7 to 64.1)	1.7 (51/2980)	3.2 (50/1547)	47.0 (21.8 to 64.2)
Hospitalization for lower respiratory tract infection from any cause up to 90 days of life	4.3 (120/2765)	6.0 (86/1430)	27.8 (4.8 to 45.3)	4.2 (125/2980)	6.6 (102/1547)	36.4 (17.4 to 51.0)

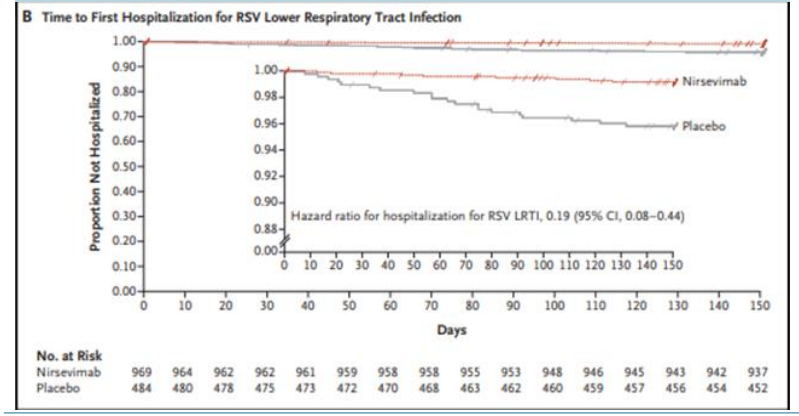
Madhi et al, *NEJM*, 2020, 383, 426 – 439.

MEDIMMUNE NIRSEVIMAB MONOCLONAL RSV PHASE 2B TRIAL DATA

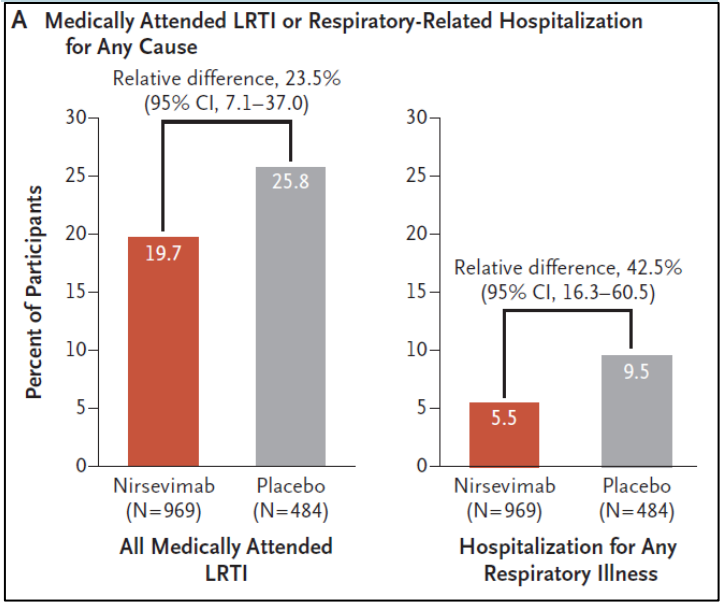
Efficacy against Medically Attended RSV LRTI: 70.1% (95% CI:52% – 81%)



Efficacy against RSV LRTI Hospitalization: 78.4% (95% CI:52% – 90%)



- 23% reduction in **ALL** medically attended LRTI for 150d
- 42.5% reduction in hospitalization for ANY respiratory illness for 150d



Griffin et al, *NEJM*, 2020, 383, 415 – 425. DOI: 10.1056/NEJMoa1913556

PFIZER MATERNAL RSV VACCINE PHASE 2B DATA

- Phase 2b trial of 406 pregnant women and their infants in four countries: favorable safety and immunogenicity profiles
- Post-hoc analysis of 508 infants enrolled in US and observed from Sept 2019 – May 2020 (n=408 with mothers who received vaccine, 103 with mothers who received placebo)

Table 2. Efficacy of Maternal Vaccination against RSV-Associated Lower Respiratory Tract Illness in the U.S. Cohort of 508 Infants.

