Maternal Immunisation: Progress & challenges

ICAVT ARVAC

June 2024

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African Leadership in Vaccinology Expertise,

University of the Witwatersrand (Wits-Alive)

Overview

- Why Immunize pregnant women?
- Recommended vaccines
  - Tetanus, Pertussis, Influenza, COVID-19
- New vaccines & Vaccines in development
  - Group B streptococcus, Respiratory syncytial virus

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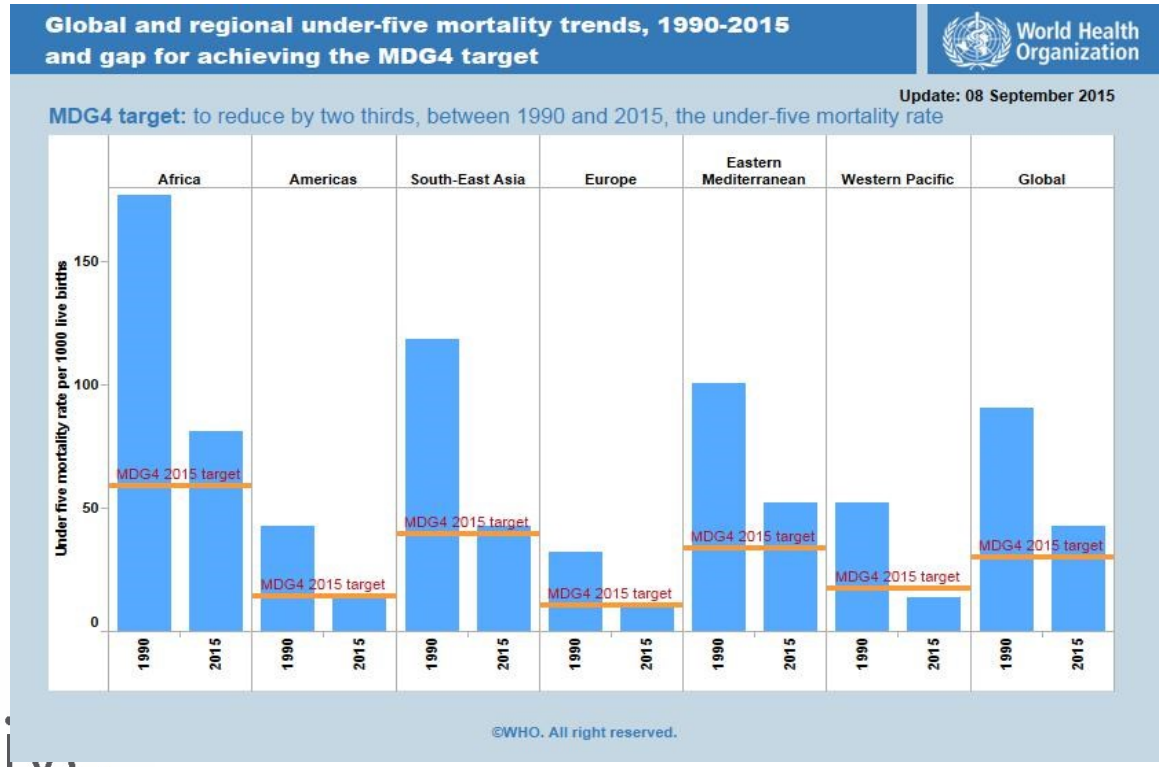
Why immunize pregnant women?

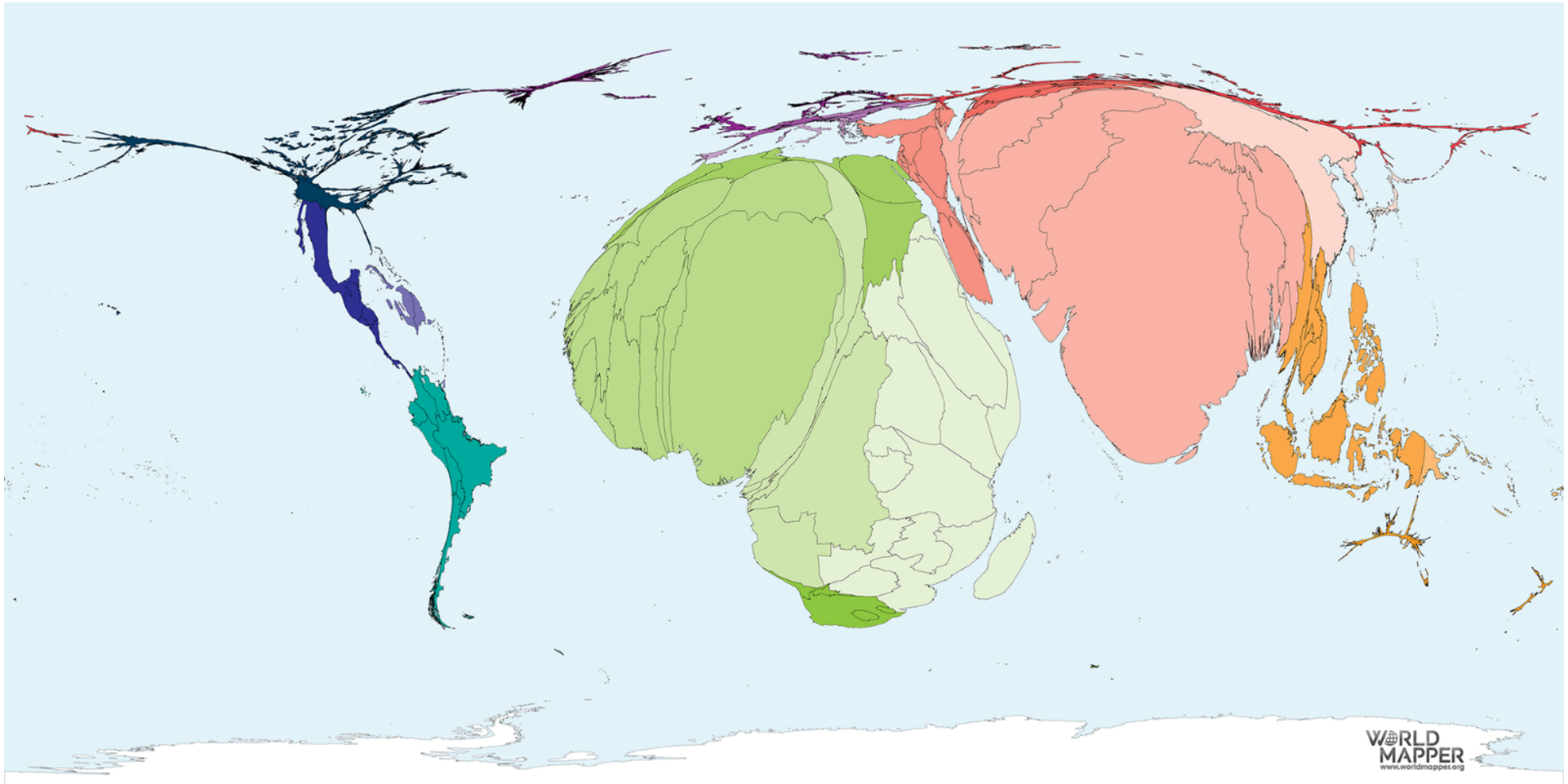
Global and Regional Under-five Mortality Trends (1990 – 2015)

12.7 million in 1990: 34 000 per day

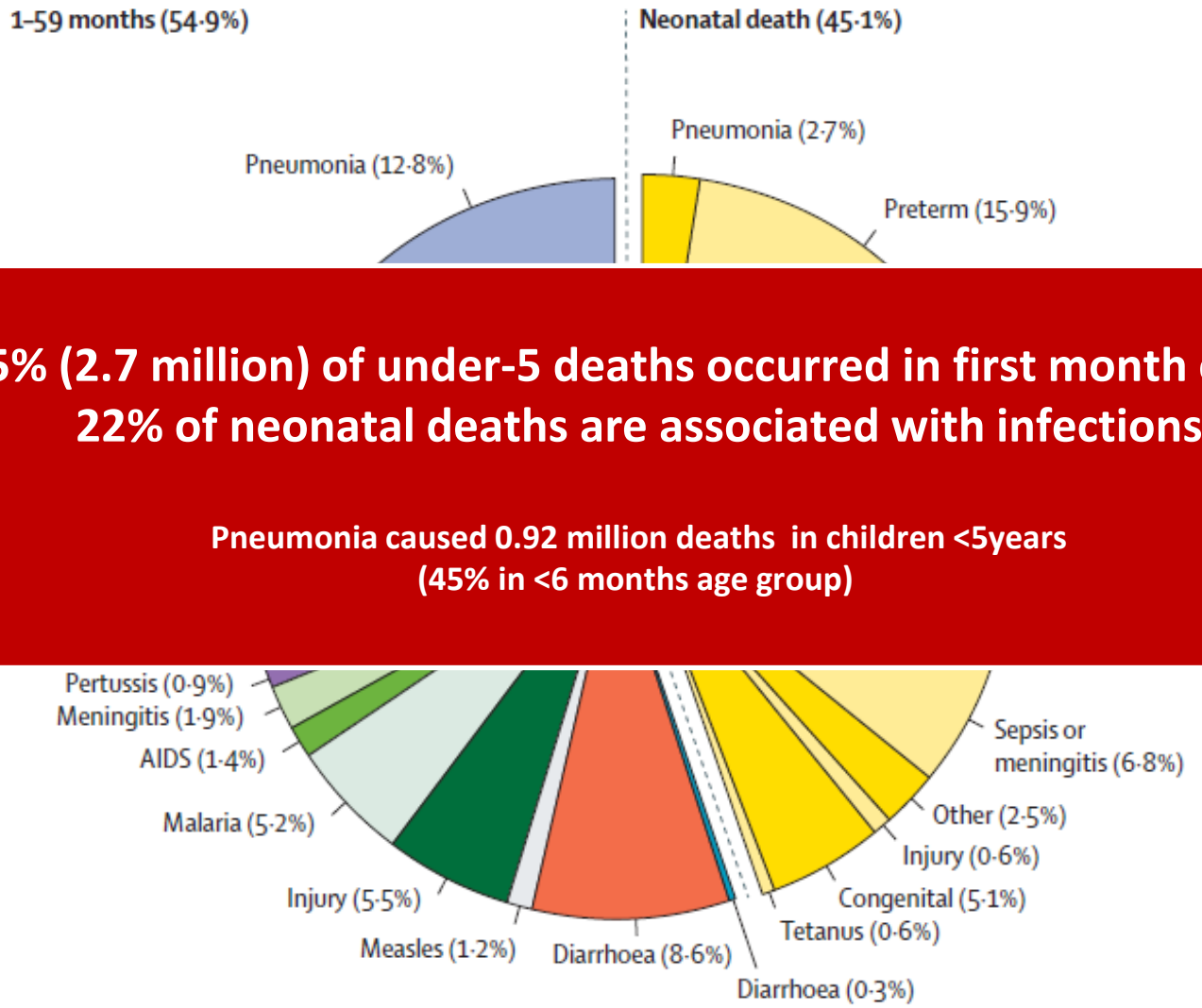
5.5 million in 2017: 15 000 per day



Where do children die? 2015



Causes of Deaths Among Children Under-5 (2015)



45% (2.7 million) of under-5 deaths occurred in first month of life
22% of neonatal deaths are associated with infections

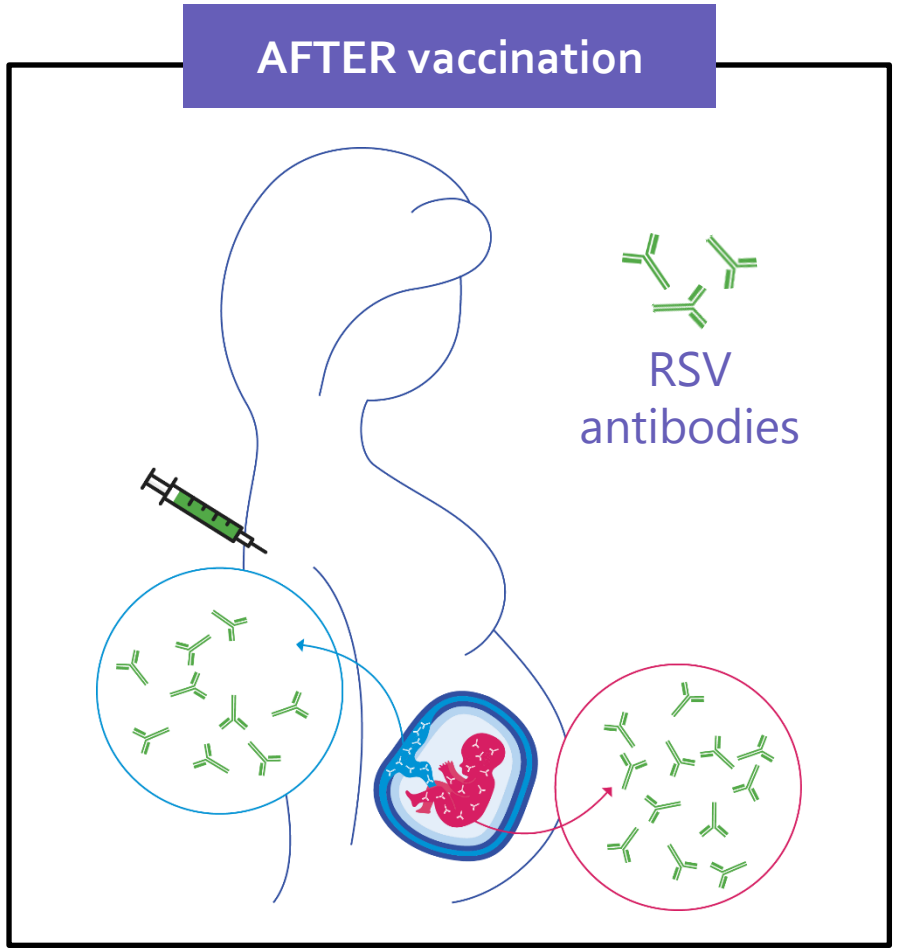
Pneumonia caused 0.92 million deaths in children <5years
(45% in <6 months age group)

Liu L, *et al. Lancet* 2016

What is a maternal vaccine?

Maternal vaccines are:

- given in pregnancy to help protect mother, baby, or both from serious infections.
- **active immunization for the mother.**
- **passive immunization for the baby** because the mother's antibodies naturally transfer across the placenta to provide protection at birth and for months thereafter.



Why are maternal vaccines needed?

- Serious infections can occur when babies are very young and their immune systems are too immature to mount an adequate immune response of their own.

