Shabir A. Madhi

Global Overview of Maternal Immunisation

National Institute for Communicable Diseases &
University of Witwatersrand, South Africa
Respiratory and Meningeal Pathogens Research Unit,
& DST/NRF: Vaccine Preventable Diseases

Overview

- Progress in under-5 and neonatal mortality.

- Currently recommended maternal vaccines.

i. Inactivated influenza vaccine.

ii. Pertussis vaccine.

- Investigational vaccines under development.

i. Group B streptococcus

ii. Respiratory Syncytial Virus

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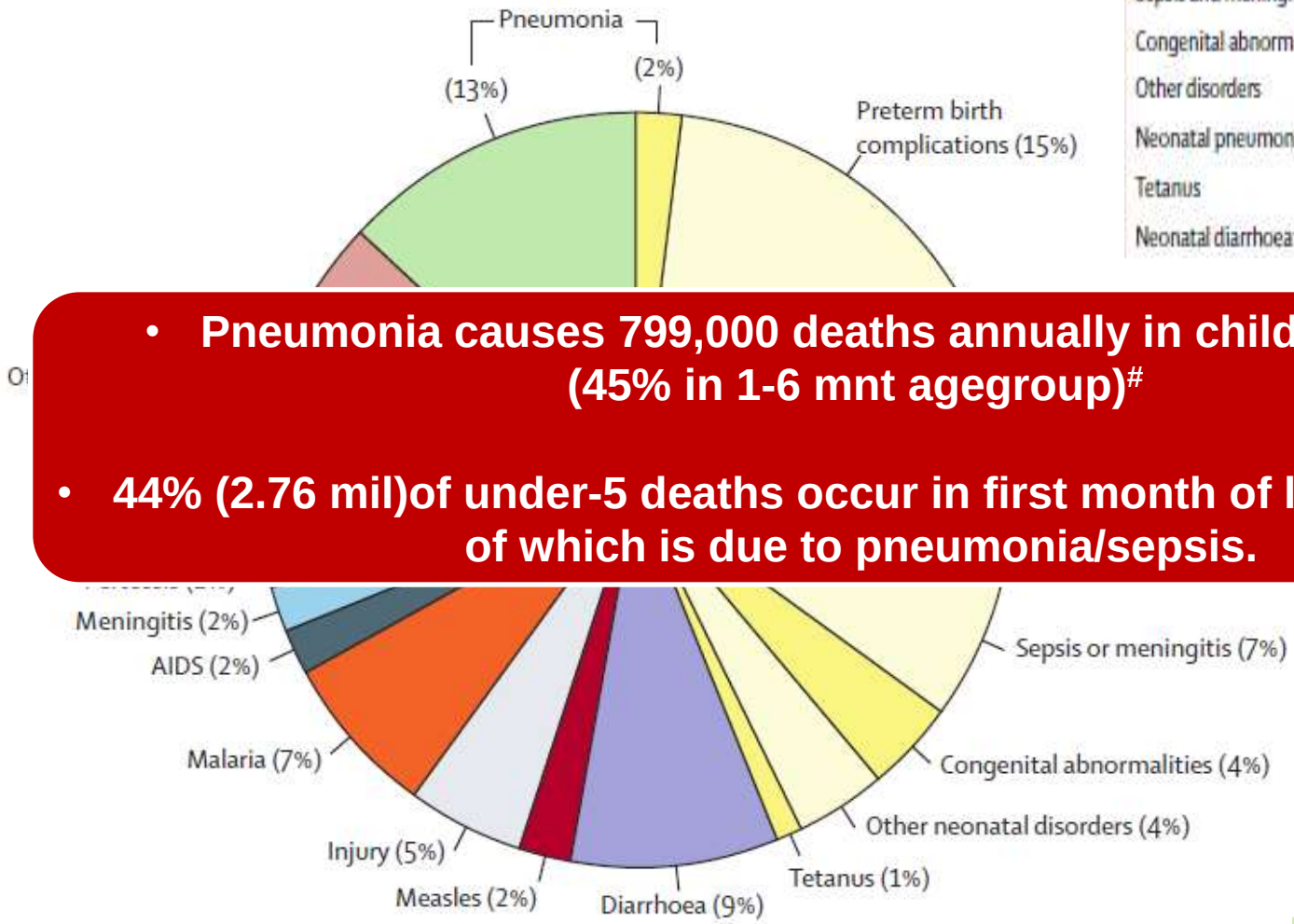
Global under-5 Mortality Estimates: 2013

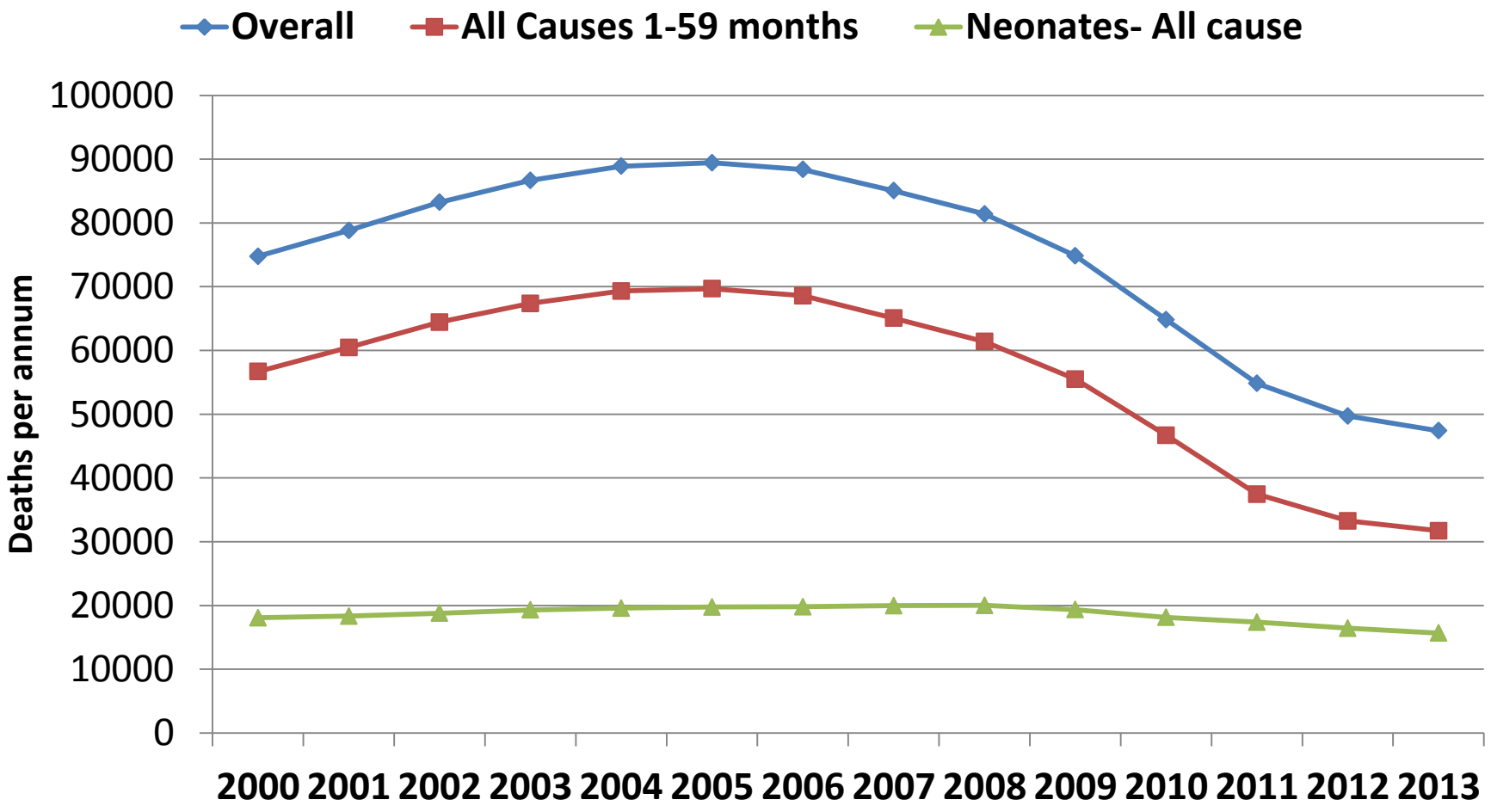
Neonates aged 0–27 days	
Preterm birth complications	0·965 (0·615–1·537)
Intrapartum-related complications	0·662 (0·421–1·054)
Sepsis and meningitis	0·421 (0·269–0·688)
Congenital abnormalities	0·276 (0·175–0·438)
Other disorders	0·232 (0·145–0·373)
Neonatal pneumonia*	0·136 (0·084–0·219)
Tetanus	0·049 (0·032–0·079)
Neonatal diarrhoea†	0·020 (0·012–0·033)



- **Pneumonia causes 799,000 deaths annually in children 1-59 mnt (45% in 1-6 mnt agegroup)#**
- **44% (2.76 mil)of under-5 deaths occur in first month of life, 20% (412,000) of which is due to pneumonia/sepsis.**