Efficacy End Point	RSVpreF Vaccine (N = 405)	Placebo (N = 103)	Estimated Vaccine Efficacy (95% CI)
	number of infants with event		*percent*
Any medically attended RSV-associated lower respiratory tract illness*	3	5	84.7 (21.6 to 97.6)
Medically attended severe RSV-associated lower respiratory tract illness†	1	3‡	91.5 (–5.6 to 99.8)

Simoes et al, *NEJM*, April 28, 2022.

RSVpreF Highly Efficacious Against Severe Infant MA-LRTI in Phase 3 IA

Potential first maternal vaccine for common, potentially life-threatening, respiratory illness in infants

Primary Endpoint: Severe MA-LRTI

	Vaccine Efficacy
First 90 days of life	**81.8%** (CI: 40.6%, 96.3%)
Six-month follow-up	**69.4%** (CI: 44.3%, 84.1%)

Primary Endpoint: MA-LRTI

	Vaccine Efficacy
First 90 days of life	**57.1%** (CI: 14.7%, 79.8%)
Six-month follow-up	**51.3%** (CI: 29.4%, 66.8%)

Interim analysis of Phase 3 MATISSE clinical trial demonstrated high efficacy against severe MA-LRTI due to RSV from birth through first six months of life

DMC indicated RSVpreF investigational vaccine was well-tolerated with no safety concerns for either vaccinated individuals or their newborns

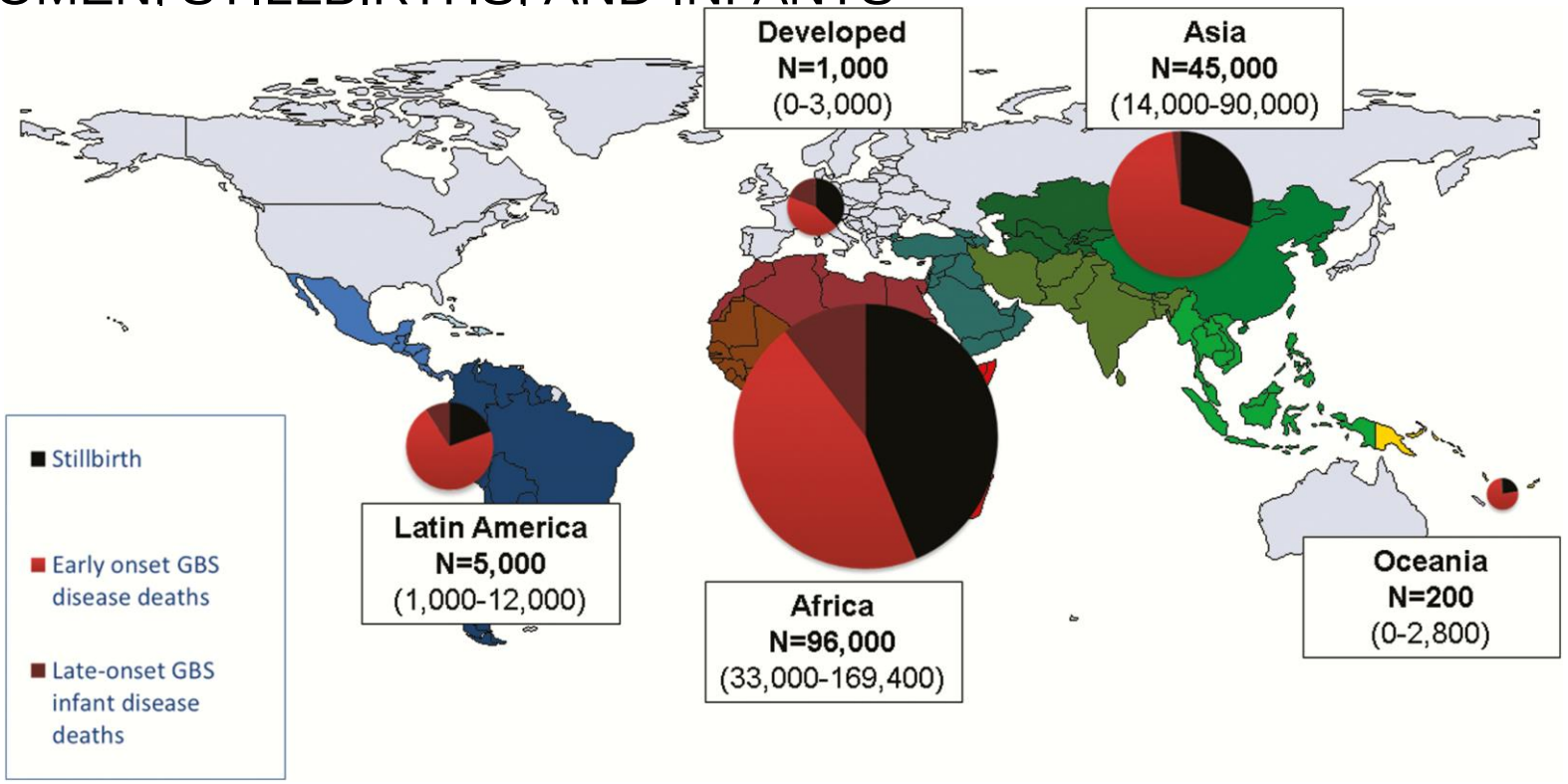
- Results met study protocol's pre-specified regulatory success criteria for severe MA-LRTI
- Success criterion was not met for MA-LRTI endpoint, however clinically meaningful efficacy was observed
- BLA submission to U.S. FDA planned by end of 2022, additional regulatory authorities in coming months