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REQUIREMENTS FOR AN EFFECTIVE MATERNAL VACCINE

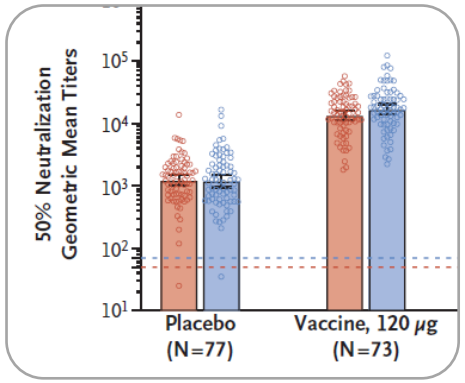
Maternal adverse event or death

Miscarriage or Stillbirth

Safety

Congenital abnormalities

Preterm birth

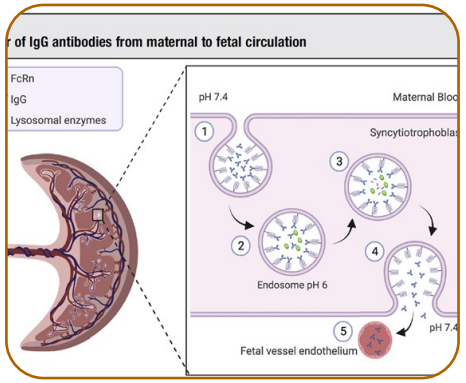


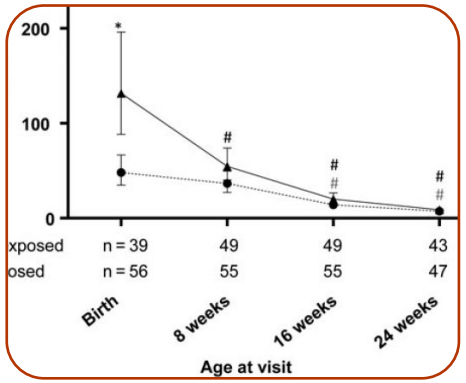
Immunogenicity

Increased and functional (protective) levels of IgG

Efficient transfer

(IgG subtype, gestational period, HIV)





Duration of protection

Seasonal timing, half life of IgG, non-interference with other vaccines

What are monoclonal antibodies (mAbs) ?

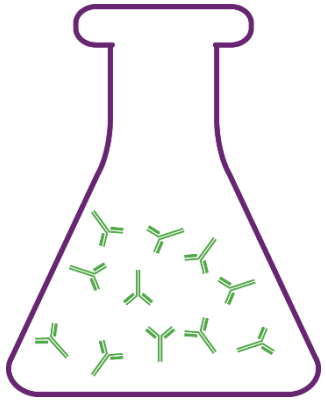
mAbs are:

- manufactured antibodies given at birth or soon thereafter that can kill a virus or other pathogen
- Protect immediately and don't require infants to produce their own antibodies
- similar to other birth dose vaccines (e.g., hepatitis B, BCG)

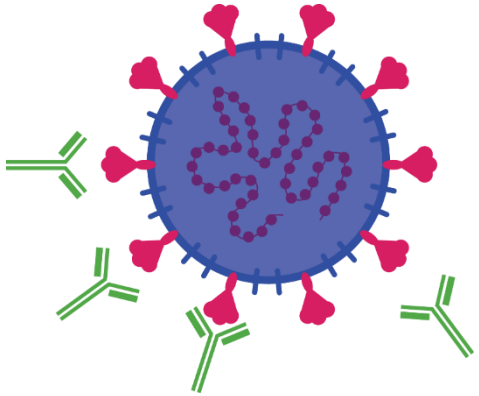
Why are mAbs needed?

- They provide protection when a newborn's immune system is still too immature to respond to vaccines.
- They avoid the need for infants to produce their own antibodies.

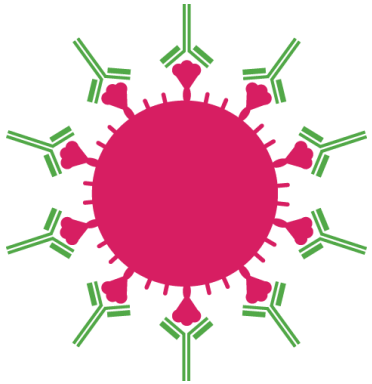
mAbs mimic human antibodies but are created in labs and tailored to a specific condition



Like human antibodies, mAbs attach to harmful pathogens and antigens, alerting the immune system to a threat



This immune response helps to neutralize the threat and overcome illness



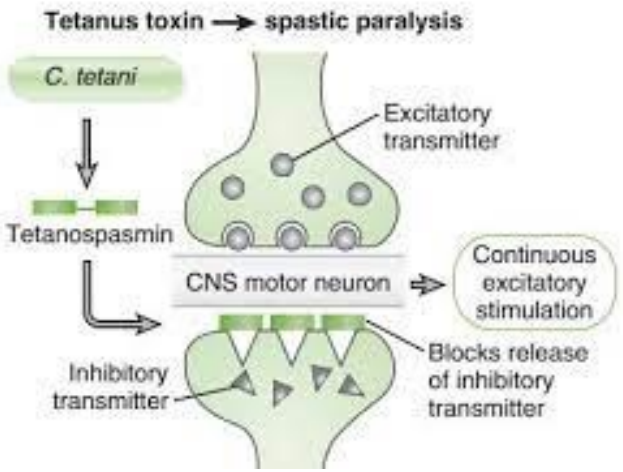
Recommended vaccines for pregnant women

Tetanus

- ***Clostridium tetani (C. tetani)***
  - Gram + bacilli
  - Ubiquitous in the environment
  - *C. tetani* forms spores which produce tetanospasm (toxin)

- **Tetanospasm moves to nervous tissue**
  - Blocks release of inhibitory transmitter in motor neuron
  - Continuous stimulation of muscles, causing increased muscle tone and painful spasms
  - Cannot be neutralised once bound to nerve

- ***Generalised tetanus***
  - *Trismus, risus sardonicus, opisthotonis*
- ***Cephalic tetanus***
  - *12 cranial nerves*
- ***Neonatal tetanus***
  - *Newborns, exposure through umbilical stump*
- ***Localised tetanus***



Prevention of Neonatal Tetanus

- 1980s: WHO estimated that >800 000 neonatal deaths every year (6.7 deaths per 1000 livebirths) were attributable to MNT.[1]

- In the early 1990s it was estimated that maternal tetanus accounted ≈5% of maternal mortality (15 000–30 000 deaths/year).

- In 1989 World Health Assembly adopted a resolution to eliminate MNT by 1995… 2000… 2015 through the increased availability of Tetanus toxoid TT vaccination , clean deliveries, and improved surveillance.

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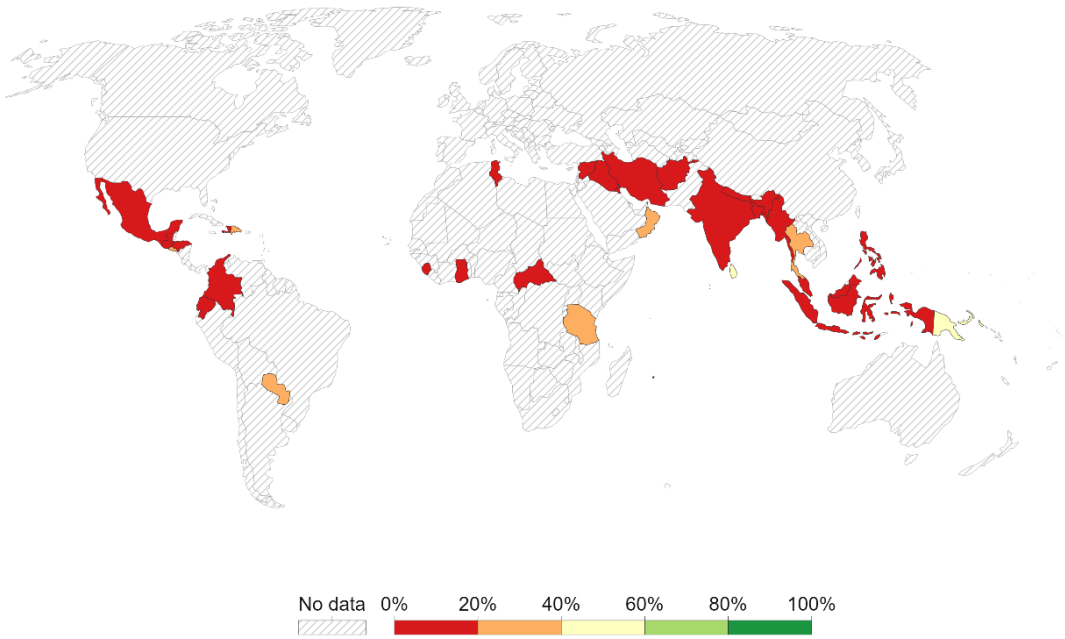
[1] WHO. Wkly Epidemiol Rec 1993; 68: 277–82.

TT coverage in antenatal care: 1980 vs 2020

The percentage of neonates protected at birth against neonatal tetanus, 1980



Source: WHO, Global Health Observatory (2022)

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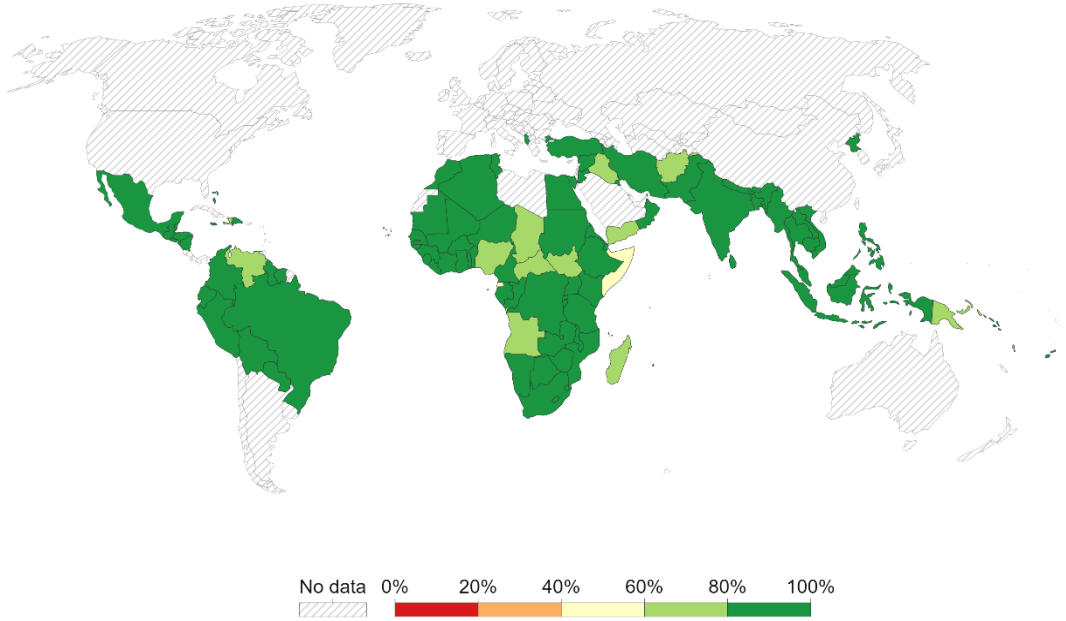
The percentage of neonates protected at birth against neonatal tetanus, 2020



Source: WHO, Global Health Observatory (2022)

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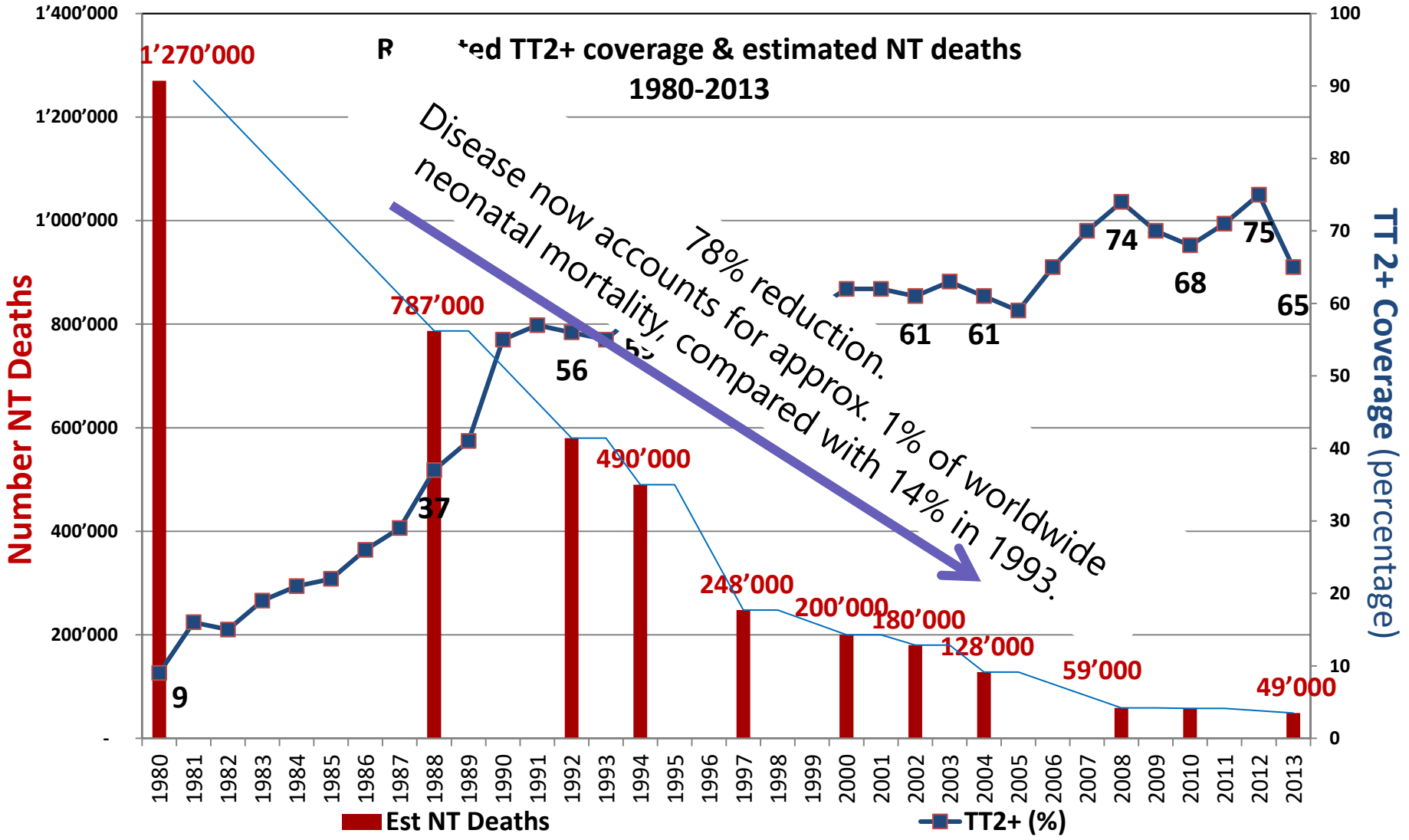
https://ourworldindata.org/tetanus#elimination-of-maternal-and-neonatal-tetanus

Neonatal Tetanus Global Annual Reported Cases and TT2plus coverage, 1980-2013



WHO-UNICEF Data & CHERG Reports

Maternal tetanus vaccination

Dose of TTCV	When to give	Expected duration of protection
TTCV1	At 1st contact/ antenatal visit, or as early as possible in pregnancy	None
TTCV2	At least 4 weeks after TTCV1 (at the latest 2 weeks prior to birth	1-3 years
TTCV3	At least 6 months after TTCV2, or during subsequent pregnancy	At least 5 years
TTCV4	At least 1 year after TTCV3, or during subsequent pregnancy	At least 10 years
TTCV5	At least 1 year after TTCV4, or during subsequent pregnancy	For all childbearing age and much of adulthood

Adapted from "Protecting all against tetanus: guide to sustaining maternal and neonatal tetanus elimination (MNTE) and broadening tetanus protection for all populations. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO".