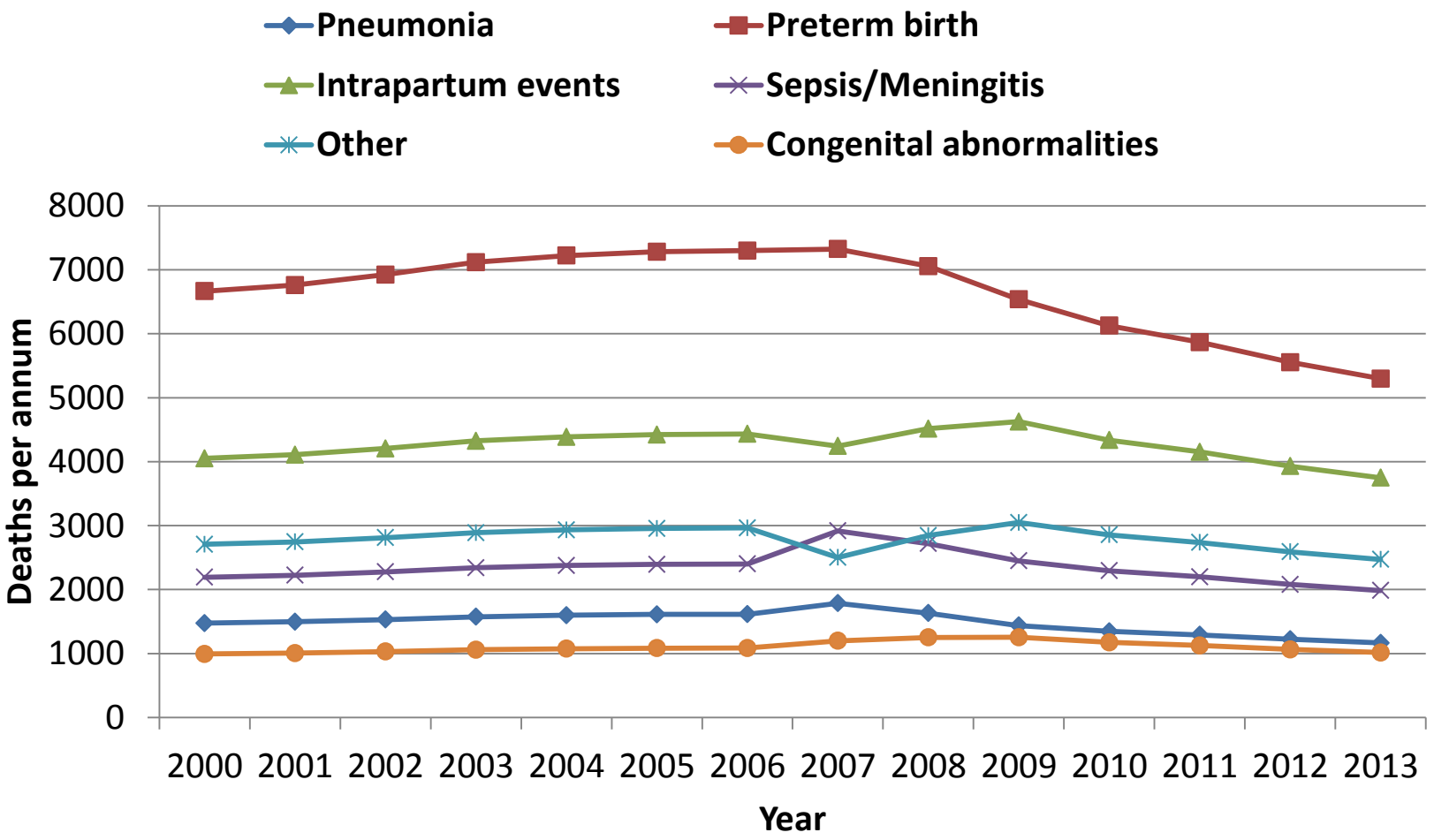
Liu L. et al. Lancet 2014; S0140-67361(14)61698-6; # PERCH unpublished data

Trends in under-5 mortality rates in South Africa, 2000 to 2013



Under-5 Childhood deaths increased from 74,753 in 2000, peaked at 89,418 in 2005 and has now declined to 47,409 in 2013.

Deaths in South African Children Under One Month of Age (2000 to 2013)



Number deaths in Neonates: 18,781 in 2000 compared to 15,607 in 2013 (Birth cohort 1,168,000)

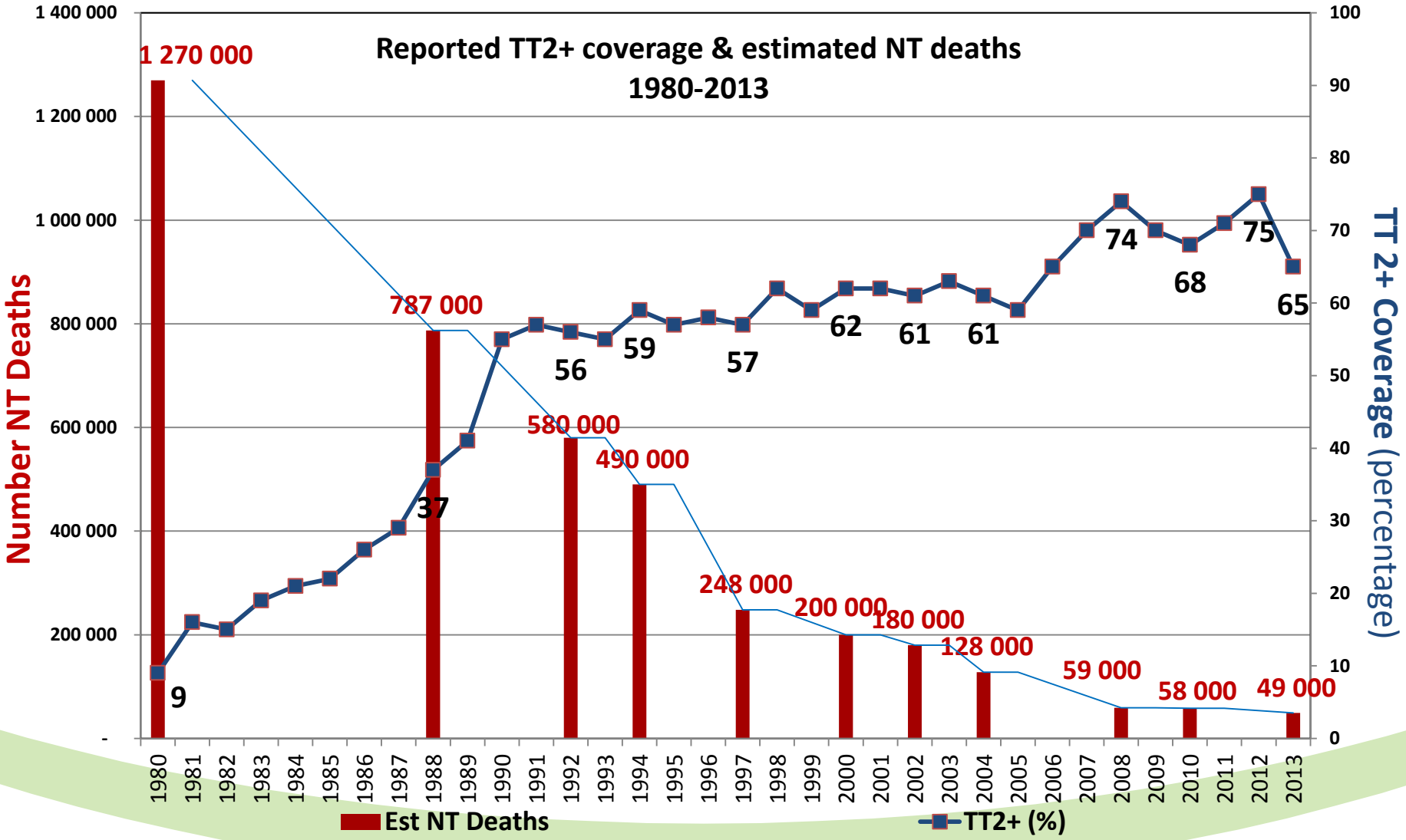
Incidence and Deaths from Vaccine Preventable Diseases in South African Infants 0-6 m. age

Pathogen	Incidence rate per 10^5 (95%CI)	Case fatality ratio	Estimated annual deaths nationally
Influenza virus[1]	412 (325-515)	4/54 (4.5%)	186
RSV[1]	3,282 (3,028-3,553)	10/841 (1.2%)	393
Group B streptococcus[2]	272 (262-281)	16/372 (17%)	549 (?x4)
Pertussis[3]	202 (152- 266)	2/40 (5%)	110

[1]SARI database- Unpublished. [2]Cutland C/Madhi SA et al Emerg Infect Dis. 2015 [3]BoSS Unpublished data