*RSV = Respiratory Syncytial Virus; IA: Interim Analysis; MATISSE: **MAT**ernal **I**mmunization **S**tudy for **S**afety and **E**fficacy; MA-LRTI: Medically Attended Lower Respiratory Tract Illness; CI: Confidence Interval; DMC: Data Monitoring Committee; BLA: Biologics License Application; FDA: Food and Drug Administration*

PROMISE OF RSV VACCINATION USING mRNA BEING PURSUED ACTIVELY BY OUR PNEUMONIA TEAM AT THE GATES FOUNDATION

- The Novavax RSV vaccine trial showed proof of principle that maternal immunization could safely deliver neutralizing Ab to protect newborns from RSV
- Pfizer is testing next generation prefusion stabilized F protein vaccines in pregnant women that induce several fold higher titers of neutralizing Ab
- mRNA vaccines containing prefusion stabilized S protein of SARS-Cov-2 have been de-risked by administration to millions of pregnant women
- Similar mRNA vaccines encoding prefusion stabilized F protein are a logical next step for development and the high levels of neutralizing Ab hopefully induced in infants >6 months of age naïve to SARS-CoV-2 could hopefully lead the way to RSV mRNA studies in similarly aged infants

DEATHS FROM GROUP B STREPTOCOCCUS IN PREGNANT WOMEN, STILLBIRTHS, AND INFANTS



DEATHS: 90,000 infants (mostly neonatal); 57,000 stillbirths

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

KLEBSIELLA PNEUMONIAE MATERNAL IMMUNIZATION STRATEGY

Klebsiella pneumoniae is the leading etiology of neonatal sepsis and deaths after the first 24 hours of life