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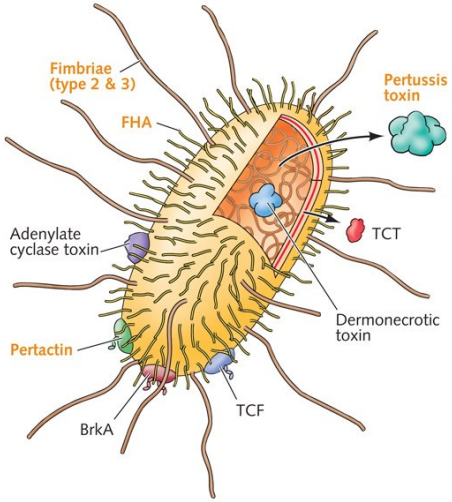
Pertussis (Whooping cough)

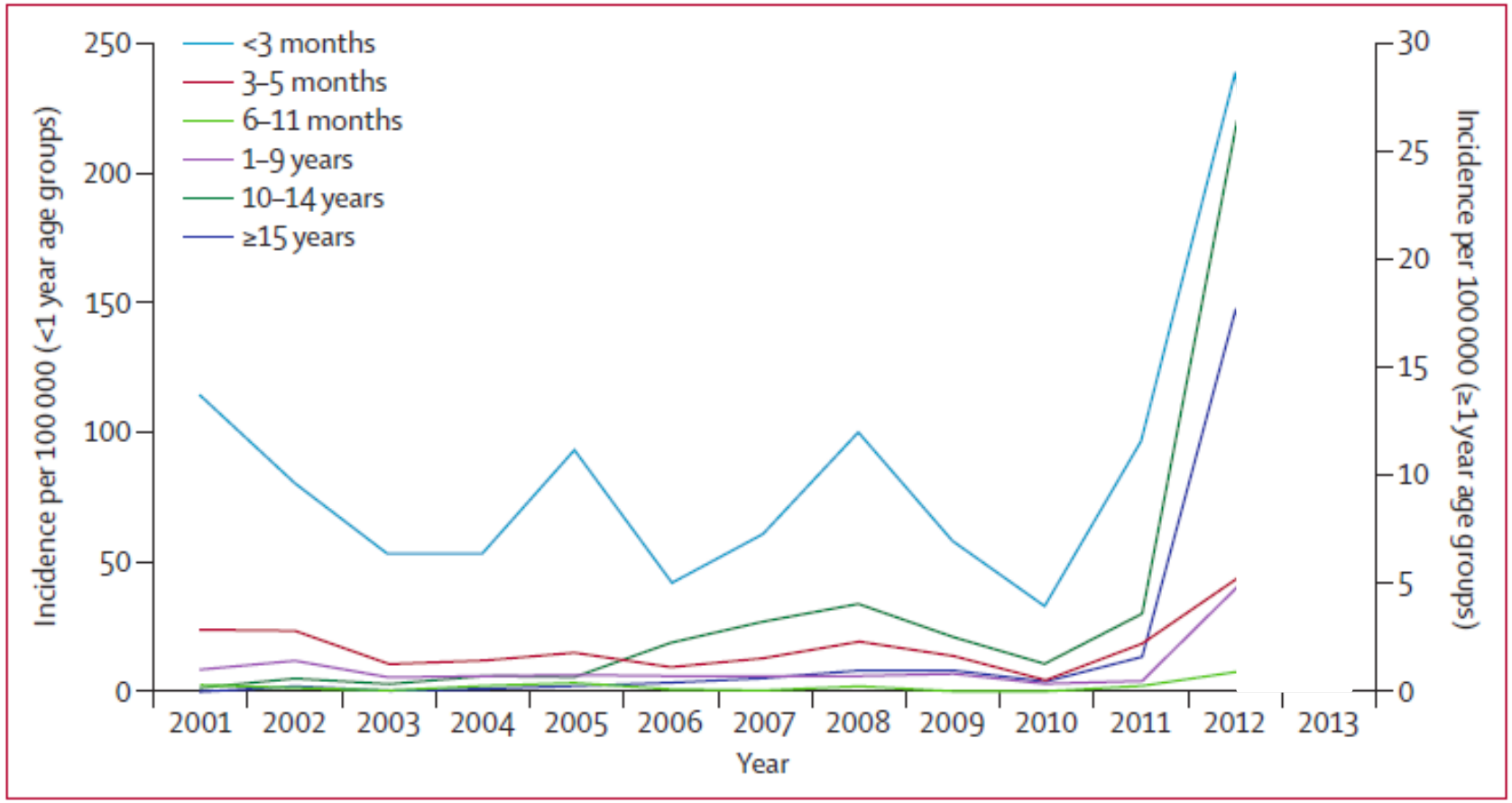
- *Bordetella pertussis,* is highly contagious, with a reproductive number of 5.5 (number of people infected per original index case)
- Affects people of all ages, but is of particular concern in young children
  - Young infants (aged <2 months) at highest risk for pertussis-associated complications and death, having the highest rates of:
    - hospitalisation (>90%), pneumonia (15–25%), seizures (2–4%), encephalopathy (0.5–1%)
    - death (0.5–1%)



- Pertussis vaccines administered in EPI at
  - 6, 10, 14 weeks (primary)
  - 18 months (booster)
- In 2009, SA switched from wP to aP vaccination in EPI
- Disease burden shifted to older children & adults

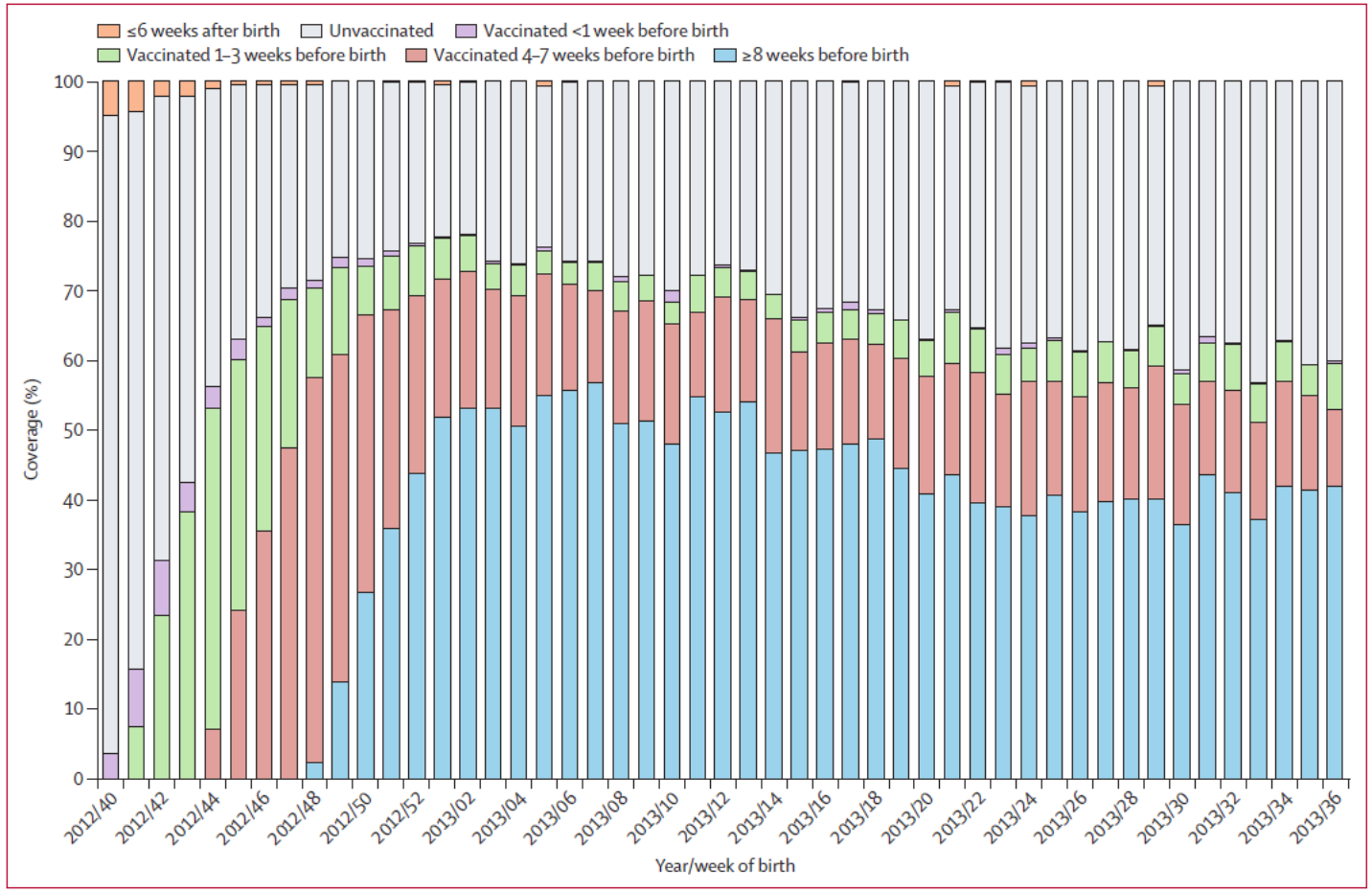
1. Kretzschmar *et al. PLoS Med* 2010;7(6):e1000291; **2.** Spokes *et al. N S W Public Health Bull* 2010;21(7–8):167–173; **3.** Grant. In: Warrell, Cox, Firth, eds. *Oxford Textbook of Medicine* 2010: Section 7.6.14; **4.** WHO. Estimates of disease burden and cost-effectiveness. 2014. www.who.int/immunization/monitoring_surveillance /burden/estimates/en/index.html Accessed 24 Jan 2014; **5.** Hong. *Korean J Pediatr* 2010;53(5):629–633; **6.** CDC. In: Atkinson, Wolfe, Hamborsky, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases* [Pink Book] 2012: 215–232; **7.** CDPH. Pertussis Report. 10 August 2011; **8.** Tan & Gerbie. *Obstet Gynecol* 2013;122 (2 Pt 1):370–373

Annual Incidence of laboratory-confirmed Cases of Pertussis by Age-group (England and Wales).



Amirthalingam G et al. Lancet; 16 July 2014

Estimated Maternal Vaccine Coverage by Week of Birth (England and Wales)- 2012-2013



Amirthalingam G et al. Lancet; 16 July 2014 (on line)

Annual Incidence of laboratory-confirmed Cases of Pertussis by Age-group (England and Wales).

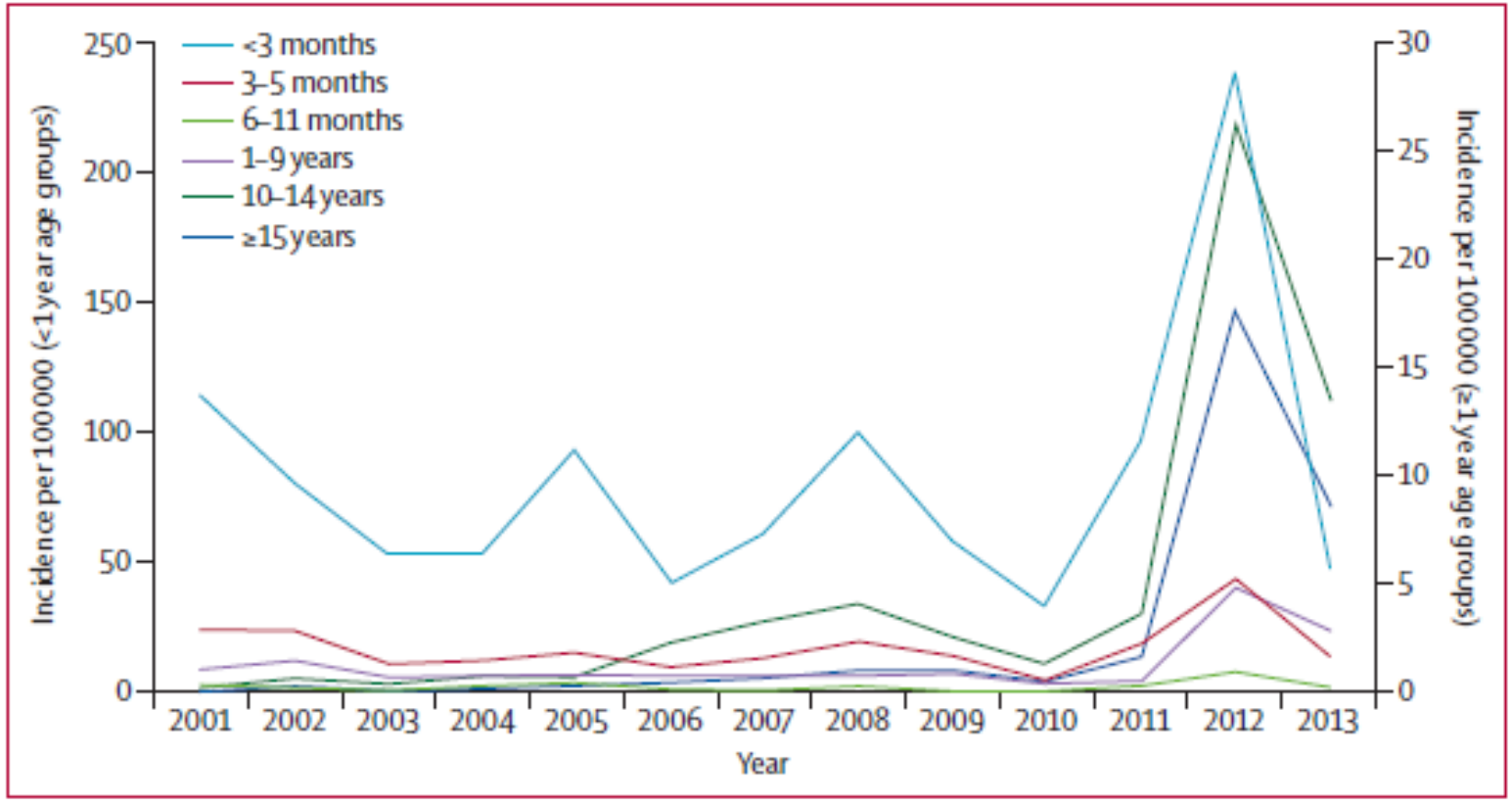


Figure 2: **Annual incidence of laboratory-confirmed cases of pertussis by age group**
Figure shows incidence from 2001 to 2013 in England only.

