Estimating the Full Potential Public Health Benefit of Maternal GBS Vaccination.

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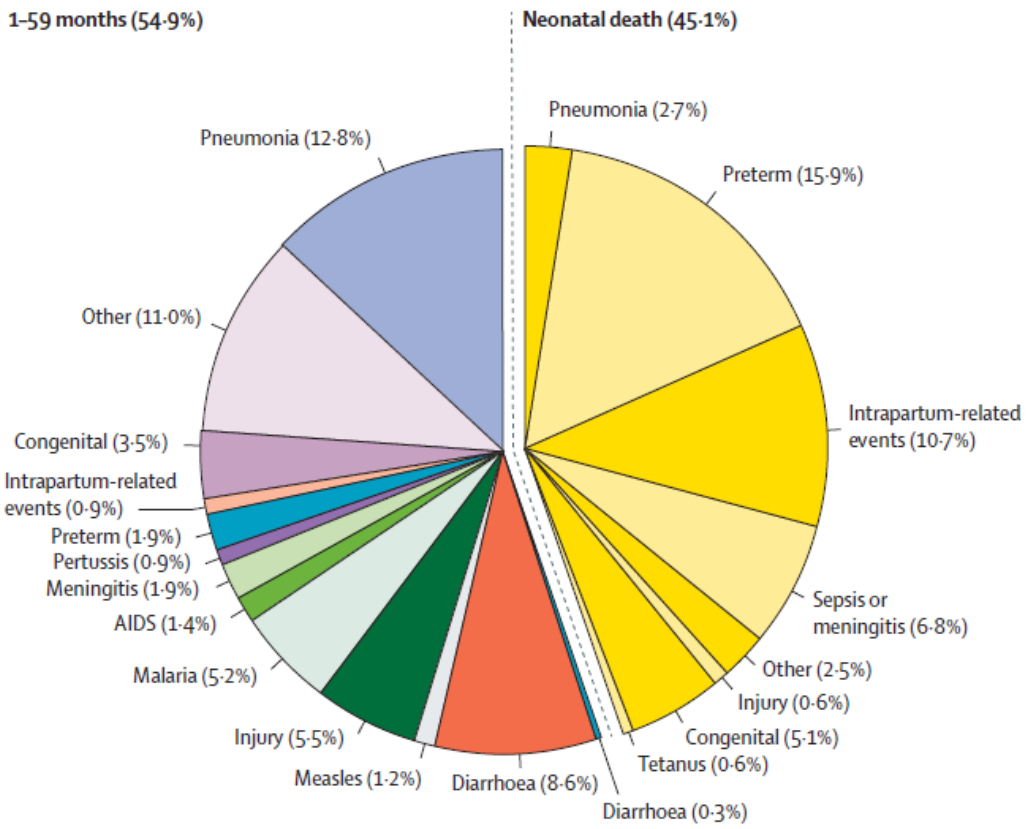
Global under-5 mortality estimates: 2015