Success of Maternal Tetanus Vaccination in Preventing Neonatal Tetanus Deaths

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



WHO-UNICEF Data & CHERG Reports

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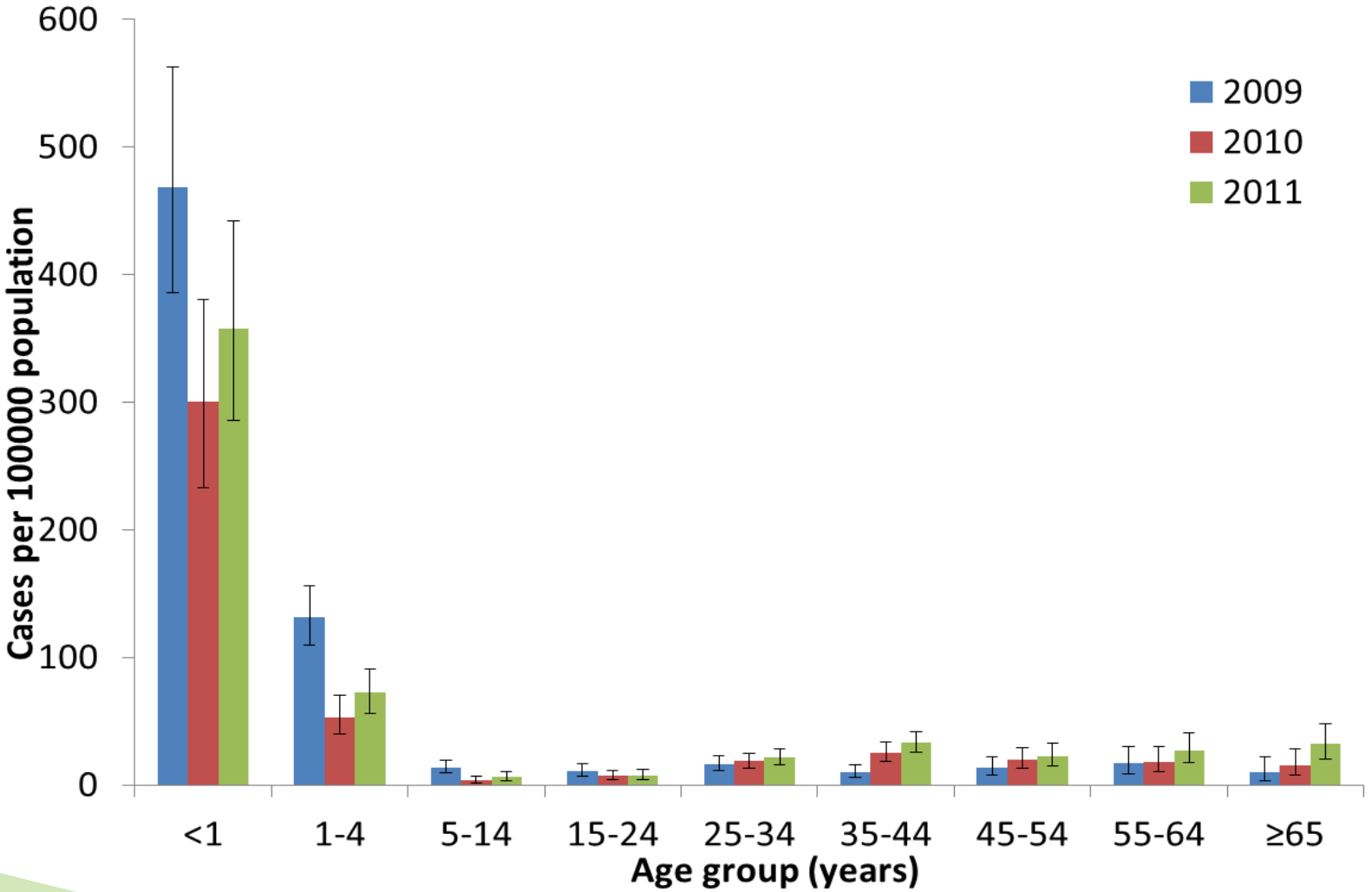
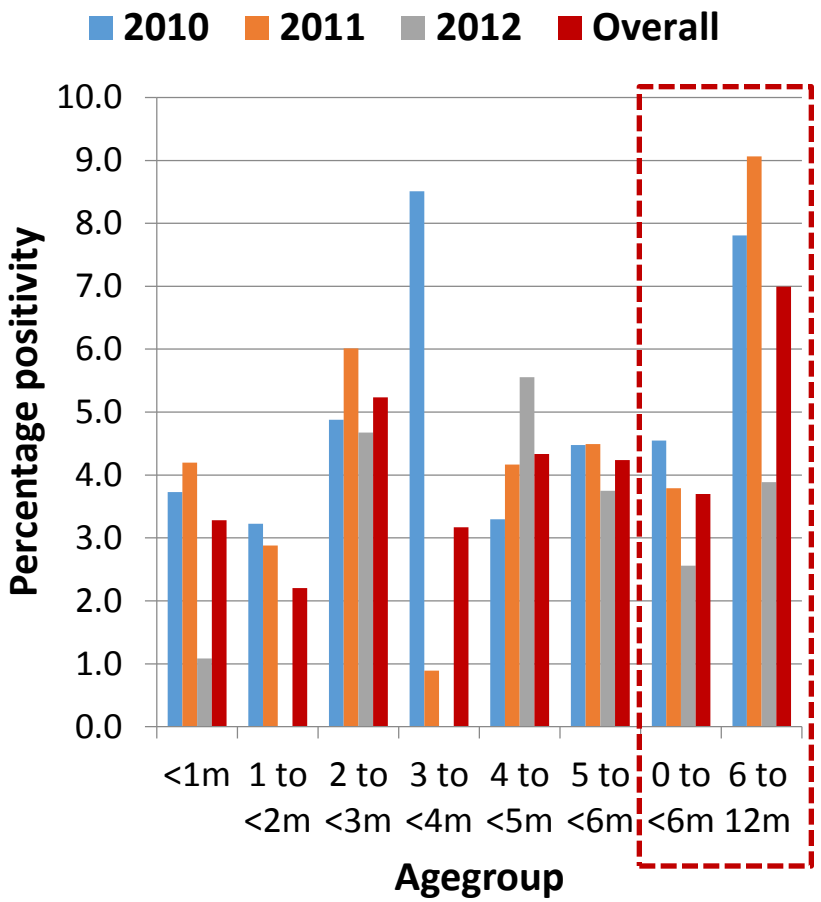
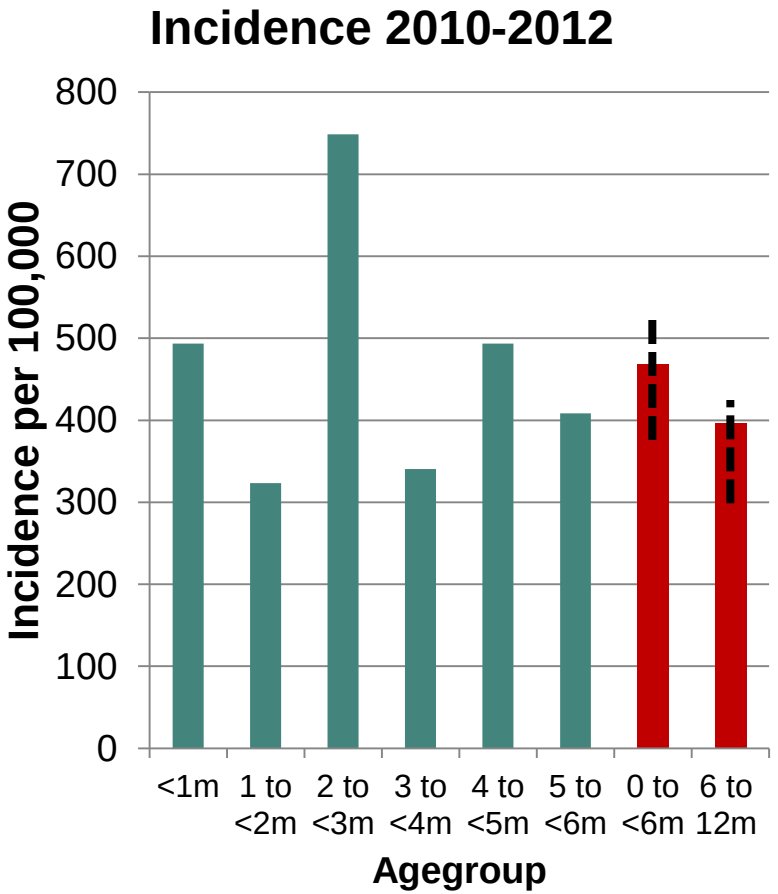
Incidence of **Laboratory-confirmed Influenza** Associated Hospitalization in Soweto, South Africa



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

Positivity and Incidence of Influenza Associated SARI Hospitalization by Age-group in South African Infants





SARI Unpublished data

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.

N Engl J Med 2008;359:1555-64.