Amirthalingam G et al. Lancet; 16 July 2014 (on line)

Maternal pertussis vaccination

- Recommended by WHO since 2015
- Recommended by CDC since 2012
- Recommended by SASOG since 2020

In 2024:

- Ongoing clinical and laboratory based surveillance for pertussis infection.
- Tdap introduced into antenatal care in all public health care facilities

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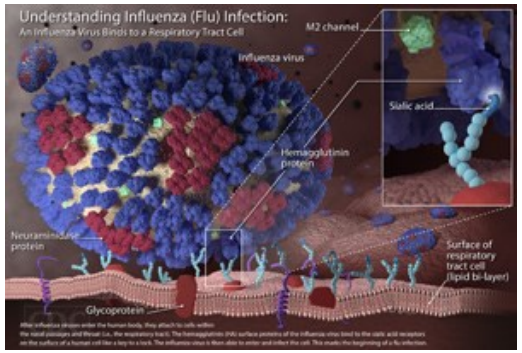
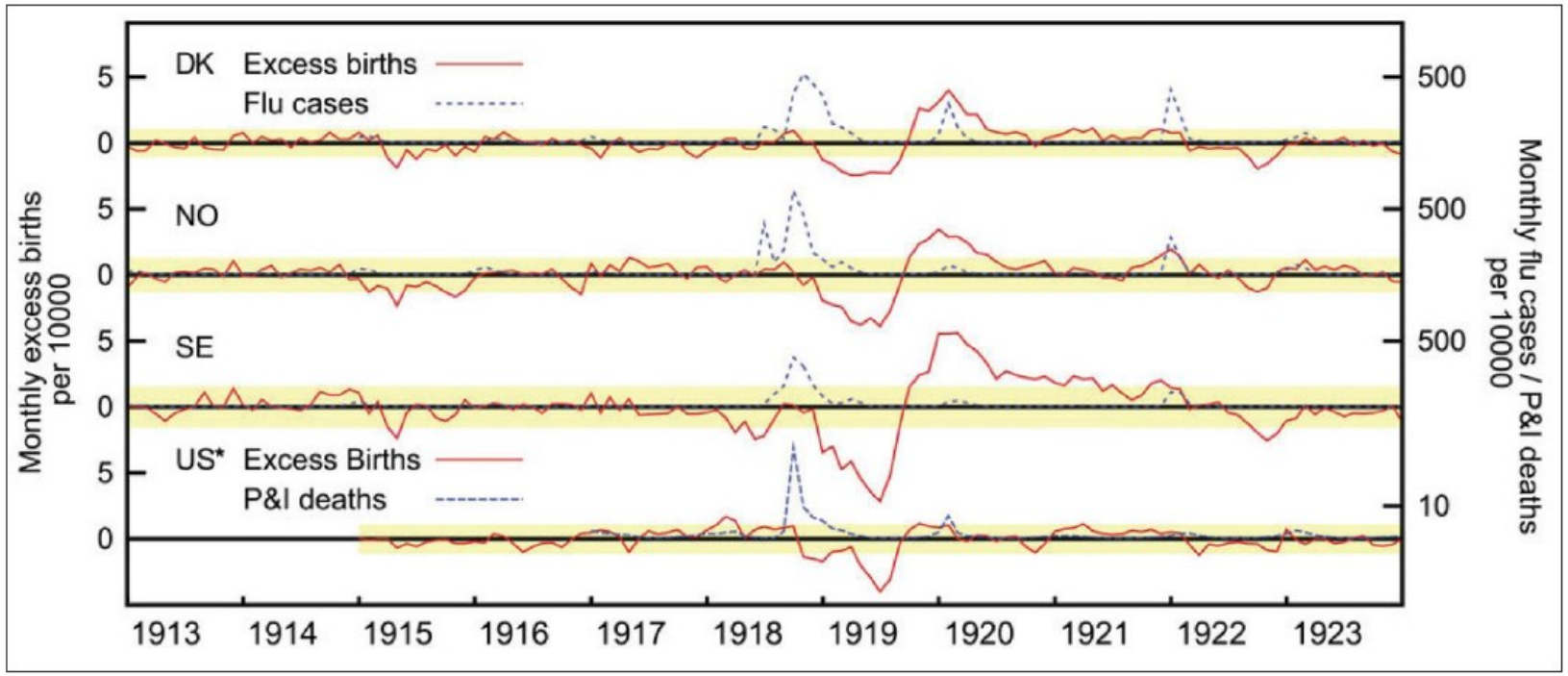
Influenza Virus



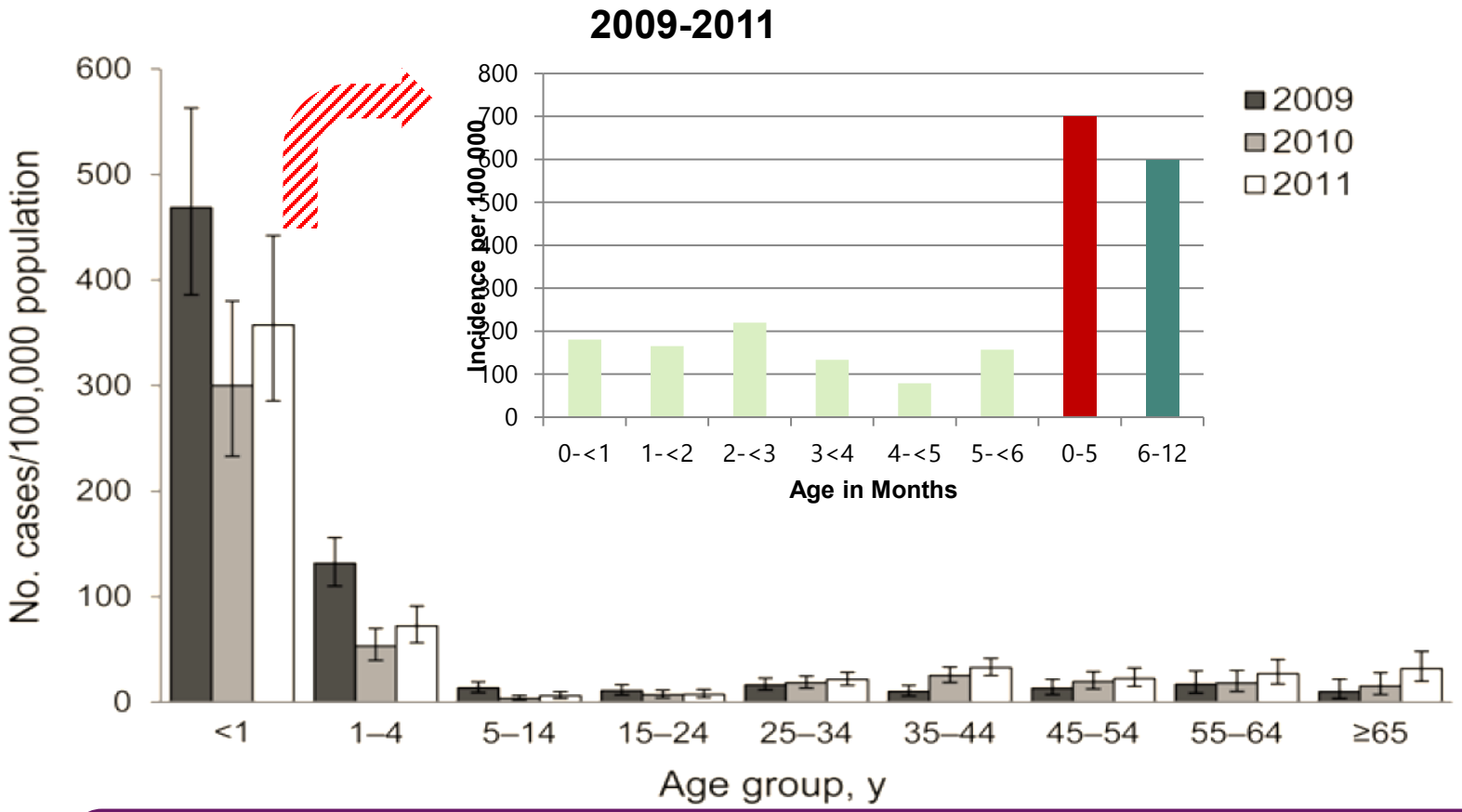


The observed birth depressions were consistent with pandemic influenza causing first trimester miscarriages in 1 in 10 pregnant women

Fetal Outcomes of the 1918 Influenza Pandemic

Bloom-Fesbach K et al. J Infect Dis 2011; 204:1157-64

Incidence of laboratory-confirmed influenza associated hospitalization in Soweto, South Africa



Pregnant women greatest adult risk group for severe influenza illness. HIV-infected adults have 4-8 fold greater risk for influenza hospitalization and 4-fold greater incidence of influenza death

Cohen C/Madhi SA et al. Emerg Infect Dis; 2013; 19; 1766-1774

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Clinical trials assessing the efficacy of maternal influenza vaccination in preventing influenza illness

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effectiveness of Maternal Influenza Immunization in Mothers and Infants

K. Zaman, M.B., B.S., Ph.D., Eliza Roy, M.B., B.S., D.C.H., Shams E. Arifeen, M.B., B.S., Dr.P.H., Mahbubur Rahman, M.B., B.S., Ph.D., Rubhana Raqib, Ph.D., Emily Wilson, M.H.S., Saad B. Omer, M.B., B.S., Ph.D., Nigar S. Shahid, M.B., B.S., M.P.H., Robert F. Breiman, M.D., and Mark C. Steinhoff, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Influenza Vaccination of Pregnant Women and Protection of Their Infants

Shabir A. Madhi, M.D., Ph.D., Clare L. Cutland, M.D., Locadiah Kuwanda, M.Sc., Adriana Weinberg, M.D., Andrea Hugo, M.D., Stephanie Jones, M.D., Peter V. Adrian, Ph.D., Nadia van Niekerk, B.Tech., Florette Treurnicht, Ph.D., Justin R. Ortiz, M.D., Marietjie Venter, Ph.D., Avy Violari, M.D., Kathleen M. Neuzil, M.D., Eric A.F. Simões, M.D., Keith P. Klugman, M.D., Ph.D., and Marta C. Nunes, Ph.D., for the Maternal Flu Trial (Matflu) Team*

N Engl J Med 2014;371:918-31.
DOI: 10.1056/NEJMoa1401480

Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial

Milagritos D Tapia, Samba O Sow, Boubou Tamboura, Ibrahima Téguété, Marcela F Pasetti, Mamoudou Kodio, Uma Onwuchekwa, Sharon M Tennant, William C Blackwelder, Flanon Coulibaly, Awa Traoré, Adama Mamby Keita, Fadima Cheick Haidara, Fatoumata Diallo, Moussa Doumbia, Doh Sanogo, Ellen DeMatt, Nicholas H Schluterman, Andrea Buchwald, Karen L Kotloff, Wilbur H Chen, Evan W Orenstein, Lauren A V Orenstein, Julie Villanueva, Joseph Bresee, John Treanor, Myron M Levine

Summary

Background Despite the heightened risk of serious influenza during infancy, vaccination is not recommended in infants younger than 6 months. We aimed to assess the safety, immunogenicity, and efficacy of maternal immunisation with trivalent inactivated influenza vaccine for protection of infants against a first episode of laboratory-confirmed influenza

Lancet Infect Dis 2016
Published Online
May 31, 2016

Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial

Mark C Steinhoff, Joanne Katz, Janet A Englund, Subarna K Khatry, Laxman Shrestha, Jane Kuypers, Laveta Stewart, Luke C Mullany, Helen Y Chu, Steven C LeClerq, Naoko Kozuki, Monica McNeal, Adriana M Reedy, James M Tielsch

Summary

Background Influenza immunisation during pregnancy is recommended but not widely implemented in some low-income regions. We assessed the safety and efficacy in mothers and infants of year-round maternal influenza immunisation in Nepal, where influenza viruses circulate throughout the year.