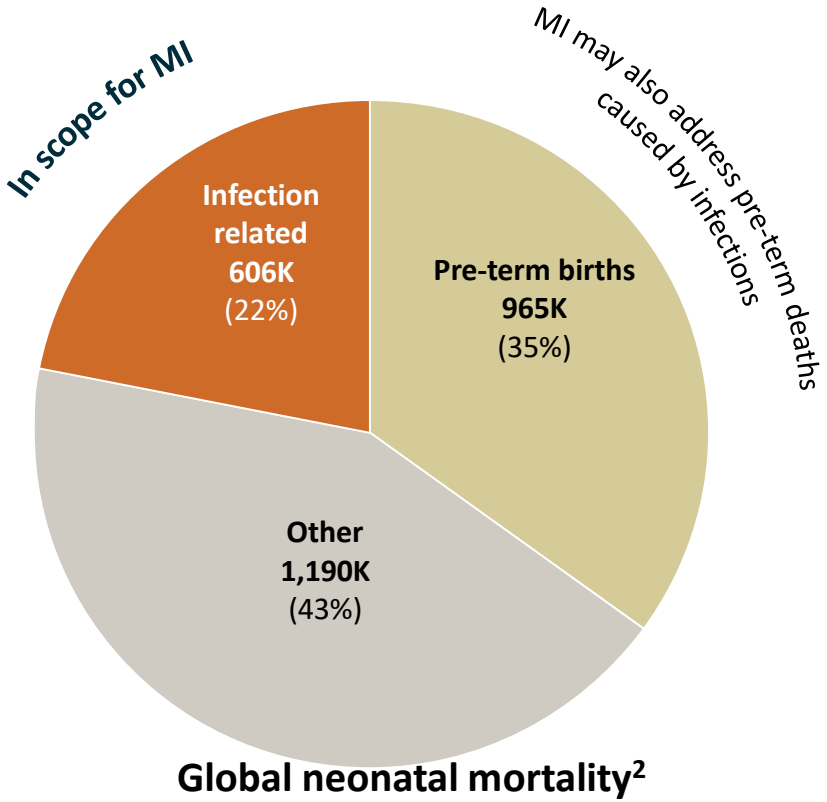
Liu L, *et al. Lancet* 2016



- » 45% (2.7 million) of under-5 deaths occurred in first month of life
- » 22% of neonatal deaths are associated with infections
- » One-third neonatal deaths related to premature birth

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

Value Proposition of Maternal Immunization (MI)



Global neonatal mortality[2]

MI **may protect infants ≤5-mo** against infection-related deaths

MI can have an **impact on maternal morbidity and mortality**

MI may also prevent a portion of **infection-related stillbirths** (10 – 50%[1] of the overall stillbirths)

1. McClure EM, "Stillbirth in Developing Countries: A review of causes, risk factors and prevention strategies" , *J. of Matern Fetal Neonatal Med.* (2014); 2. WHO-CHERG 2013

Overview

- **Defining the burden of vaccine preventable GBS disease in neonates and young infants.**

- **Maternal GBS infection and adverse fetal outcomes (stillbirths and preterm births).**

- **Potential for GBS polysaccharide-protein conjugate vaccines to reduce maternal recto-vaginal colonization.**

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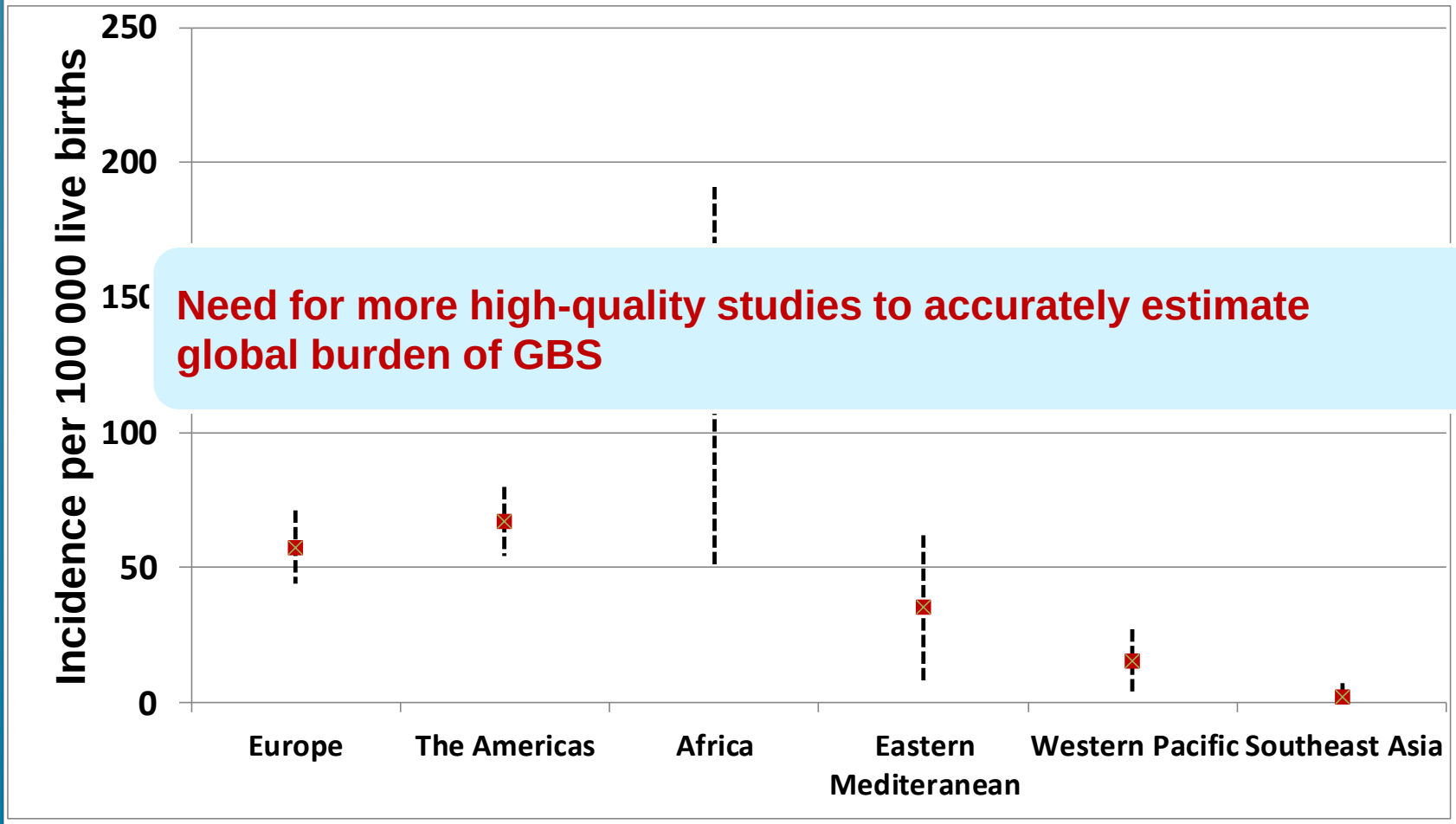
Regional Meta-analysis of Incidence of Invasive GBS Disease, 2000-2011