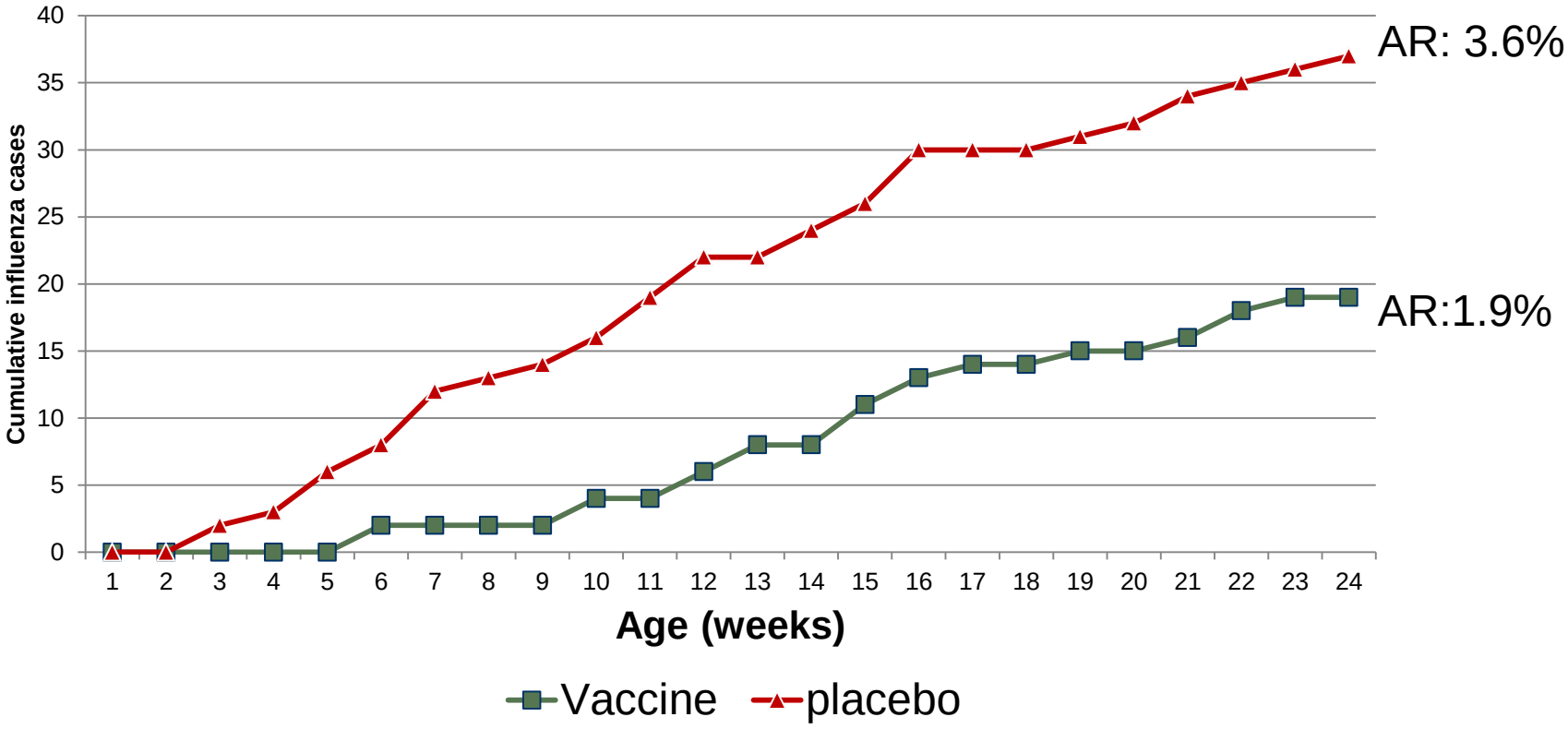
ORIGINAL ARTICLE

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

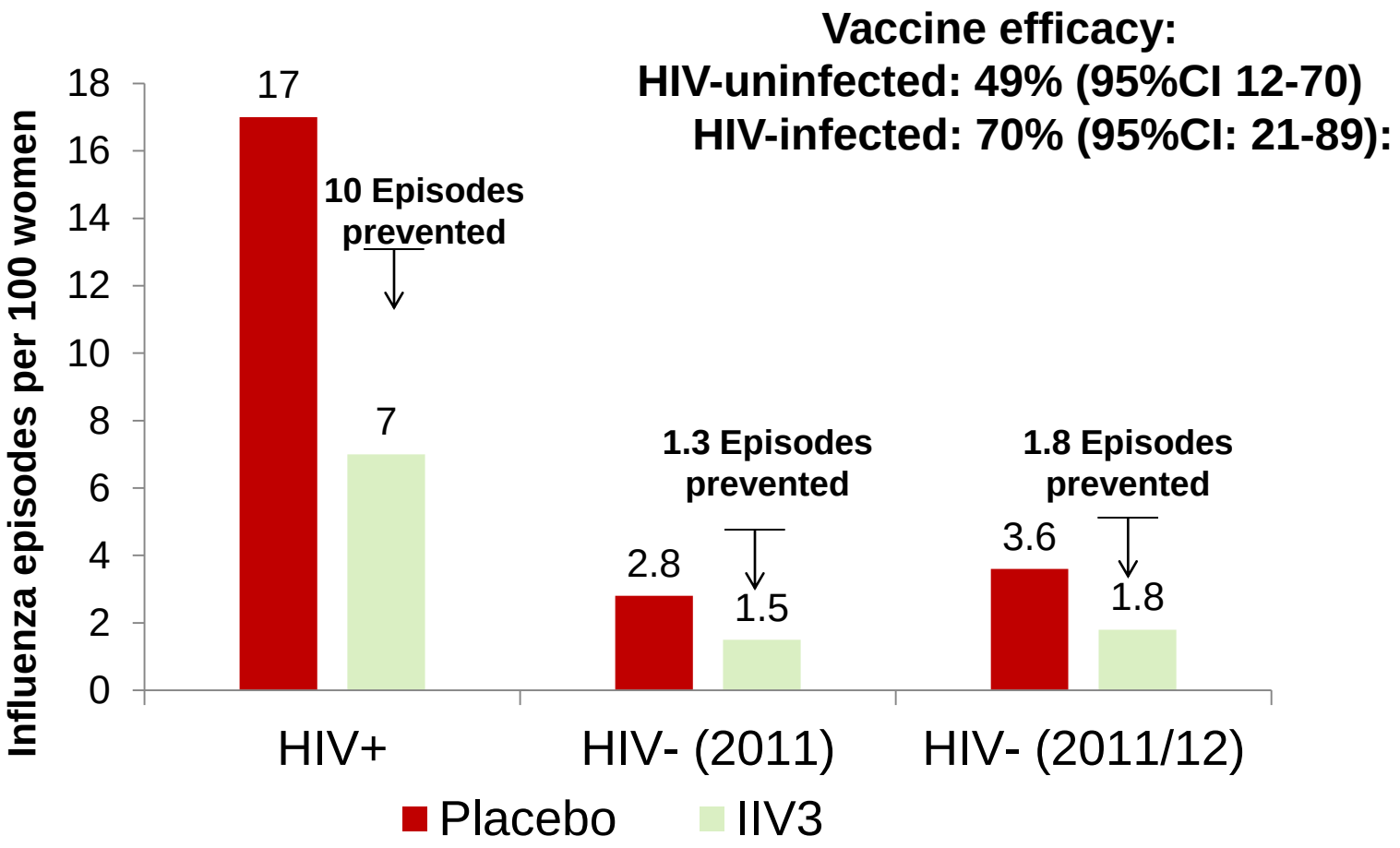
Vaccination of HIV- Pregnant Women in Preventing Influenza-Confirmed illness in their Infants up until 24 Weeks of age.



Vaccine Efficacy (ITT): 48.8% (95%CI: 11.5; 70.3)

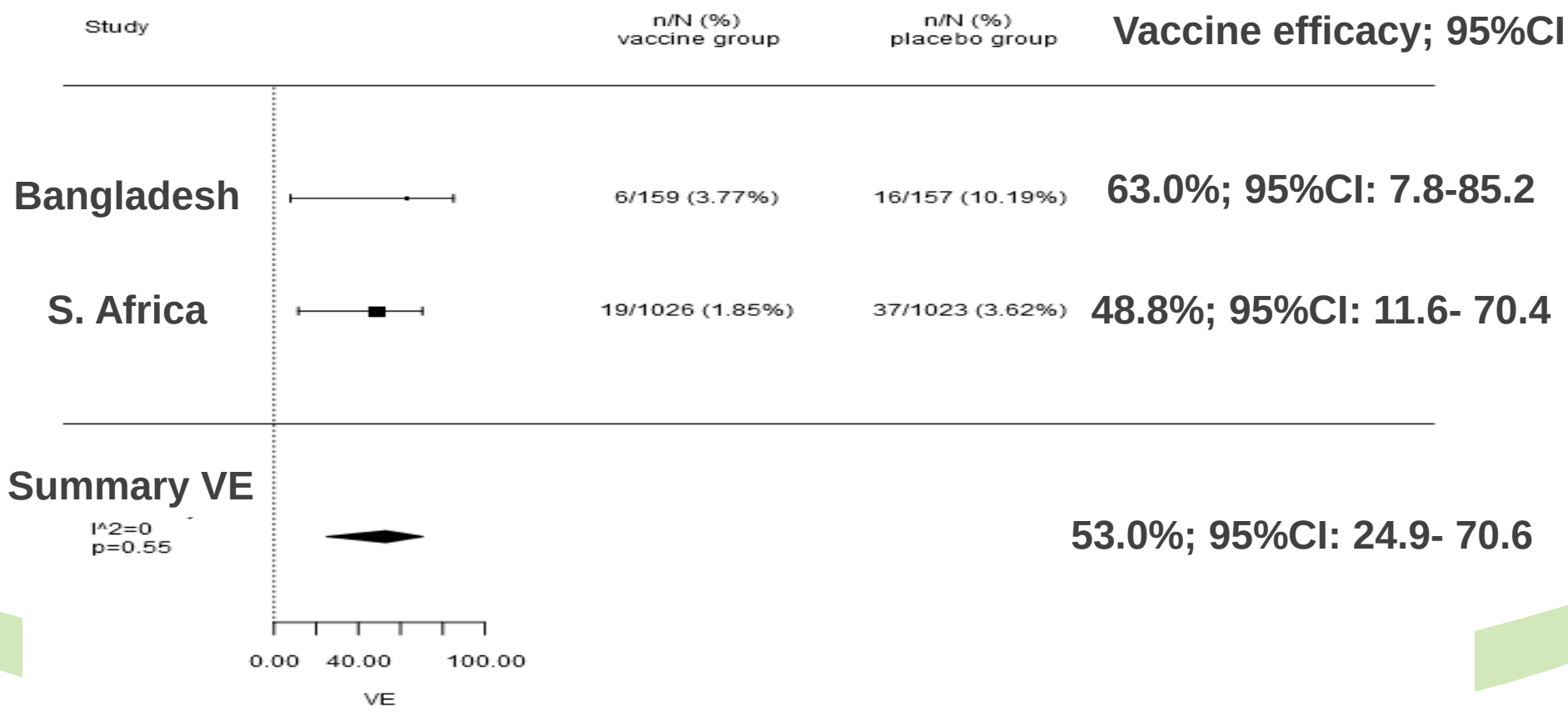
Madhi SA et al. New Engl J Med; 2014 ; 2014; 371: 918-31

IIV3 Efficacy and Influenza Illness Prevented per 100 Person years in HIV-infected and HIV-uninfected Pregnant Women.



Madhi SA et al. New Engl J Med; 2014 ; 2014; 371: 918-31

Vaccination of **HIV- Pregnant Women** in Preventing Influenza-Confirmed illness in their **Infants** <6 months age.



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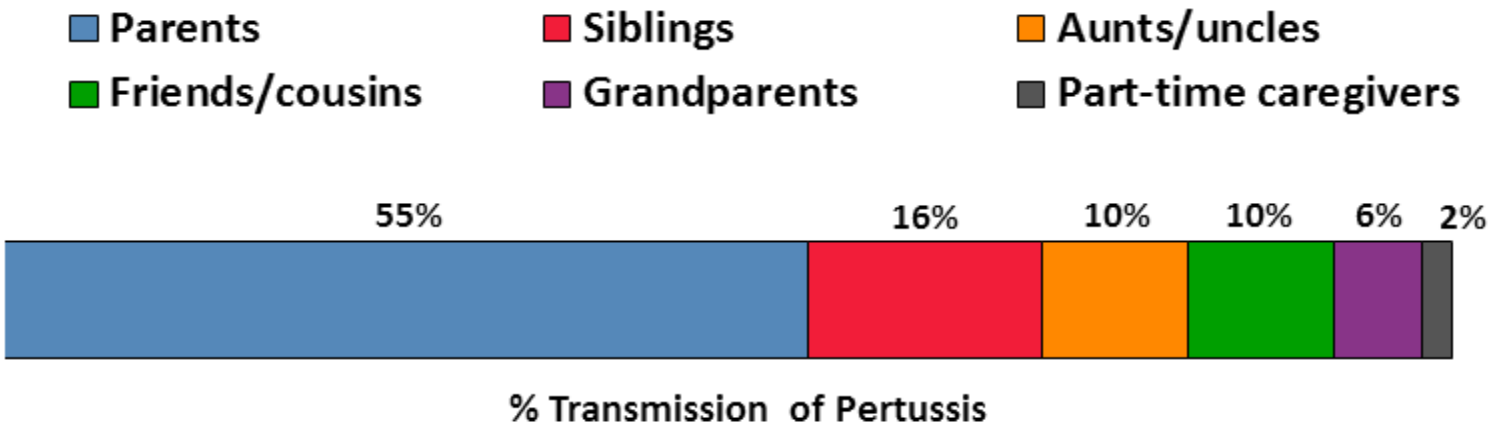
Pertussis epidemiology