Lancet Infect Dis 2017
Published Online
May 15, 2017

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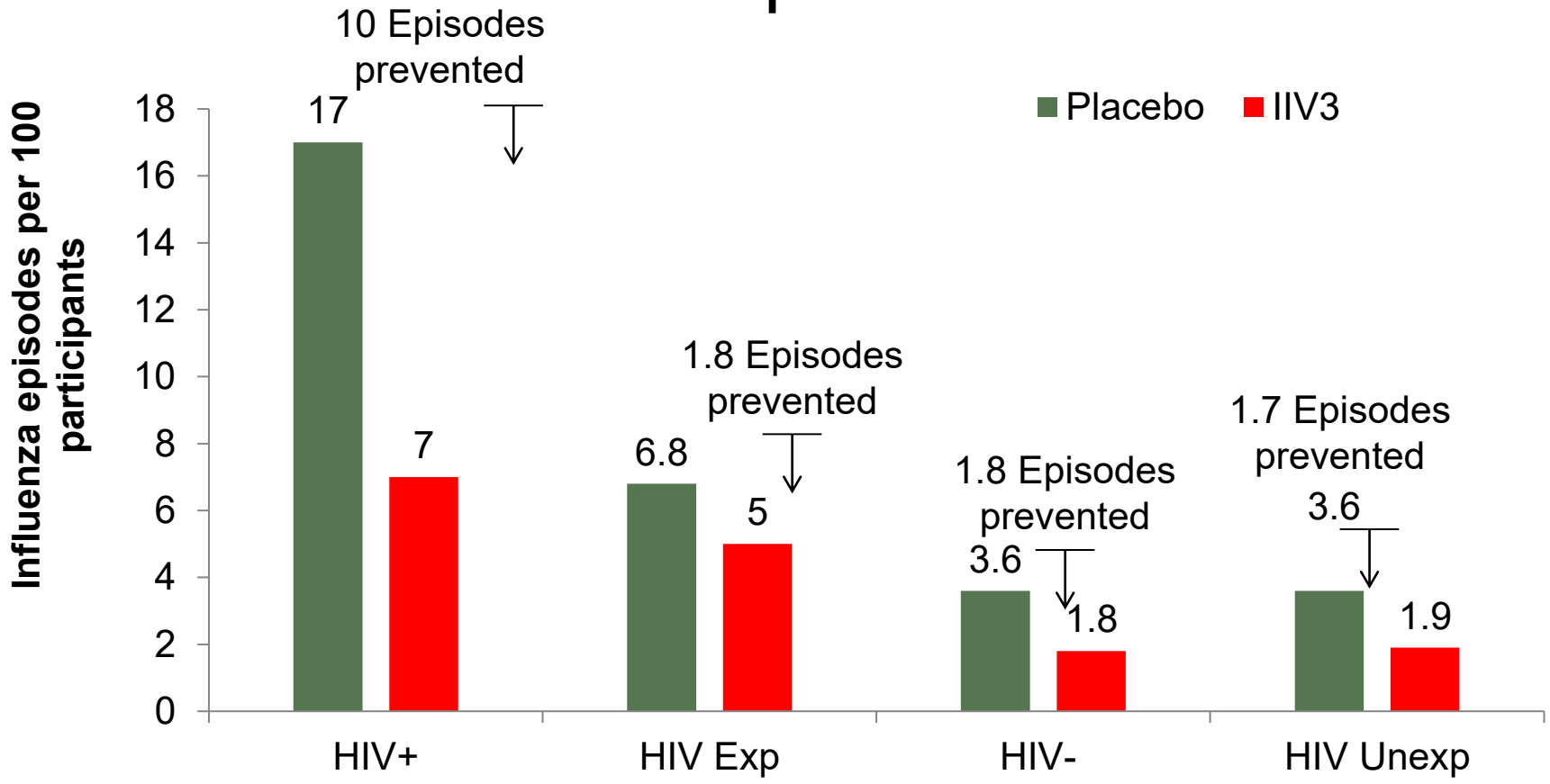
IIV3 efficacy and influenza episodes prevented per 100 persons



	mothers	infants	mothers	infants
Efficacy	**57.7%**	**26.7%**	**50.4%**	**48.8%**
	(0.2, 82.1)	(-132.0, 76.8)	(14.5, 71.2)	(11.6, 70.4)

Madhi SA et al NEJM; 2014; 371: 918-31

WHO recommends seasonal influenza vaccination for

- Highest priority:
  - Pregnant women
- Priority (in no particular order):
  - Children aged 6-59 months
  - Elderly
  - Individuals with specific chronic medical conditions
  - Health-care workers

http://www.who.int/influenza/vaccines/use/en/
Nov2015

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COVID-19 vaccines

- ❑Pregnant & postpartum women & their infants are at high risk of severe COVID-19-related outcomes
- ❑COVID-19 vaccines safe
- ❑COVID-19 vaccines protect against adverse outcomes in maternal-foetal-newborns

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Smith et al, AJOG, 2023;
Piekos et al Lancet Digital Health 2023

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

COVID-19 vaccines including the Comirnaty® (Pfizer) vaccine and the Janssen® (J&J) vaccine should be offered to all pregnant and breastfeeding women who are eligible to be vaccinated and who have completed 14 weeks of gestation.

Private Bag X828, PRETORIA, 0001, Civitas Building, 242 Struben Street, Pretoria

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

COVID-19 Vaccines and Pregnancy

COVID-19 vaccination is recommended for everyone aged 6 months and older, including people who are pregnant, breastfeeding, trying to get pregnant now, or might become pregnant in the future. This recommendation includes getting boosters when it is time to get one. If you have questions about getting vaccinated, talking with your healthcare professional might help, but is not required.

World Health Organization | Health Topics | Countries

Can pregnant women get vaccinated against COVID-19?

Yes, pregnant women can be vaccinated against COVID-19.

Key Recommendations

- The American College of Obstetricians and Gynecologists (ACOG) strongly recommends that pregnant individuals be vaccinated against COVID-19.
- Vaccination may occur in any trimester, and emphasis should be on vaccine receipt as and fetal health.

ACOG

Royal College of Obstetricians & Gynaecologists

Key messages

- COVID-19 vaccines are strongly recommended in pregnancy. Vaccination is the best way to protect against the known risks of COVID-19 in pregnancy for both women and babies, including admission of the woman to intensive care and premature birth of the baby.
- In the UK, all pregnant women are urged to book their latest COVID-19 booster vaccine for the autumn/winter season as they are recognised as a clinical risk group.

New vaccines and Vaccines in development

GBS = *Group B Streptococcus*

- GBS is a leading cause of meningitis and sepsis in newborn
- Early-onset disease: <7 days of life
- Late-onset disease: 7-90 days of life
- About 25% of pregnant women carry GBS in the rectum or vagina.
- GBS may come and go in people's bodies without symptoms.

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15 November 2017
Volume 65
Supplement 2

IDSA Infectious Diseases Society of America

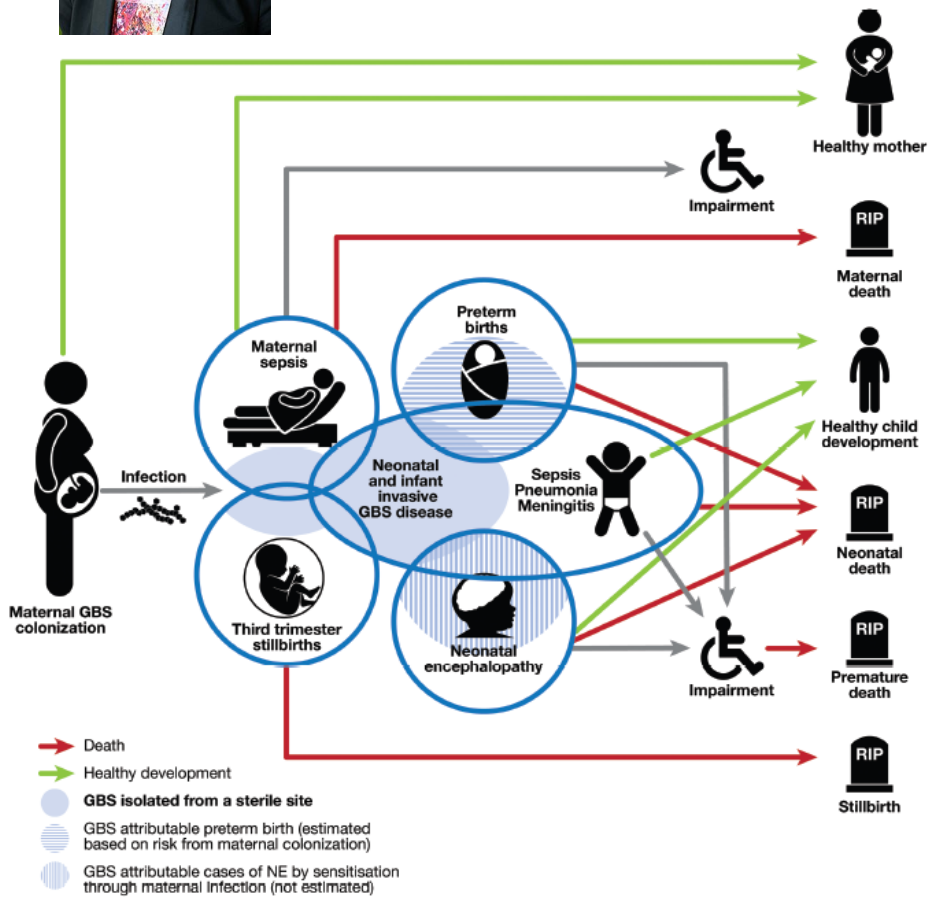
hivma hiv medicine association

Clinical Infectious Diseases

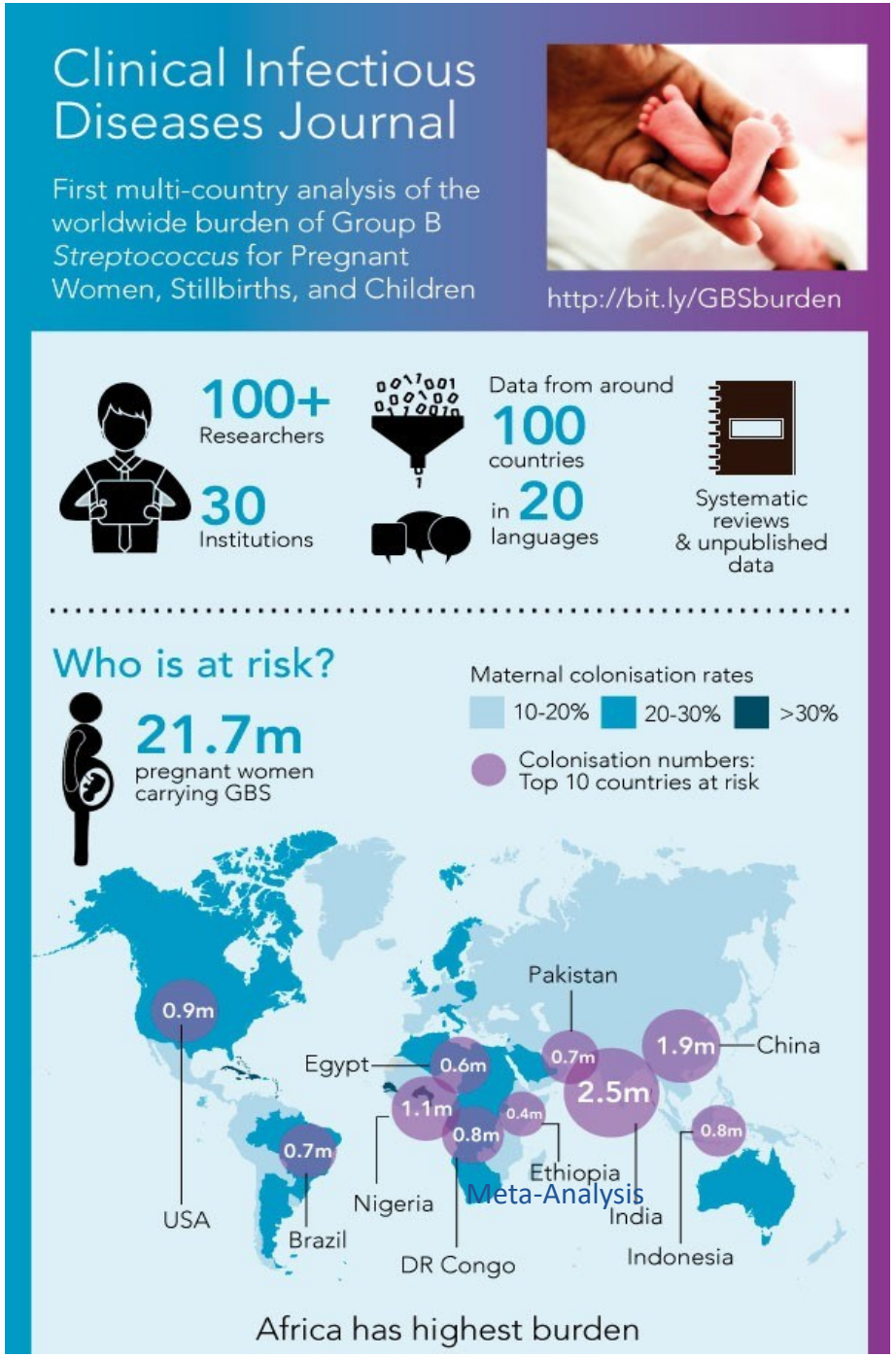
The Burden of Group B *Streptococcus* Worldwide for Pregnant Women, Stillbirths, and Children

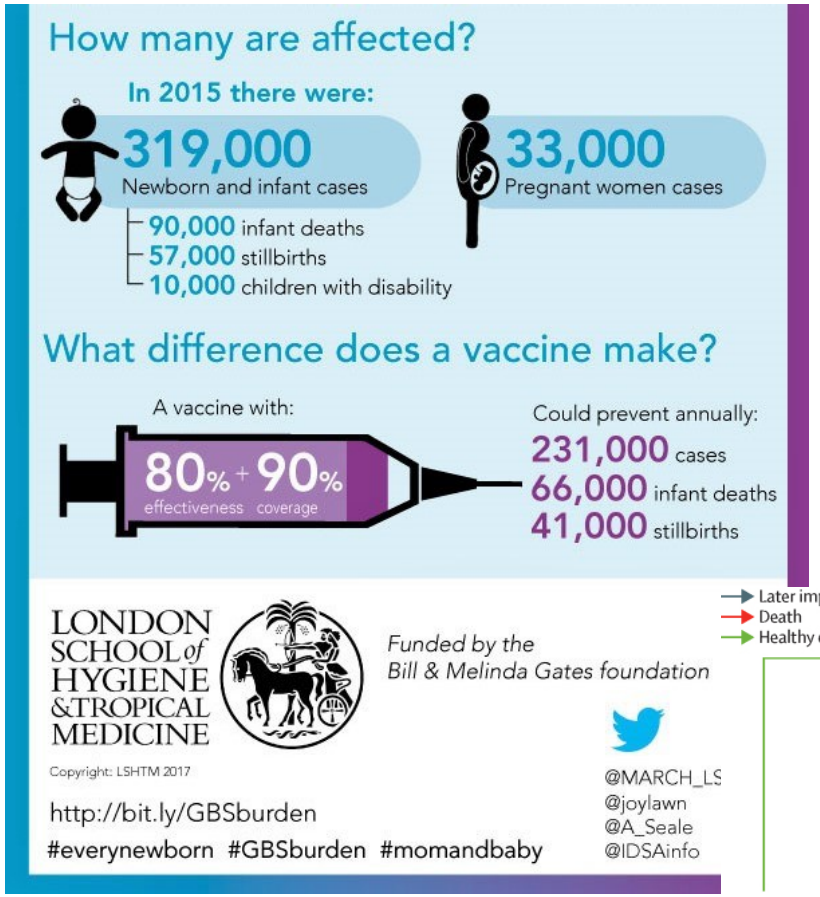
OXFORD UNIVERSITY PRESS
academic.oup.com/cid