CHAMPS: *Klebsiella pneumoniae* Testing and Death Summary by Age

Age Group	Tested	K. pneumoniae TAC positive*	K. pneumoniae in causal chain
Stillbirth (n=1159)	1098	122 (11%)	7 (0.6%)
Death within first 24 hours (n=540)	539	88 (16%)	28 (5%)
Early neonate (24 to <72hr) (n=329)	329	106 (32%)	51 (16%)
Early neonate (72hr to 6d) (n=201)	200	97 (49%)	71 (36%)
Late Neonate (7 to 27 days) (n=240)	239	132 (55%)	89 (37%)
Infant (28 days to less than 6 months) (n=281)	280	152 (54%)	100 (36%)
Infant (6 months to less than 12 months) (n=161)	161	96 (60%)	31 (19%)
Child (12-59 months) (n=407)	404	201 (50%)	88 (22%)
TOTAL n=3318 (%)	3250	994 (31%)	465 (14%)

* Positive in blood, CSF and/or lung

- In CHAMPS platform ***K. pneumoniae* is in the causal chain of 37% of all neonatal deaths occurring on days 3-28 of life[1].**
- *K. pneumoniae* is **the leading etiology of neonatal sepsis** in GARDP's 11-country neonatal sepsis cohort study and was **independently associated with increased mortality**[2].

Prevention of *K. pneumoniae* neonatal sepsis: potential for a maternal conjugate vaccine approach

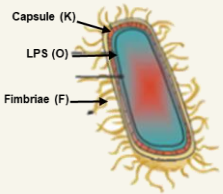
Lipopolysaccharide (LPS) O-antigens and capsular K antigens are potential targets for conjugate vaccines

K (capsular) antigens

- 77 defined serotypes but >140 K loci defined on the basis of gene content
- Preliminary analysis[3] estimate that the most common 20 K loci among neonatal sepsis isolates (adjusting for local clonal expansions) account for >70% of population

O (LPS) antigens:

- There are fewer (8) distinct O loci
- Preliminary analysis[3] estimate the top 5 O loci account for >95% of the adjusted population.



Considering a high valency O-Ag + K-Ag conjugate vaccine approach

- 15-20-valent conjugate vaccine which covers 60-70% of K-types, and majority of O-types

Current *Klebsiella pneumoniae* vaccine development priorities

- More complete characterization of genomic and sero-epidemiology of *K. pneumoniae* neonatal sepsis
- Development of *K. pneumoniae* neonatal sepsis animal maternal immunization model
- Development of OPK assay for K & O antigens

Sources: [1]CHAMPS data as of 1 April 2022; [2]GARDP's Neonatal observational cohort (unpublished); [3]Ongoing unpublished analysis by Kat Holt and Kelly Wyres

SUMMARY

- Deaths are declining in children, but pneumonia remains a major killer
- Pneumococcal conjugate vaccine has rolled out in many developing countries where it is reducing mortality and increasing equity, but residual disease remains.
- Next generation 20+ PCV's may address that burden
- More than 45% of childhood deaths occur in neonates, and neonatal mortality has reduced to a lesser extent
- We have recently achieved first proof of concept for a maternal immunization RSV vaccine and an infant dose of anti – RSV monoclonal Ab. mRNA for RSV prevention is very promising. Maternal immunization GBS vaccines are in development
- Maternal immunization has the potential to reduce neonatal mortality due to AMR Klebsiella through the development of a conjugate *Klebsiella pneumoniae* vaccine

THE 2ND GLOBAL FORUM ON CHILDHOOD PNEUMONIA

Building a world where every child survives and thrives

April 26-27, 2023

CaixaForum Madrid, Spain

- The 2nd Global Forum on Childhood Pneumonia will **build on the momentum for action** generated by the first Global Forum in Barcelona in 2020 and focus **political attention on the government actions needed to reduce child pneumonia deaths**.
- The two-day event will serve as a platform for new and ambitious political **commitments to accelerate introduction and scale up of lifesaving interventions** including full coverage of pneumonia-fighting vaccines, nutrition, and rapid access to diagnosis and treatment as part of strong primary health care systems.


THE WORK IS
COMPLICATED.
WHY WE DO IT IS NOT.