- Pertussis, caused by *Bordetella pertussis,* is highly contagious, with a reproductive number of 5.5 (number of people infected per original index case)[1]
- Pertussis affects people of all ages, but is of particular concern in young children[2]
  - Worldwide, pertussis is among the top ten leading causes of childhood mortality from any individual pathogen[3,4]
  - Young infants (aged <2 months) are most at risk for pertussis-associated complications and death, having the highest rates of:[5]
    - hospitalisation (>90%)
    - pneumonia (15–25%)
    - seizures (2–4%)
    - encephalopathy (0.5–1%)
    - death (0.5–1%)
  - During 2004–2008 in the USA, 83% of all pertussis-related deaths were in infants aged ≤3 months[6]
    - In the 2010 California outbreak, 72% of hospitalised cases were infants <6 months of age; all deaths occurred in infants ≤2 months of age[7,8]

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

Transmission of Pertussis to Young Infants

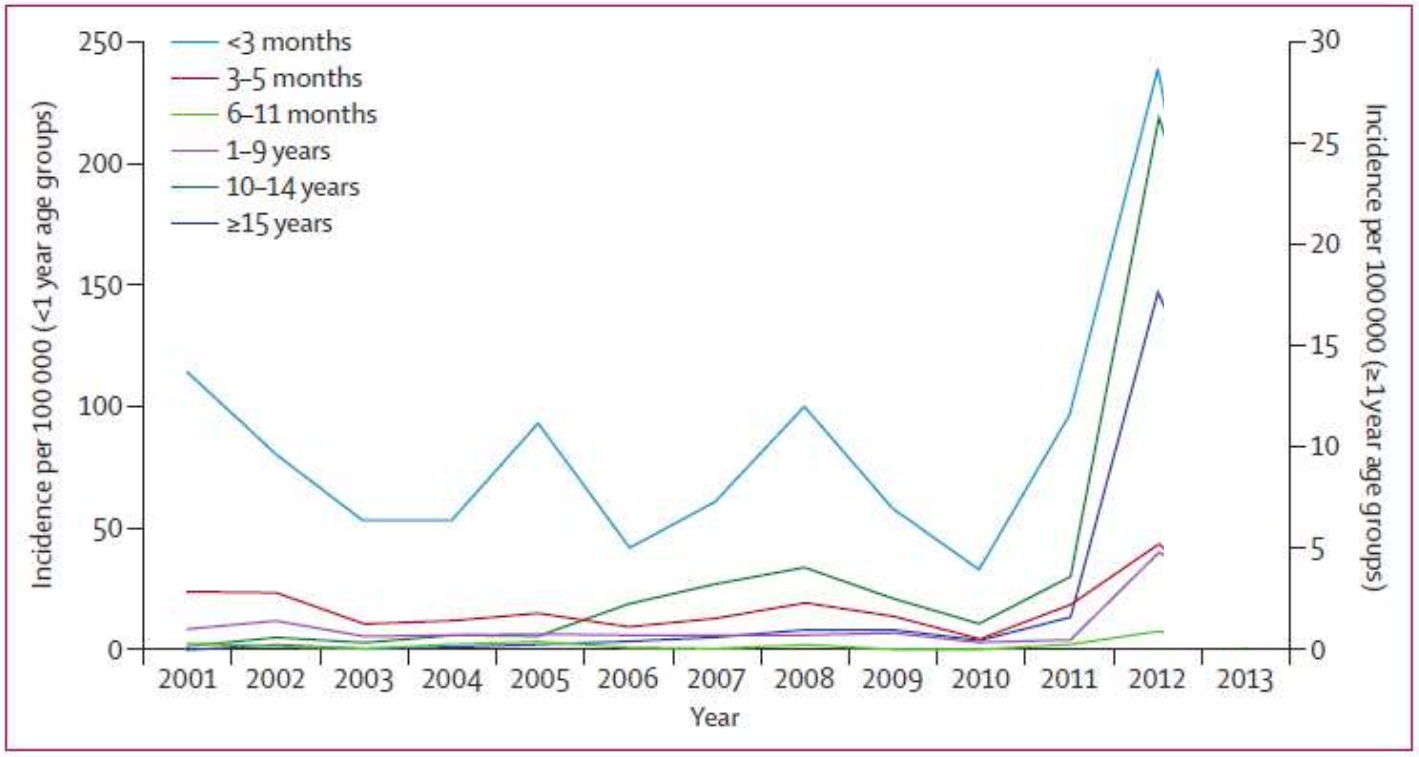


- Prospective international study of infants ≤ 6 months with confirmed pertussis*
- Household members were responsible for 76%-83% of pertussis transmission

*95 index cases and 404 contacts; source identified for 48% of infants in primary analysis (78% in sensitivity analyses)

Adapted from Wendelboe AM, et al. *Pediatr Infect Dis J.* 2007;26(4):293-299.

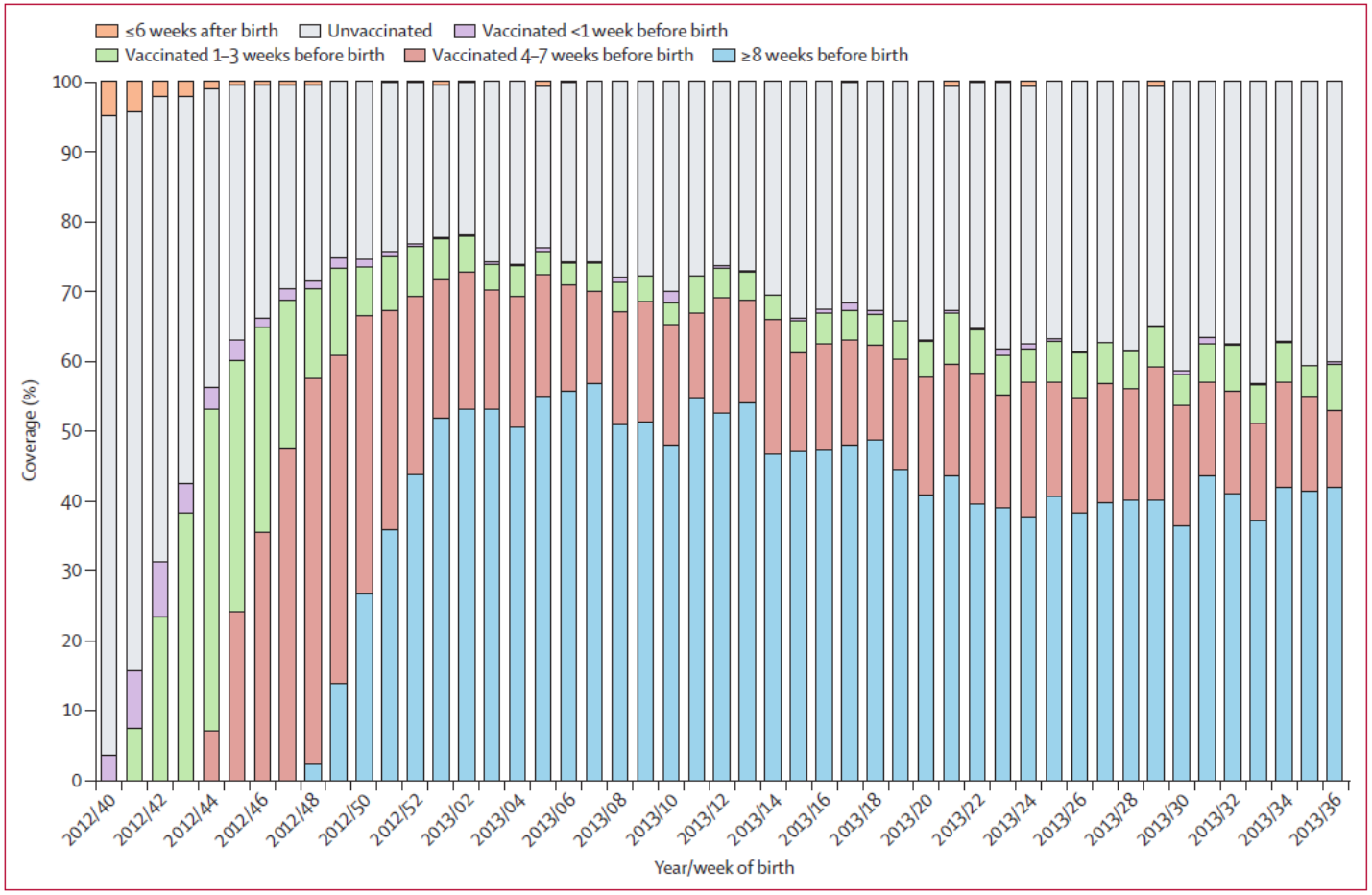
Annual incidence of laboratory-confirmed cases of pertussis by age-group.



????Contribution of effect of changes in laboratory assays and physician awarenes to increase detection of pertussis in 2012/3.