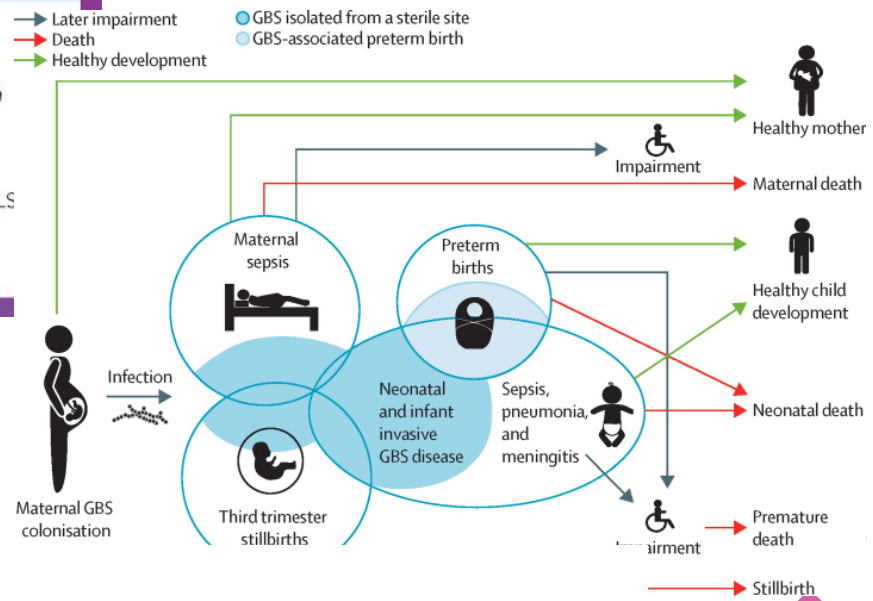
A Supplement to *Clinical Infectious Diseases*



Parameter	Case definitions used for estimates	Study
Group B *Streptococcus* maternal colonization	Isolation by culture of GBS from either the vagina (high or low), rectum or peri-anal region at any time during pregnancy	Russell et al. [40]
Maternal GBS disease	Laboratory isolation of GBS from sterile site in pregnant or postpartum woman (up to 42 days postpartum), with clinical signs of sepsis	Hall et al. [41]
Stillbirth GBS invasive disease	Birth of a fetus weighting >1000g and/or ≥28 weeks' gestation age with no signs of life and evidence of GBS invasive disease from a normally sterile site such as fetal blood, lung aspirate or cerebrospinal fluid	Seale et al. [42]
Neonatal and infant GBS invasive disease	Laboratory isolation of Streptococcus agalactiae from a normally sterile site in an infant aged 0 to 89 days with signs of clinical disease, including meningitis, sepsis or bacteremic pneumonia	Madrid et al. [44]
Neonatal encephalopathy with invasive GBS disease	Laboratory isolation of GBS from a sterile site (blood, cerebrospinal fluid analysis or on a post mortem sample) in cases of neonatal encephalopathy, hypoxic-ischaemic encephalopathy and intrapartum-related death	Tann et al. [45]
Neurodevelopment impairment in children after GBS invasive disease	Cognitive and/or motor, vision or hearing impairment in survivors of invasive infant GBS disease isolated from a normally sterile site	Kohli-Lynch et al. [46]
Preterm birth associated with GBS maternal colonization	Delivery prior to completion of 37 weeks' gestation from mother with maternal GBS colonization isolated from vaginal, cervical and/or rectal swabs	Bianchi Jassir et al. [43]





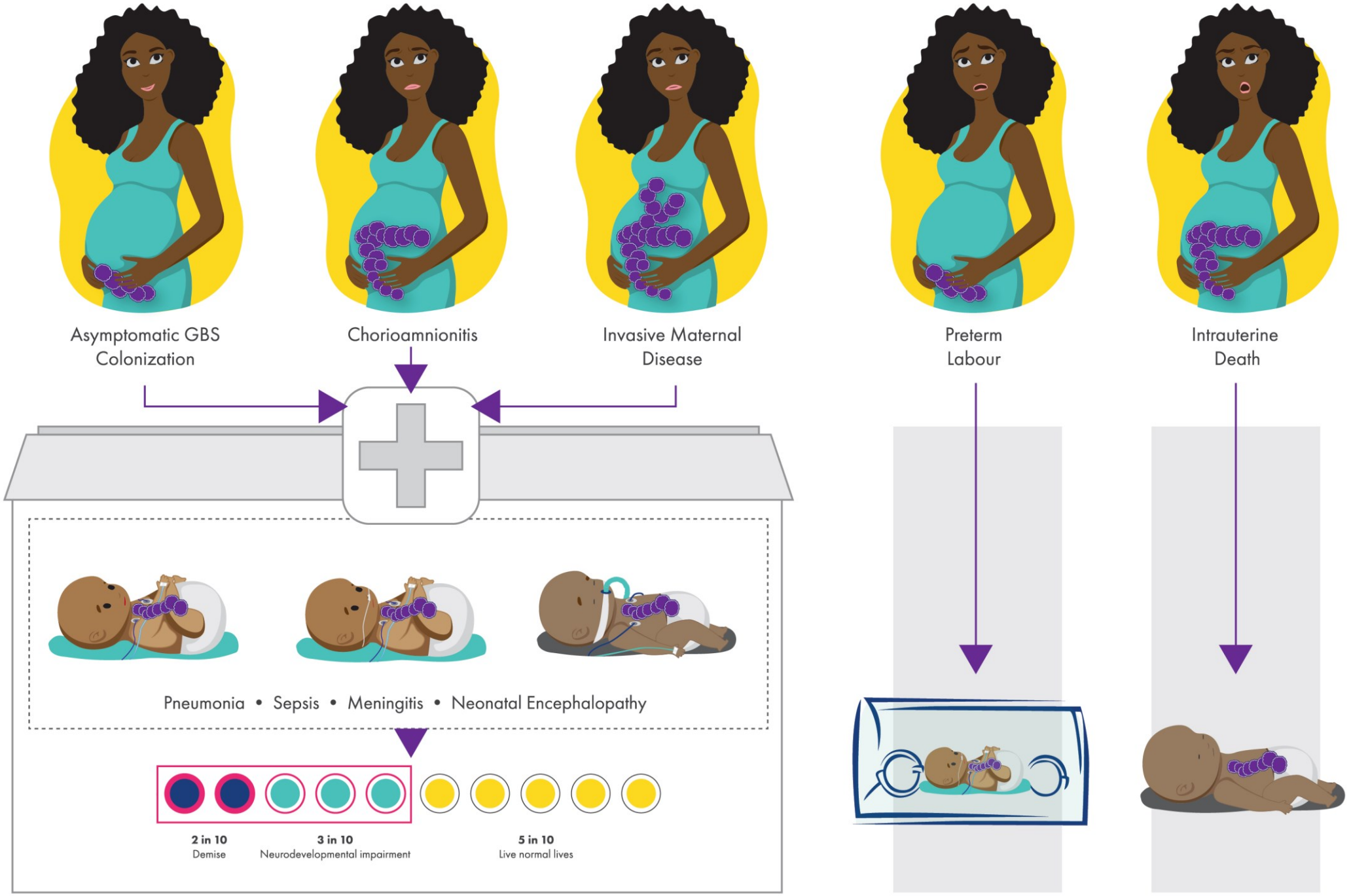


November 2017

Lancet Global Health 2022 Jun;10(6):e807-e819.
doi: 10.1016/S2214-109X(22)00093-6. Epub 2022 Apr 28.

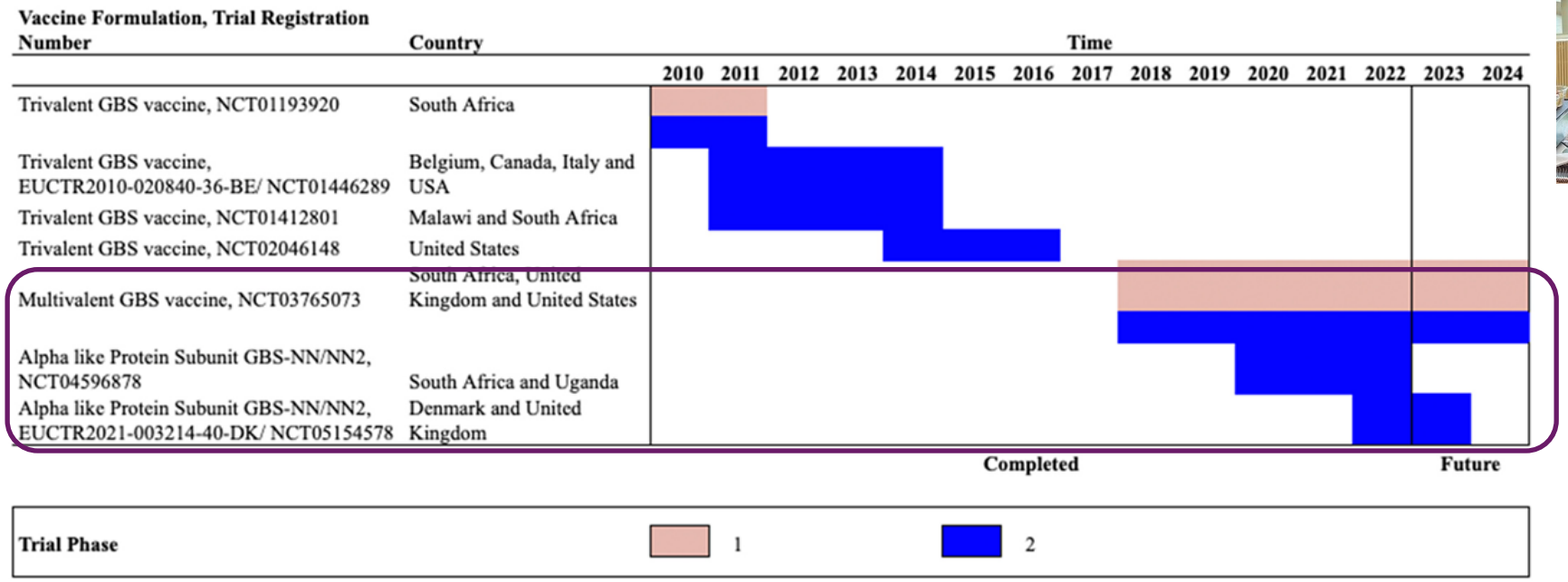
Group B streptococcus infection during pregnancy and infancy: estimates of regional and global burden

Meta-Analysis


Asymptomatic GBS Colonization
Chorioamnionitis
Invasive Maternal Disease
Preterm Labour
Intrauterine Death
Pneumonia • Sepsis • Meningitis • Neonatal Encephalopathy
2 in 10
Demise
3 in 10
Neurodevelopmental impairment
5 in 10
Live normal lives

GBS vaccine candidates

1st trial: 1978- purified type III CPS- not immunogenic



Present:

- Polysaccharide conjugate hexavalent vaccine (Pfizer)
- Protein vaccine (Minervax)

Future:

- Bi functional PEG Linker technology (Inventprise)
- Multiple antigen presenting system (Affinivax- GSK)

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Citation: Delara, M.; Vadlamudi, N.K.; Sadarangani, M. Strategies to Prevent Early and Late-Onset Group B *Streptococcal* Infection via Interventions in Pregnancy. *Pathogens* **2023**, *12*, 229. https://doi.org/10.3390/pathogens12020229

Table 2. GBS vaccine candidates in the development pathway

Vaccine candidate	Serotype target	Preclinical	Phase 1	Phase 2	Trials in Pregnant Women	Phase 3	Trial locations
Polysaccharide conjugate vaccines							
Monovalent and bivalent conjugates (TT / CRM197 CPS)	*TT monovalent:* Ia, Ib, II, III, IV[a], V, VI[a], VII[a], VIII[a] *TT bivalent:* II, III *CRM197 monovalent:* V	√	√	√	√		No longer in development
Trivalent CRM197-CPS conjugates	Ia, Ib, III	√	√	√	√		No longer in development
Pentavalent TT CPS conjugates	TBC	√	√				TBC
Hexavalent CRM197-CPS conjugates	Ia, Ib, II, III, IV, V	√	√	√	√	√[b]	South Africa, UK, US, Uganda
Biotinylated CPS conjugates		√					
Protein-based vaccines							
N-terminal domains of the Rib and AlphaC proteins	N/A	√	√	√	√	√[b]	Denmark, South Africa, Uganda, UK
Pilus proteins		√					
Other proteins		√					

[a]Only in preclinical trials.
[b]Planned for 2023.
TBC, to be confirmed.