Need for more high-quality studies to accurately estimate global burden of GBS

CFR: 7%(4-10) 11%(6-16) 22%(12-32) 9% (6-13)

Edmond KM et al. Lancet; 2012; 379: 547-56

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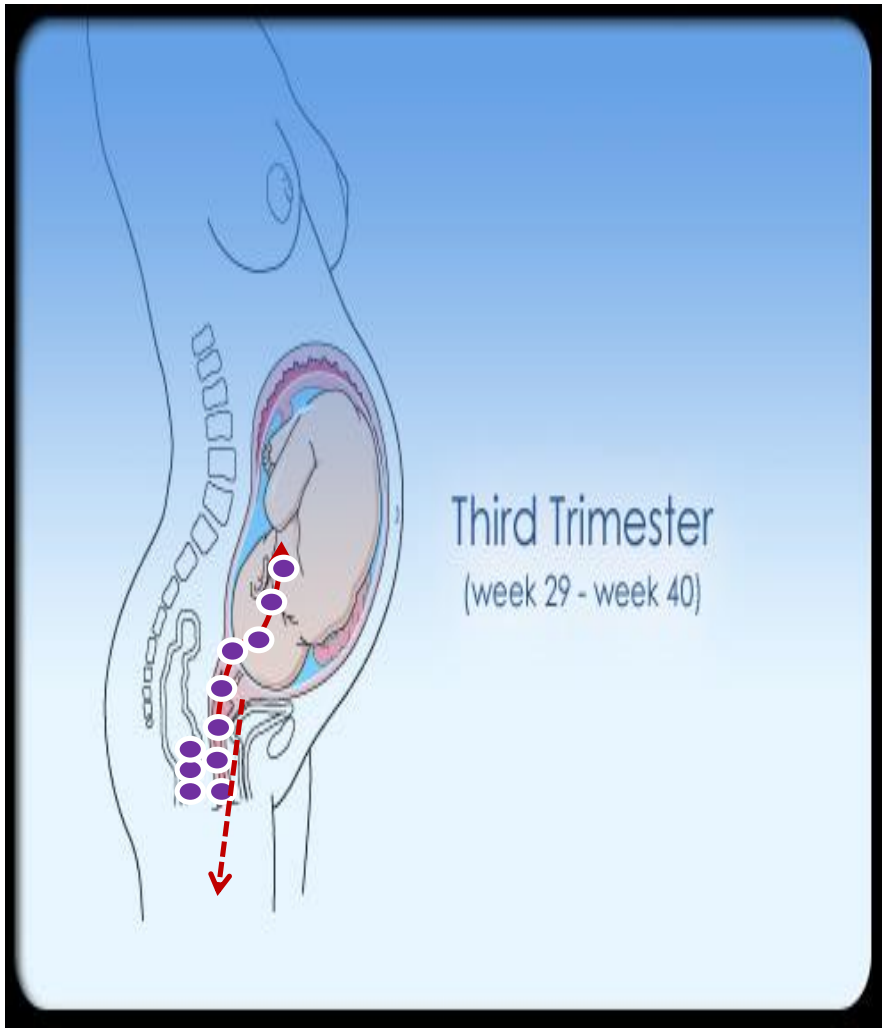
Pathogenesis of Early Onset GBS Invasive Disease (and GBS associated Stillbirths)



Maternal risks factors for EOD:

1. GBS bacteriuria during pr

2. Intrapartum mate

3. Prolonged mbranes (>18 Hou

4. bor and birth.