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

Estimated Maternal Vaccine Coverage by Week of Birth; United Kingdom



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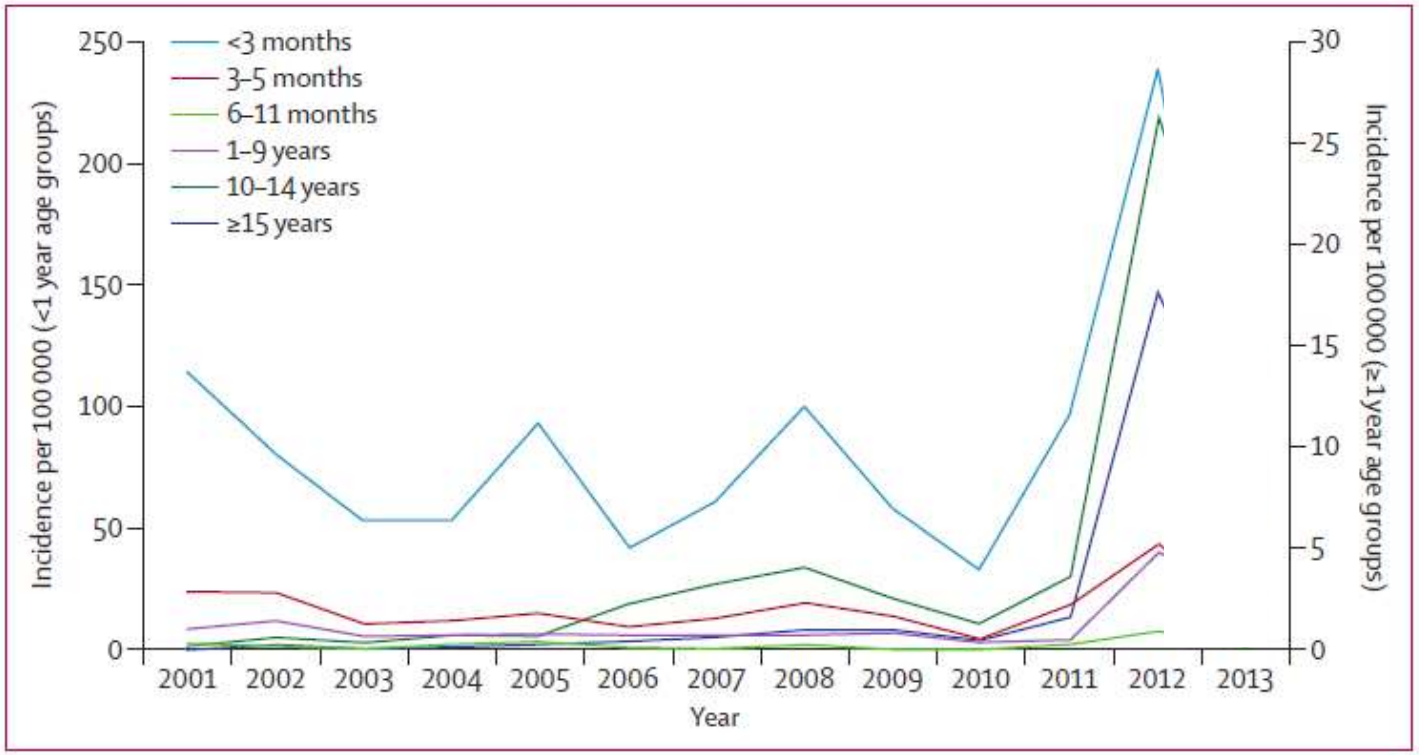

Amirthalingam G et al. Lancet; 16 July 2014 (on line)

Case-control study on effectiveness of pertussis vaccination during pregnancy on infant pertussis illness.

Cases		Controls			
Total No.	History of Maternal Pertussis Vaccination, No. (%)	Total No.	History of Maternal Pertussis Vaccination, No. (%)	Unadjusted VE, % (95% CI)	Adjusted VE[a], % (95% CI)
58	10 (17)	55	39 (71)	91 (77–97)	93 (81–97)

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

[a] Adjusted for sex, geographical area, and birth period.

Dabrera G et alClin Infect Dis; 2015; 60:333-337.

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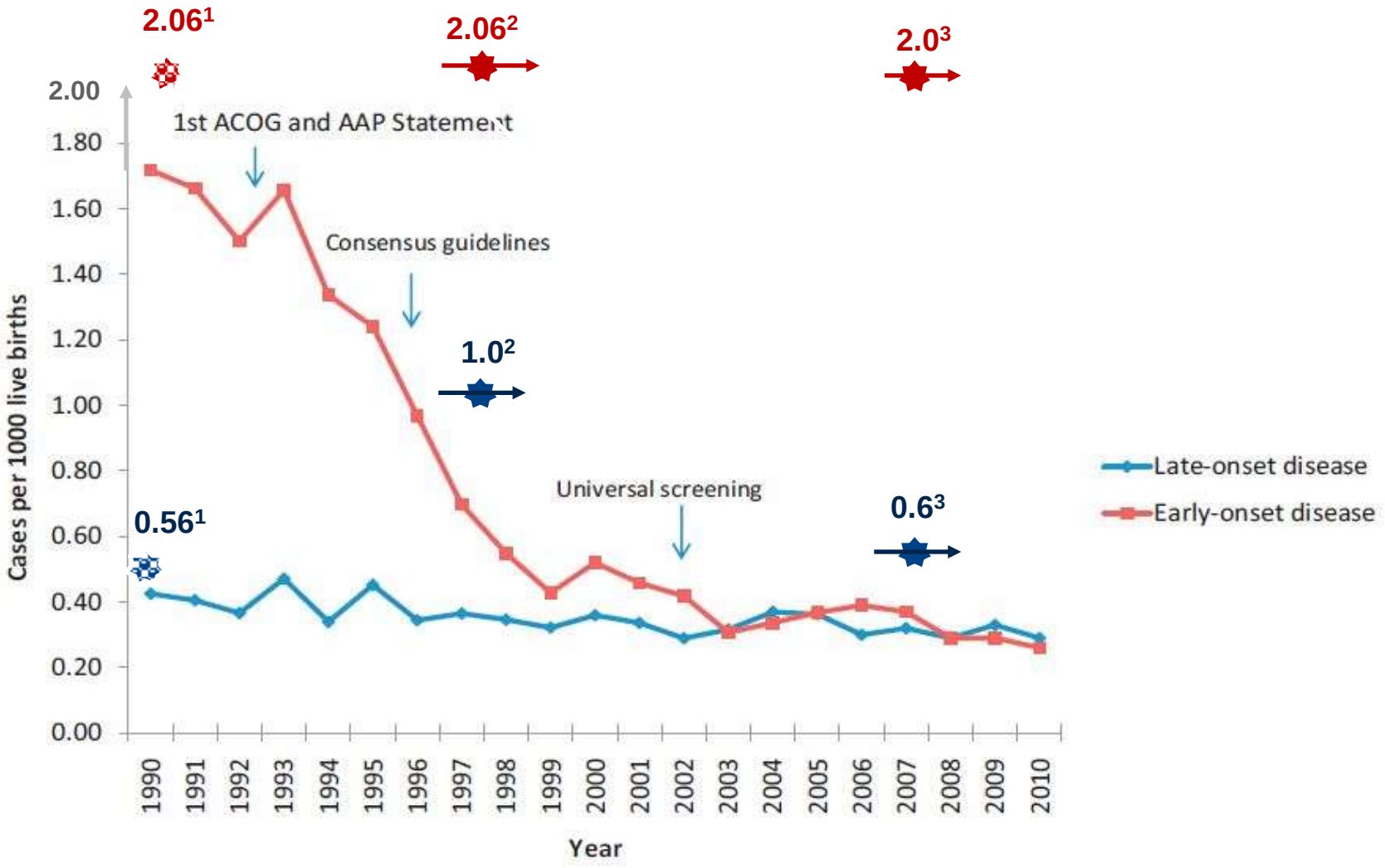
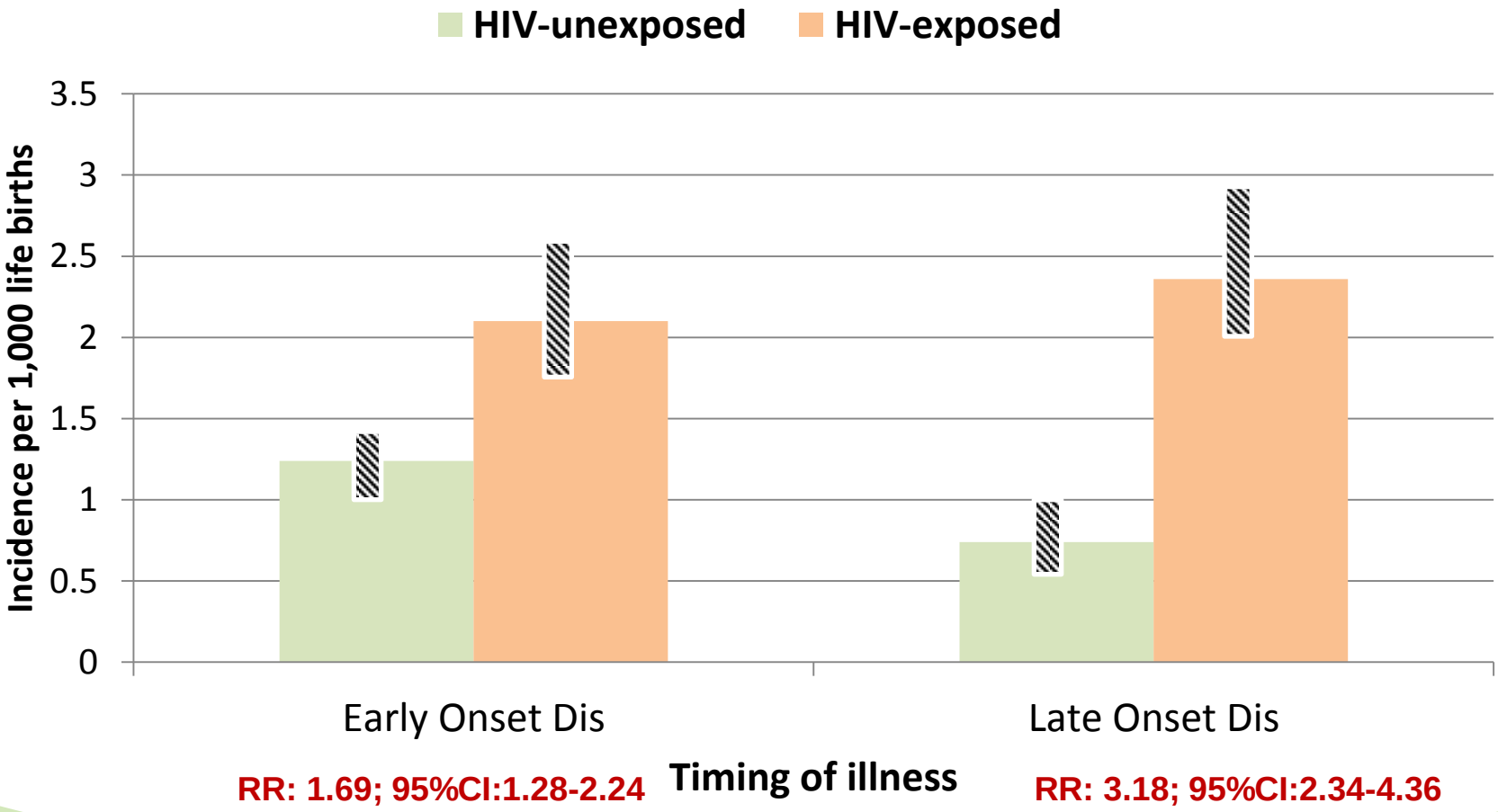
Invasive Group B Streptococcal Disease in USA and South Africa.