Paul et al. Curr Opin Pediatr 2023, 35:223–230

Overview of Pfizer GBS vaccine program

GBS6 vaccine

- Hexavalent polysaccharide CRM_{197} conjugate vaccine containing serotypes Ia-V, covering >98% of disease
- Maternal vaccine designed to protect infants against invasive GBS disease in first 90 days of life
- Dose/formulation: 20 µg dose per serotype without $AlPO_4$

Phase 1/2 study C1091002

- GBS6 has an acceptable safety profile in pregnant women and their infants
- GBS6 induced robust immune responses to all 6 serotypes in pregnant women
- GBS6-elicited antibodies were transferred to infants at concentrations associated with a reduced risk of invasive group B streptococcal disease based on natural immunity
- Based on safety and immunogenicity, 20 µg dose without $AlPO_4$ selected for evaluation in Phase 3

Phase 3 study C1091009

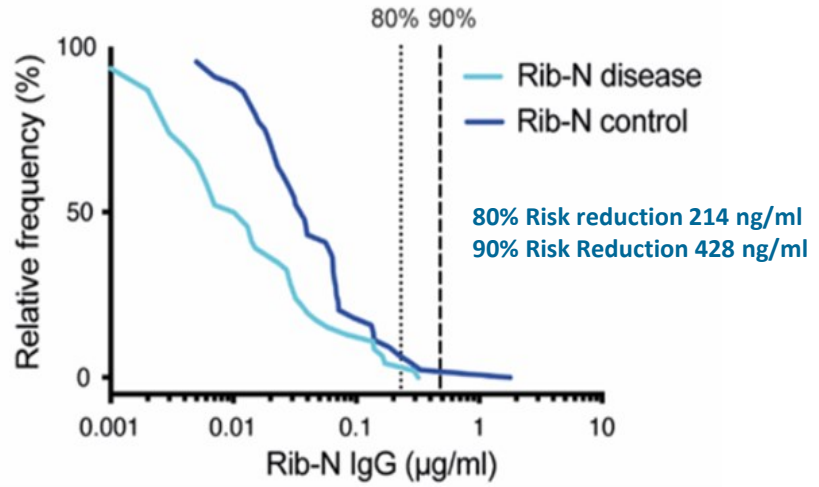
- Pivotal study for licensure, immunological endpoint trial
- Phase 3 design being discussed with regulators
- Safety database: 3000 maternal participants
- Global study in HIC and LMIC
- Timelines under discussion

Buurman E, et al. JID. 2019; 220(1):105-115; Absalon J, et al. Lancet Infect Dis. 2021; 21(2):263-74; Madhi S, et al. *N Engl J Med* 2023; 389:215-227

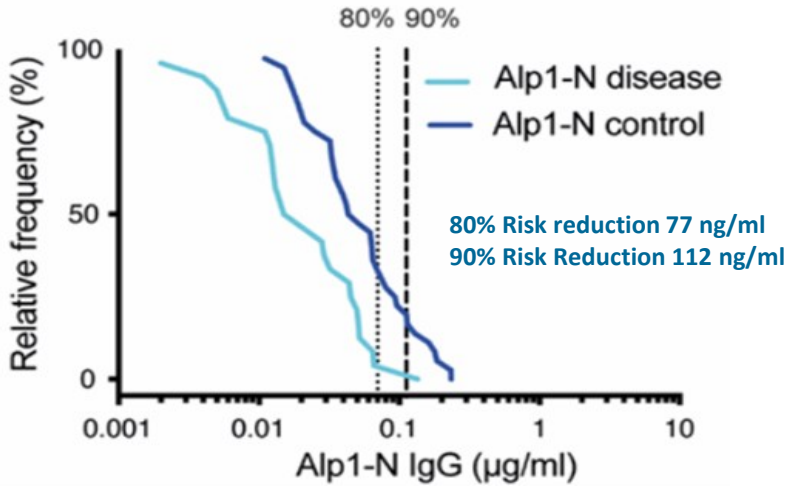
Overview of the Minervax vaccine programme

- Naturally occurring AlpN antibodies develop as a consequence of GBS clonization
- Natural history studies reveal lower levels of AlpN antibodies in infants with disease compared to controls
- This allows for development of a correlate of protection threshold, which may be used as surrogate efficacy endpoint in Phase 3
- FDA and EMA has so far agreed to the principle
- A validated CoP currently being developed from natural history study in GBS disease cases and controls derived from >60,000 pregnant persons (200-300 case samples)

Anti-RibN Antibodies

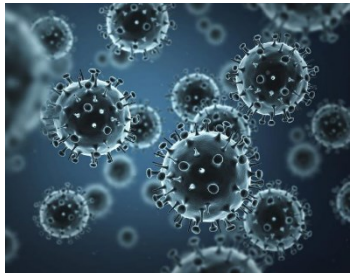


Anti-Alp1N Antibodies



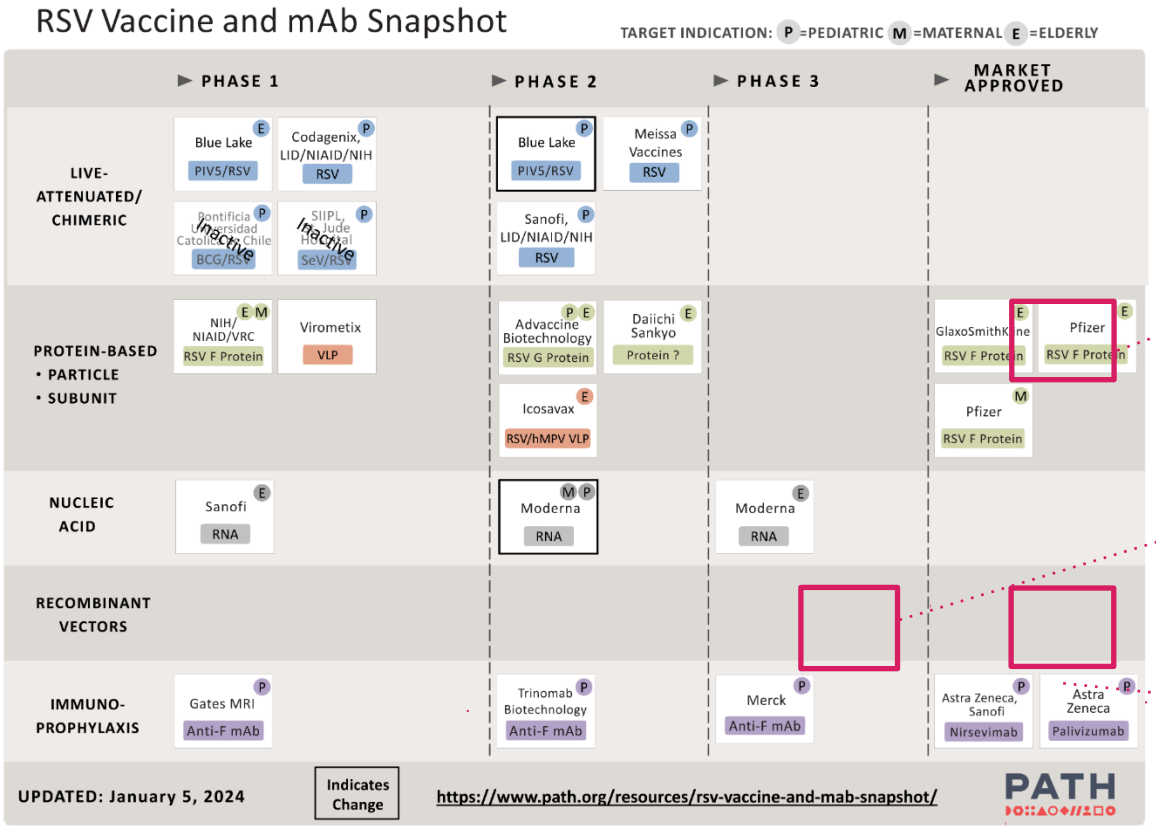
Dangor et al. Vaccine 2023

Respiratory Syncytial Virus



- The leading viral cause of severe lower respiratory tract disease in infants and young children.
- 2nd leading cause of death in children under one year of age.
- ~ 77% of all first-year RSV infections occur before six months of age.
- 102 000 deaths annually globally, 50% <6-month old infants

New hope of preventing RSV in infants—a product development renaissance



New pre-F technologies appropriate for protecting infants

- Maternal vaccines
- Long-acting monoclonal antibodies (mAbs)

Pfizer — RSV F Protein

Maternal vaccine licensed in US and Europe

Merck — Anti-F mAb

Long-acting mAb in Phase 3

Astra Zeneca, Sanofi — Nirsevimab

Long-acting mAb licensed in Europe and US

www.path.org/resources/rsv-vaccine-and-mab-snapshot/

New RSV maternal vaccine for protecting infants

product information and evidence

Phase 3 clinical study evidence

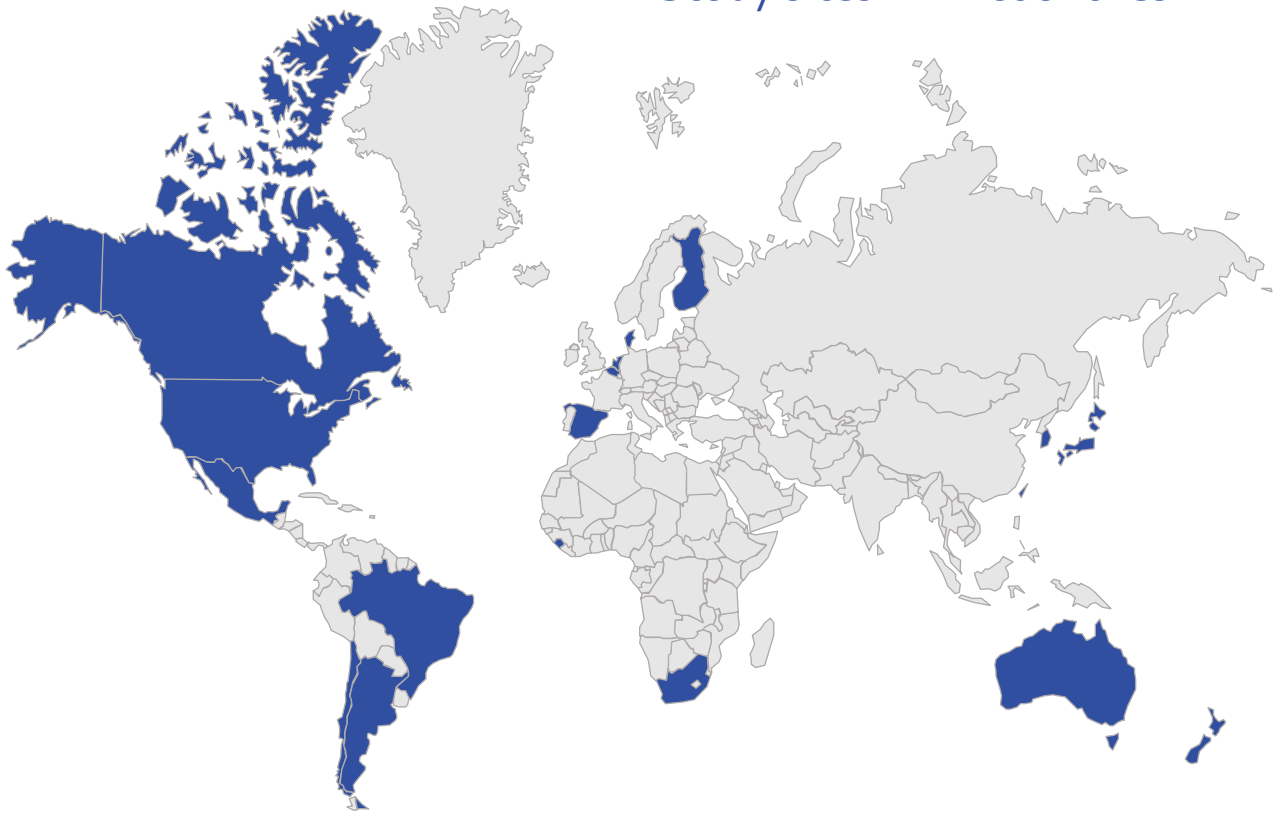
pre-F RSV maternal vaccine efficacy and safety in infants born to women vaccinated during pregnancy

Study product: Abrysvo™

7,392 pregnant participants ≤49 years between ≥ 24 and ≤ 36 weeks gestation

7,128 infants enrolled

Study sites in 18 countries



Reference: Kampmann B, et al. *New England Journal of Medicine.* 288(16):2023.

Original slide developed by the World Health Organization and PATH. Last updated: January 2024.

Pre-F RSV maternal vaccine efficacious against severe medically attended RSV in infants

	EFFICACY (%) FROM BIRTH THROUGH **90 DAYS** (CONFIDENCE INTERVAL)	EFFICACY (%) FROM BIRTH THROUGH **180 DAYS** (CONFIDENCE INTERVAL)
Severe medically attended RSV-LRTI	81.8% (95% CI, 40.6% to 96.3%)	69.4% (95% CI, 44.3% to 84.1%)
Medically attended RSV-LRTI	57.1%* (95% CI, 14.7 to 79.8) **did not reach pre-specified level of statistical significance*	51.3% (95% CI, 29.4% to 66.8%)

Efficacy remains high through first, most critical 6 months after birth—when infants are at greatest risk.

Reference: Kampmann B, et al. *New England Journal of Medicine.* 288(16):2023.

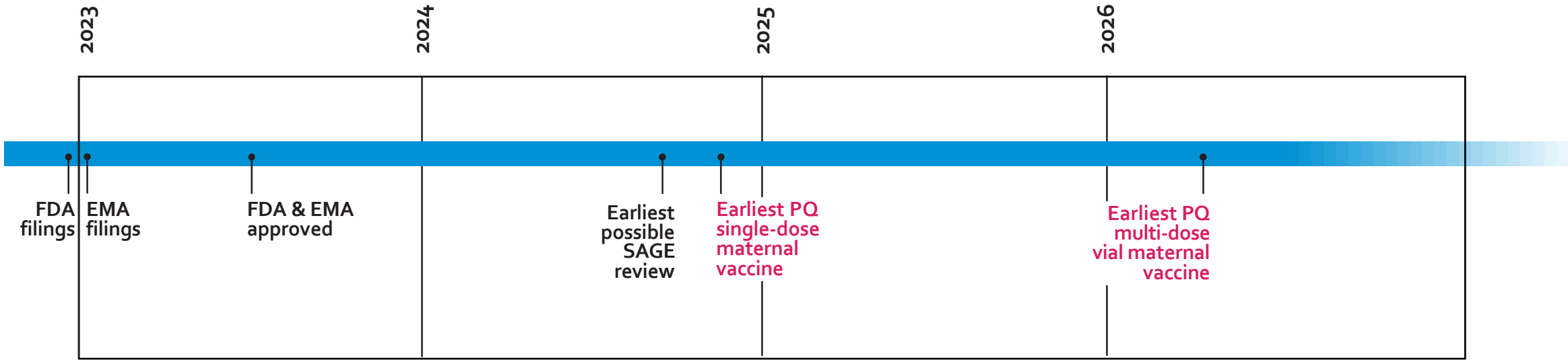
Original slide developed by the World Health Organization and PATH. Last updated: January 2024.

New RSV maternal vaccine licensed to protect infants

DEVELOPED BY	Pfizer, Inc. (Abrysvo™)	
APPROVAL	in Europe (August 2023)	in the US (August 2023)
MATERNAL IMMUNIZATION INDICATION	• For immunization of pregnant individuals to help protect their infants from birth through 6 months of age from lower respiratory tract disease due to RSV • Vaccination likely needed with each pregnancy	
APPROVED GESTATIONAL AGE WINDOWS	24-36 weeks (Europe)	32-36 weeks (US)
ABOUT THE PRODUCT	• For intramuscular injection • Uses standard cold chain • Lyophilized (freeze-dried) prefilled syringe; single-dose vial / multi-dose vial presentation in development • Can be co-administered with other maternal vaccines	

Will RSV pre-F maternal vaccine be available for low- and middle-income markets and when?

Pfizer maternal vaccine



EMA=European Medicines Agency

FDA=US Food and Drug Administration

SAGE=WHO Scientific Advisory Group of Experts

PQ=WHO prequalification

Development of an affordable **multi-dose vial** presentation is underway to support delivery in low- and middle-income economies.