5. ous sibling with invasive GBS ase.

Recto-vaginal GBS colonization at time of delivery.

Images adapted from: http://www.medicinenet.com/stages_of_pregnancy_pictures_slideshow/article.htm

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Mother to Infant Transmission of GBS and Risk for Early Onset Invasive Disease (In absence of IAP)

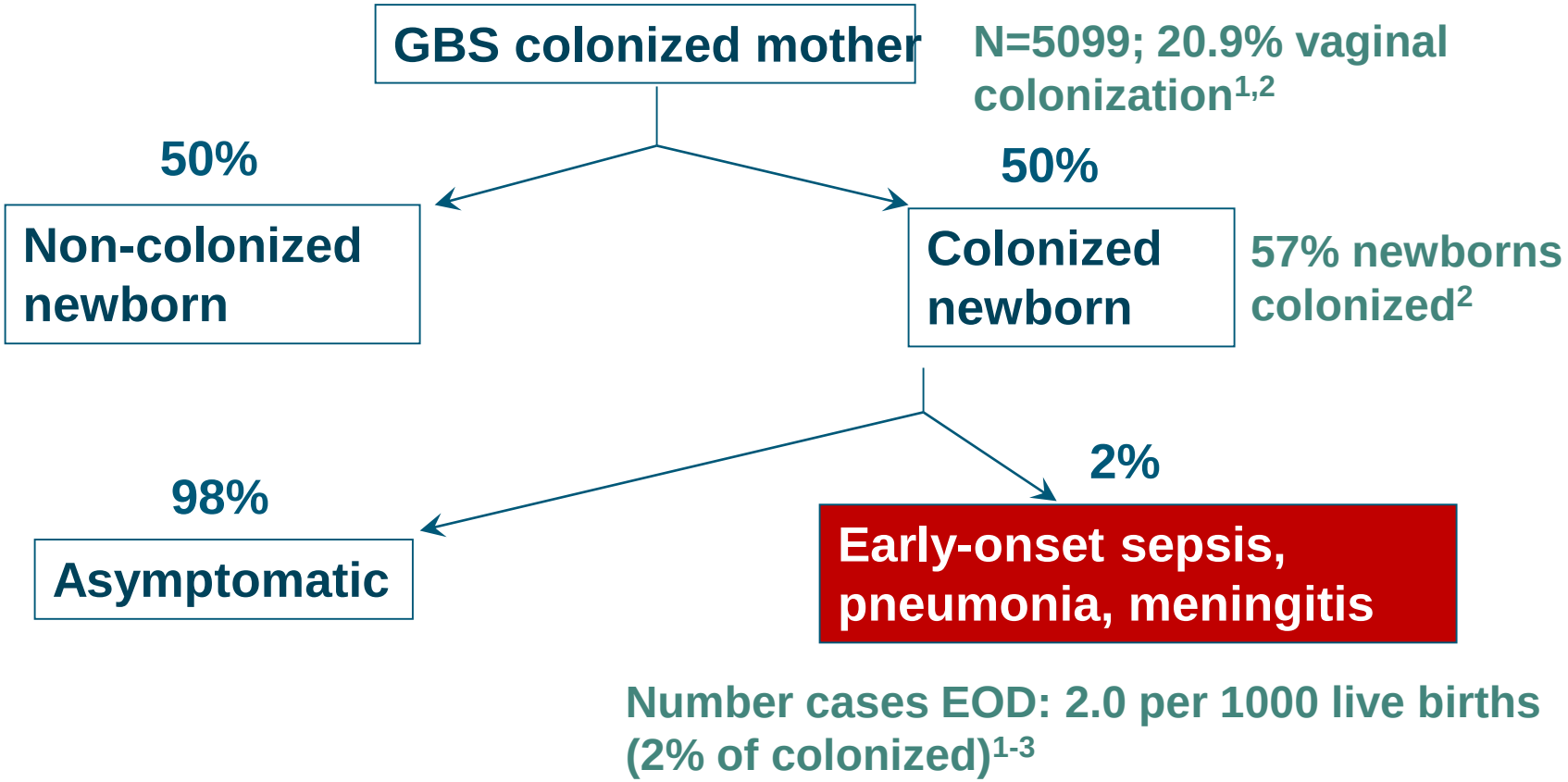

Diagram source: http://www.cdc.gov/groupbstrep/clinicians/neonatal-providers.html#slidesets