Schrag, S. J. and Verani, J. R. Vaccine 2013; D20-D26; [1]Haffejee IE J Infect 1991; 22:225-31; [2]Madhi SA et al, Annals Trop Pediatr; 2003; 23; 15-23; [3]Cutland C et al. Pediatrics 2012; 130: e581-90

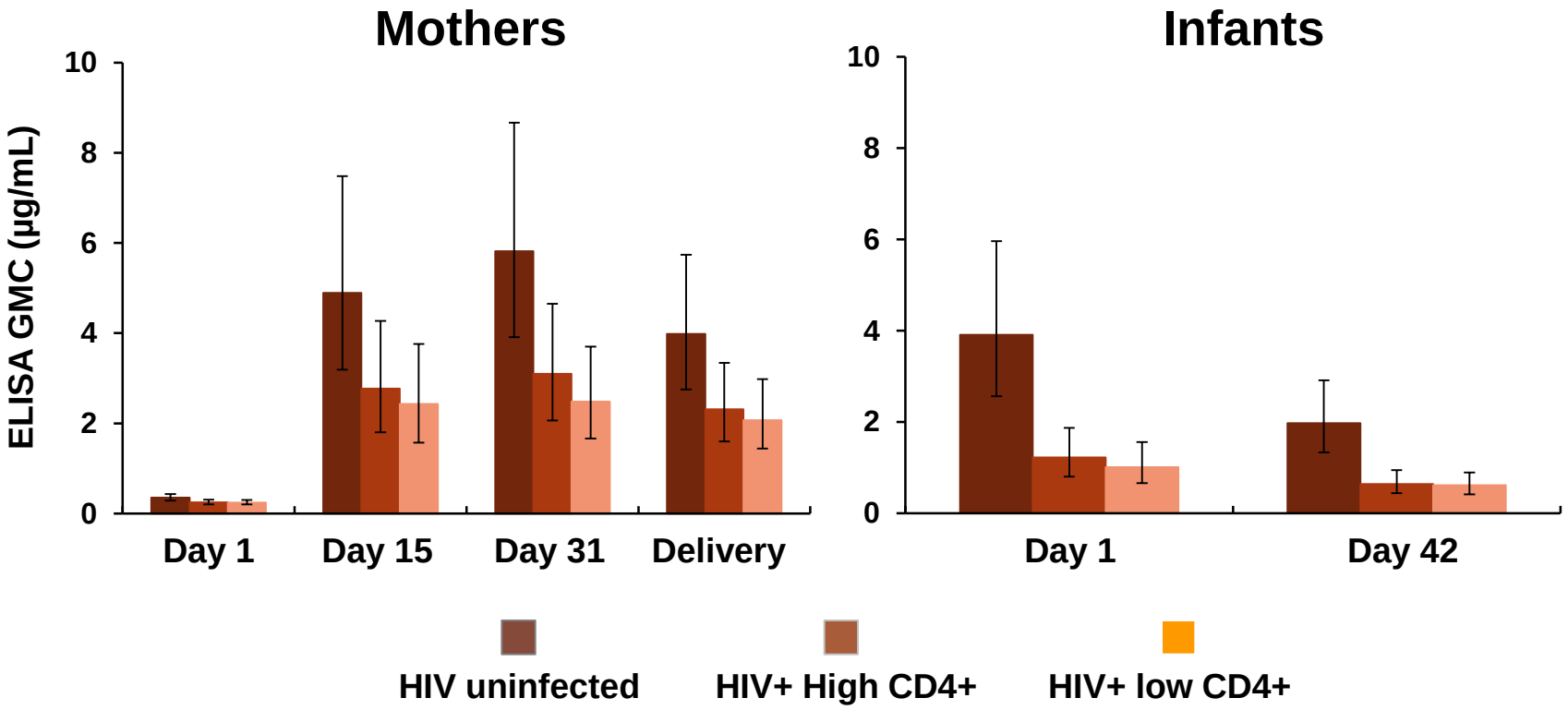
HIV-exposed Infants at Increased Risk of Invasive GBS Disease



Cutland C et al. Emerg Infect Dis; 2015: 21: 638-645

GBS Serotype Ia antibodies Following Trivalent GBS Conjugate Vaccine In HIV-infected and HIV-uninfected Pregnant Women.

In mothers and infants with one 5.0 µg dose of GBS vaccine



- Similar immunogenicity trends observed for serotypes Ib and III

Heyderman R , Madhi SA et al. Lancet Infect Dis 2016

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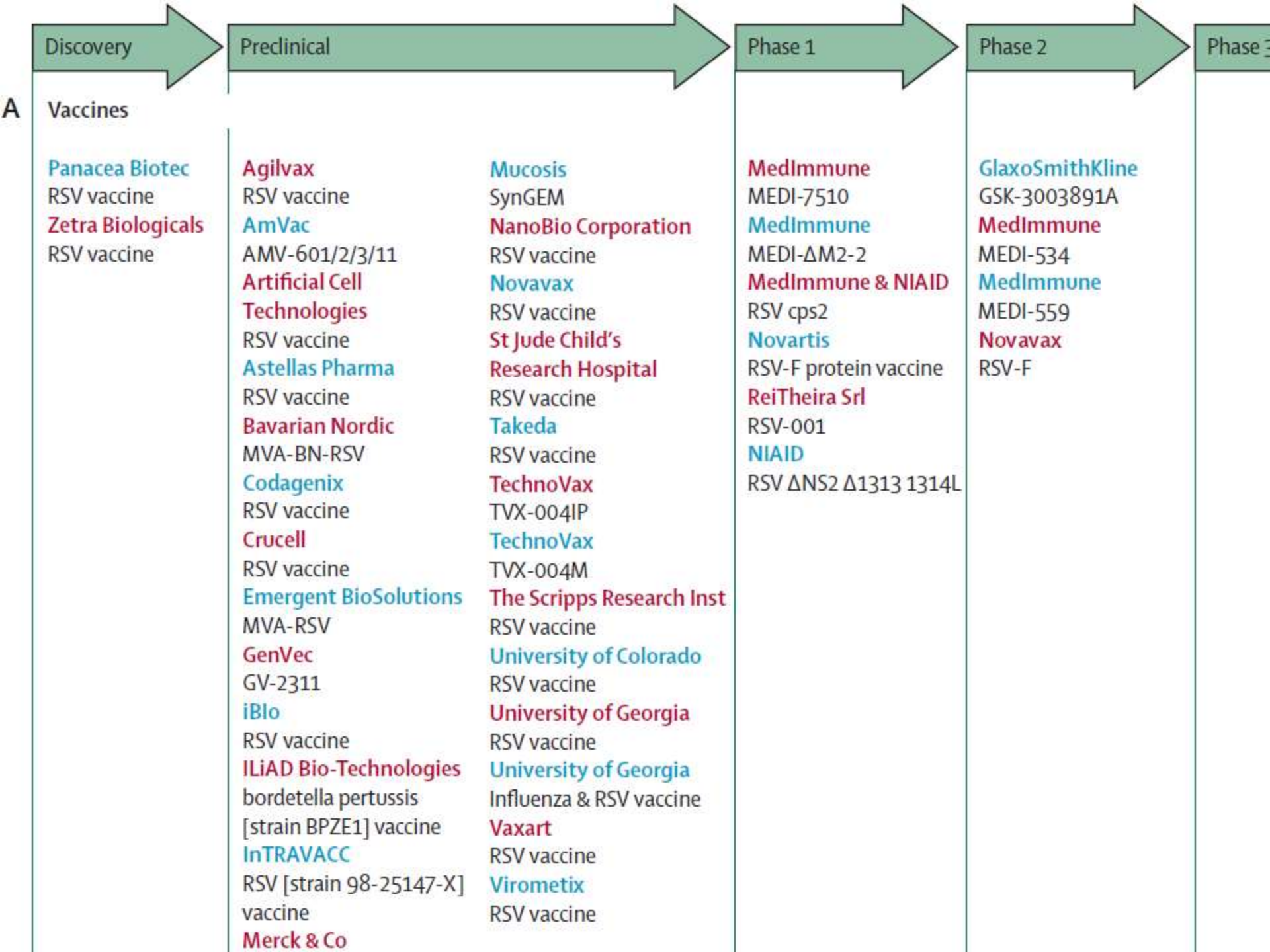
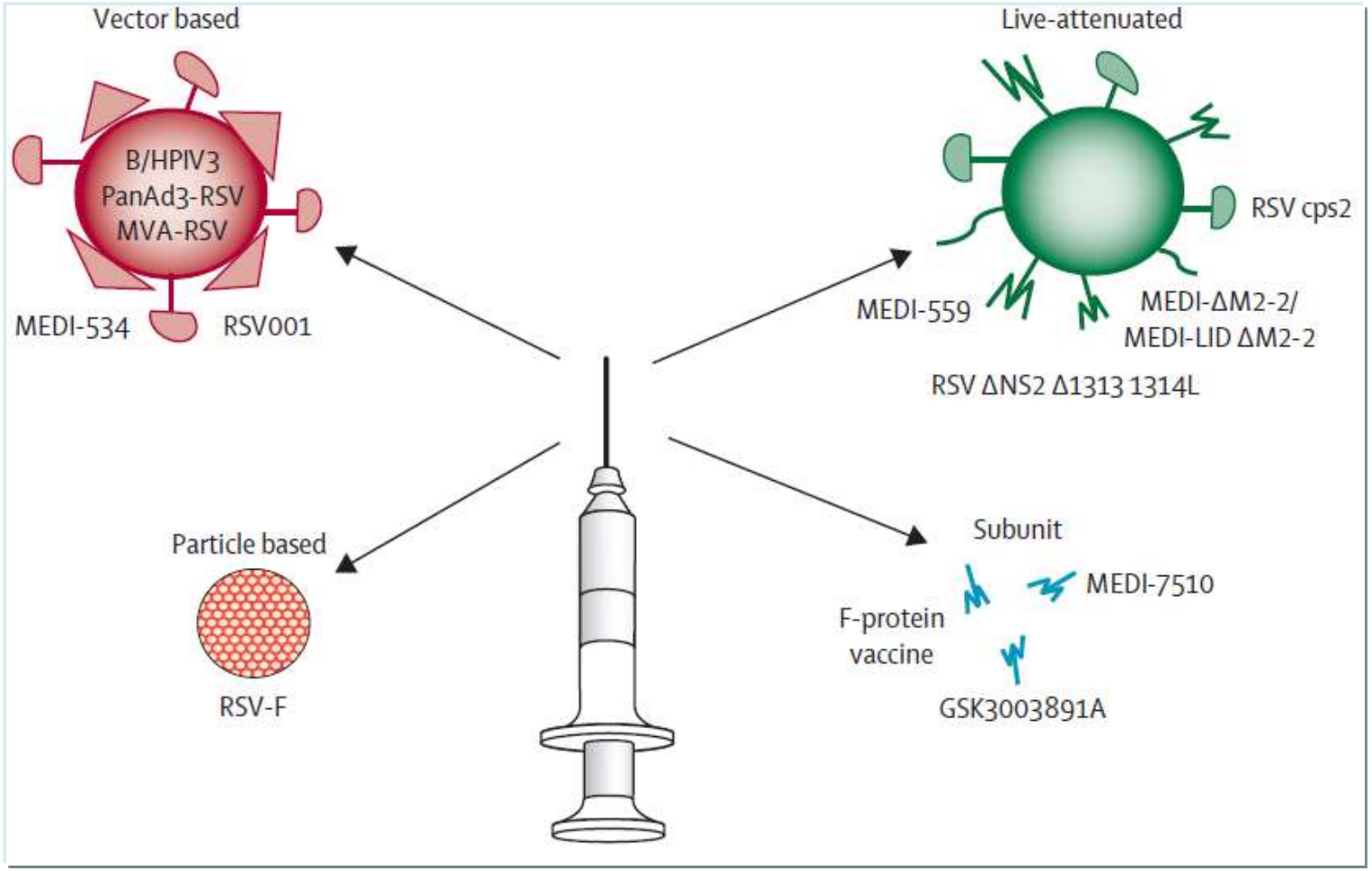