New long-acting RSV monoclonal antibodies given at birth

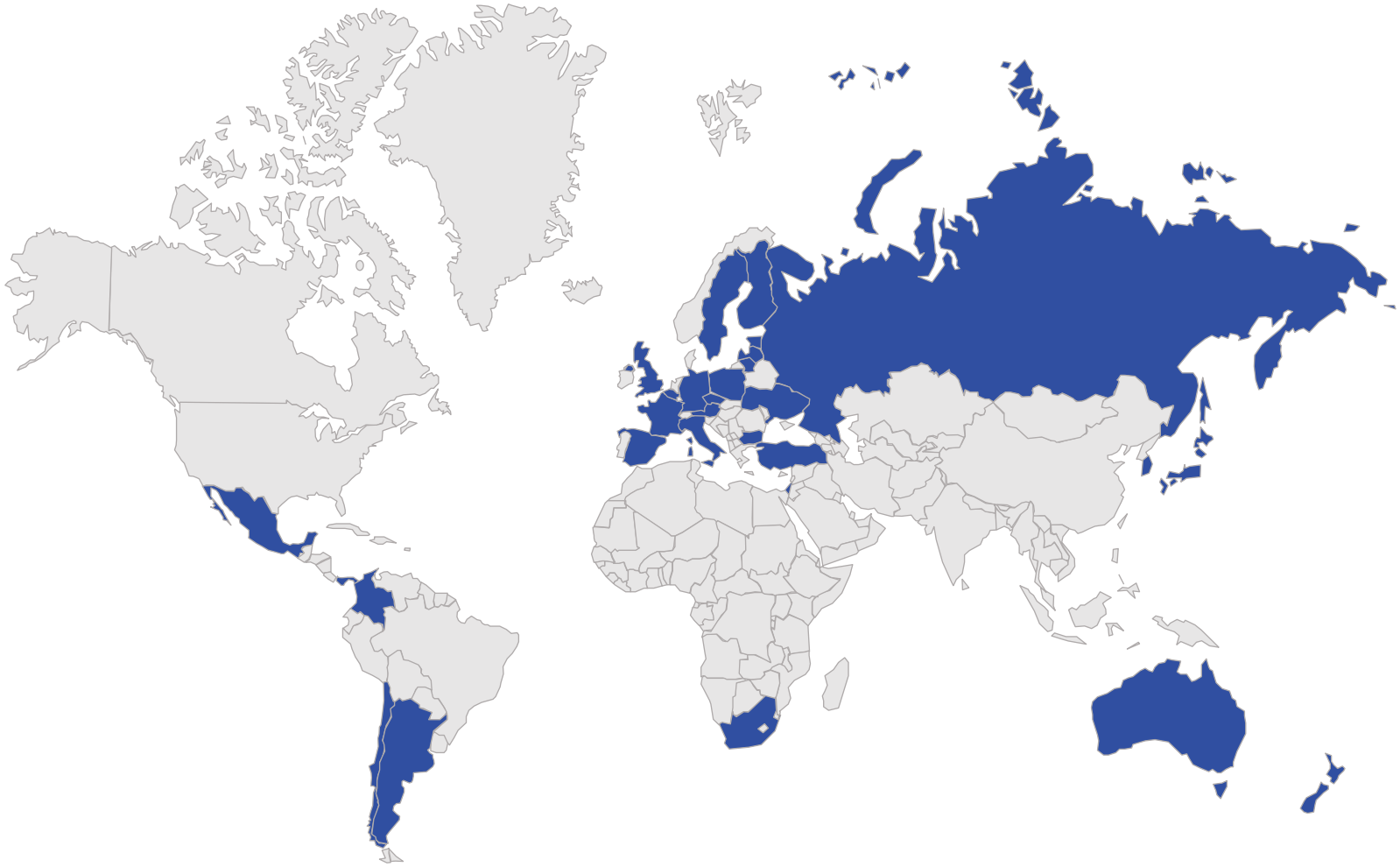
product information and evidence

Assessing long-acting mAb efficacy and safety in infants

Phase 3 clinical study (MELODY)

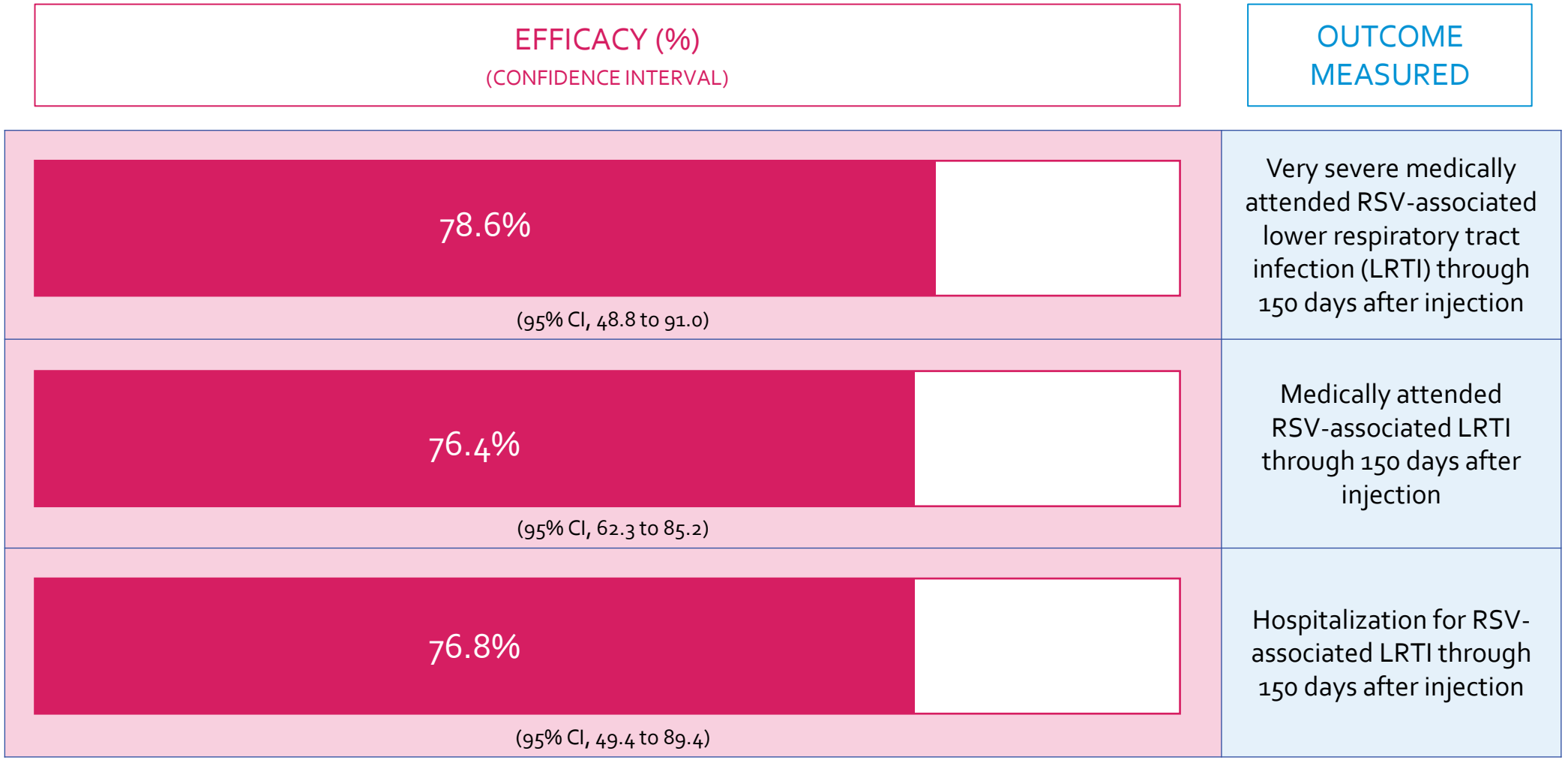
- Study product: nirsevimab (AstraZeneca / Sanofi Pasteur)
- Randomized, double-blind, placebo-controlled study
- 3,012 healthy infant participants born at term or late preterm (gestational age ≥ 35 weeks)

160 sites across 29 countries



Reference: Muller WJ, et al. *NEJM. 2023.*

Long-acting pre-F mAb (nirsevimab) Phase 3 efficacy results



Efficacy remains high through 5 months after administration—
when infants are at greatest risk.

Reference: Muller WJ, et al. *NEJM. 2023.*

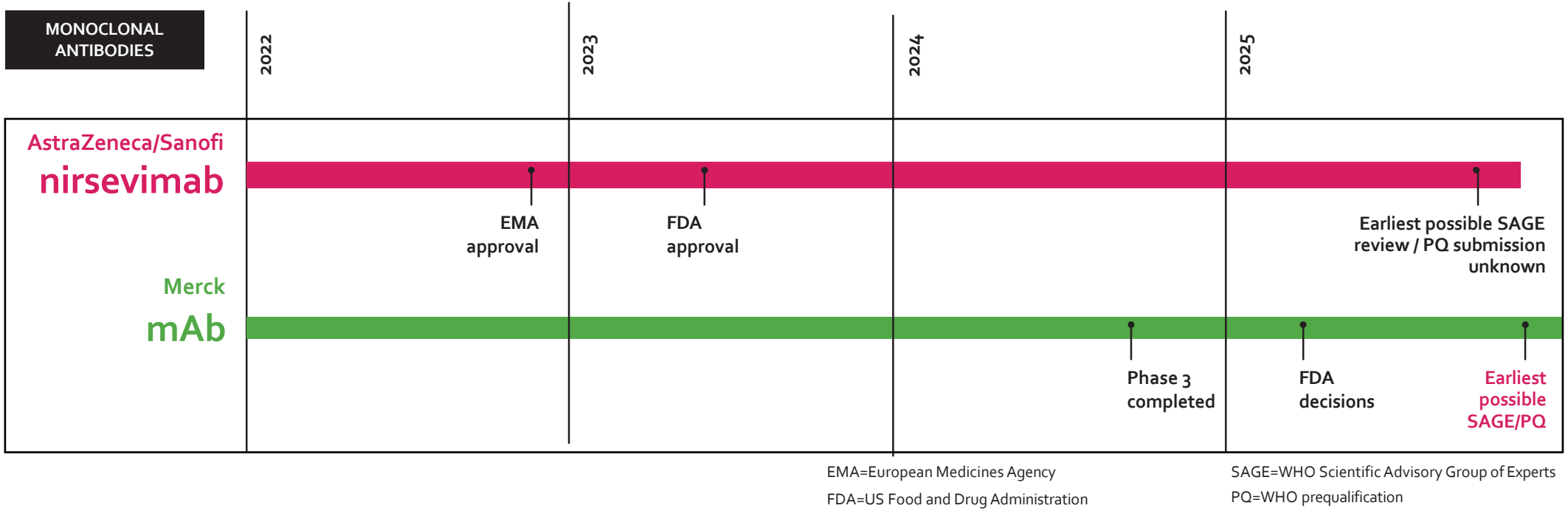
Original slide developed by the World Health Organization and PATH. Last updated: January 2024.

New long-acting RSV mAb (nirsevimab) given to newborns and young infants

DEVELOPED BY	AstraZeneca and Sanofi (Beyfortus®)	
LICENSED	in Europe (November 2022)	in the US (July 2023)
INDICATION	• For prevention of serious lower respiratory tract disease due to RSV in newborns and infants during their first RSV season • US approval goes up to 24 months of age for children who remain vulnerable to RSV disease entering their second RSV season.	
ABOUT THE PRODUCT	• Sterile liquid / pre-filled syringe • 50 mg (0.5 mL) for infants <5 kg or 100 mg (1.0 mL) dose for infants ≥5 kg. • Intramuscular injection in thigh, similar to a vaccine. • Given at birth or as soon as possible; can be given with other infant vaccines.	

Reference: Sanofi web page. "Beyfortus™: Dosing and Administration."Accessed on December 15, 2023.

Long-acting mAb development, approvals, and market entry status



Nirsevimab is not expected to be globally accessible in the near term due to price and supply barriers.

HOWEVER

It sets the stage for other RSV long-acting mAbs becoming more widely available in the future (e.g., Merck).

Global Alignment of Immunisation Safety Assessment in Pregnancy

- Standard for collection of vaccine safety data in clinical trials involving pregnant women
- Guidance for collection of high-quality data to allow interpretation
- No guidance on assessment of causal relationship

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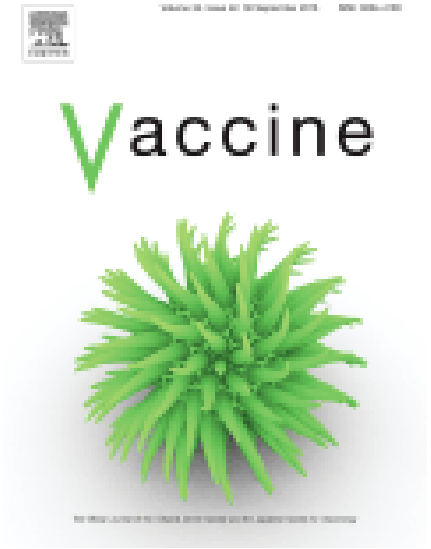
1. Bonhoeffer J, et al. *Vaccine*. 2016;34(49):5993-5997. 2. Jones CE, et al. *Vaccine*. 2016;34(49):6007-6014.

GAIA Definitions Published 2016, 2017, 2019

Neonatal:

- Neonatal death
- Stillbirth
- Preterm birth
- Neonatal infection
- Congenital anomalies
- SGA
- Low birth weight
- Neonatal encephalopathy
- Respiratory distress
- Failure to thrive
- Microcephaly
- Seizures
- Neurodevelopmental delay



Maternal:

- Maternal death:
- Pre-/eclampsia
- Fetal distress:
- Pathways to premature labor
- Postpartum hemorrhage
- Abortion
- Antenatal bleeding
- Fetal growth restriction
- Gestational diabetes
- Dysfunctional labor
- Chorioamnionitis
- Postpartum endometritis

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1. GAIA working group; 10 publications. *Vaccine*. 2016;34(49):6027-6109. 2. GAIA working group; 12 publications. *Vaccine*. 2017;35(48 Pt A):6472-6574.
3. GAIA working group; 4 publications. *Vaccine*. 2019;37(52):7585-7641.

Conclusions

- Vaccine-preventable infectious diseases are responsible for significant [maternal], neonatal and young infant morbidity and mortality.
- Maternal immunization can:
  - Protect the mother directly against infections
  - Provide a cocooning effect that can potentially protect the newborn and the contacts
  - Induce antibodies secreted in breast milk
  - Provide direct foetal /infant protection against infection via the transport of specific antibodies to the foetus prior to birth
- There is reassuring evidence about the safety of several vaccinations during pregnancy.
- Several vaccines are recommended for use in pregnancy (Tetanus, pertussis, influenza, COVID-19)
- Exciting advances in development of vaccines against other diseases (RSV, GBS)

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