Discovery
Preclinical
Phase 1
Phase 2
Phase 3
A
Vaccines
Panacea Biotec
RSV vaccine
Zetra Biologicals
RSV vaccine
Agilvax
RSV vaccine
AmVac
AMV-601/2/3/11
Artificial Cell Technologies
RSV vaccine
Astellas Pharma
RSV vaccine
Bavarian Nordic
MVA-BN-RSV
Codagenix
RSV vaccine
Crucell
RSV vaccine
Emergent BioSolutions
MVA-RSV
GenVec
GV-2311
iBio
RSV vaccine
ILiAD Bio-Technologies
bordetella pertussis [strain BPZE1] vaccine
InTRAVACC
RSV [strain 98-25147-X] vaccine
Merck & Co
Mucosis
SynGEM
NanoBio Corporation
RSV vaccine
Novavax
RSV vaccine
St Jude Child's Research Hospital
RSV vaccine
Takeda
RSV vaccine
TechnoVax
TVX-004IP
TechnoVax
TVX-004M
The Scripps Research Inst
RSV vaccine
University of Colorado
RSV vaccine
University of Georgia
RSV vaccine
University of Georgia
Influenza & RSV vaccine
Vaxart
RSV vaccine
Virometix
RSV vaccine
MedImmune
MEDI-7510
MedImmune
MEDI-ΔM2-2
MedImmune & NIAID
RSV cps2
Novartis
RSV-F protein vaccine
ReiTheira Srl
RSV-001
NIAID
RSV ΔNS2 Δ1313 1314L
GlaxoSmithKline
GSK-3003891A
MedImmune
MEDI-534
MedImmune
MEDI-559
Novavax
RSV-F

RSV Vaccine Development Options



Mazur N et al. Lancet Resp Med; Sep 2015

Novel RSV F Vaccine

Novel RSV Fusion-protein vaccine (**RSV F Vaccine**) developed using recombinant nanoparticle technology

Six clinical trials completed or initiated, demonstrating safety and immunogenicity in **over 2,000 participants**

Positive data in all 3 target populations

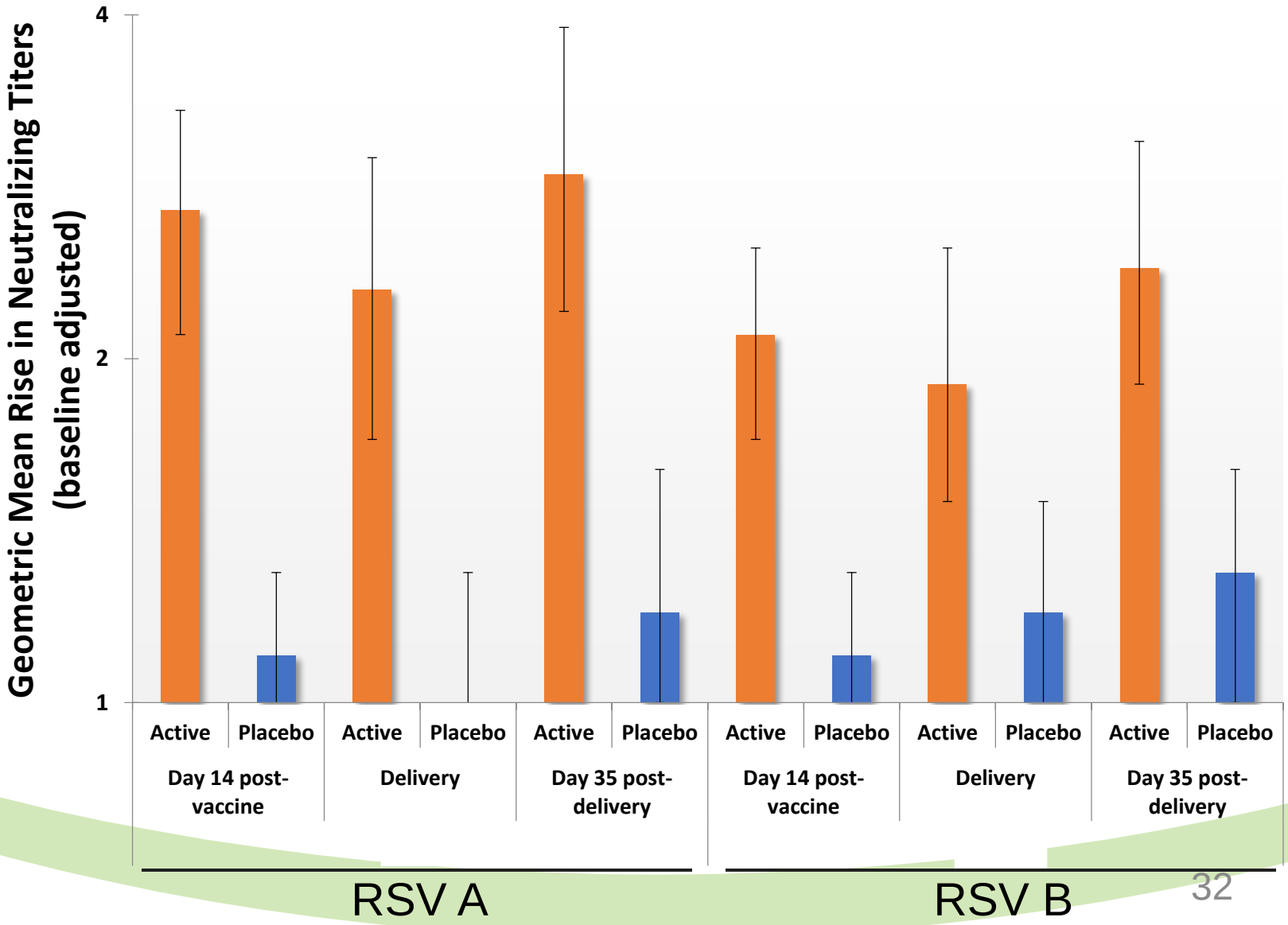
Elicits **palivizumab competing antibodies** (**PCA**)

Palivizumab levels correlate to protection

First RSV vaccine to demonstrate efficacy in any population

Proof-of-principle in maternal immunization

P2 Maternal participants: RSV A and B Microneutralizing Antibodies



Conclusions

- **Next frontier in vaccinology is targeting vaccination of pregnant women for reducing death from neonatal and early-infancy vaccine-preventable diseases.**
- **Maternal vaccination effective in preventing influenza illness and pertussis in young infants.**
- **Further study of clinical relevance of maternal dTaP interference with immune responses to aP and PCV-CRM$_{197}$.**
- **Studies on maternal vaccination with GBS and RSV candidates underway.**

Vaccination of Pregnant Women: An Evolving Paradigm Shift Aimed at Protection of Young Infants and Improving Birth Outcomes.