Cutland C et al. Lancet 2009; 374:1909-16; Cutland C et al. Pediatrics 2012; 130:e581-90; Madhi SA et al. Vaccine; 2013: ; 315: D52-57

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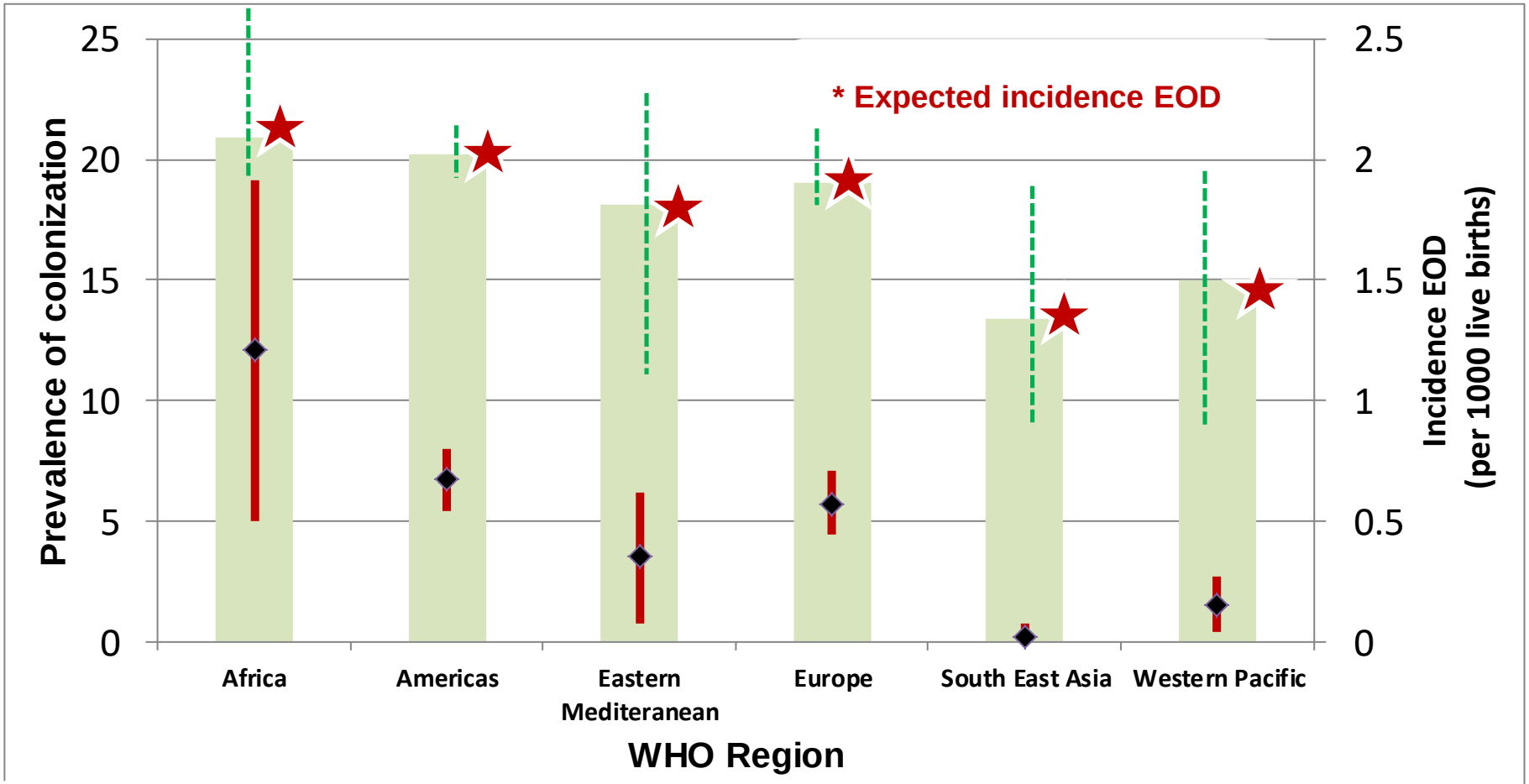
Prevalence of Maternal GBS Colonization at Birth and Observed Incidence of GBS Invasive Disease within 7 days of Birth, WHO Regions.



Expected incidence EOD= %Colonization x 50% x 2%

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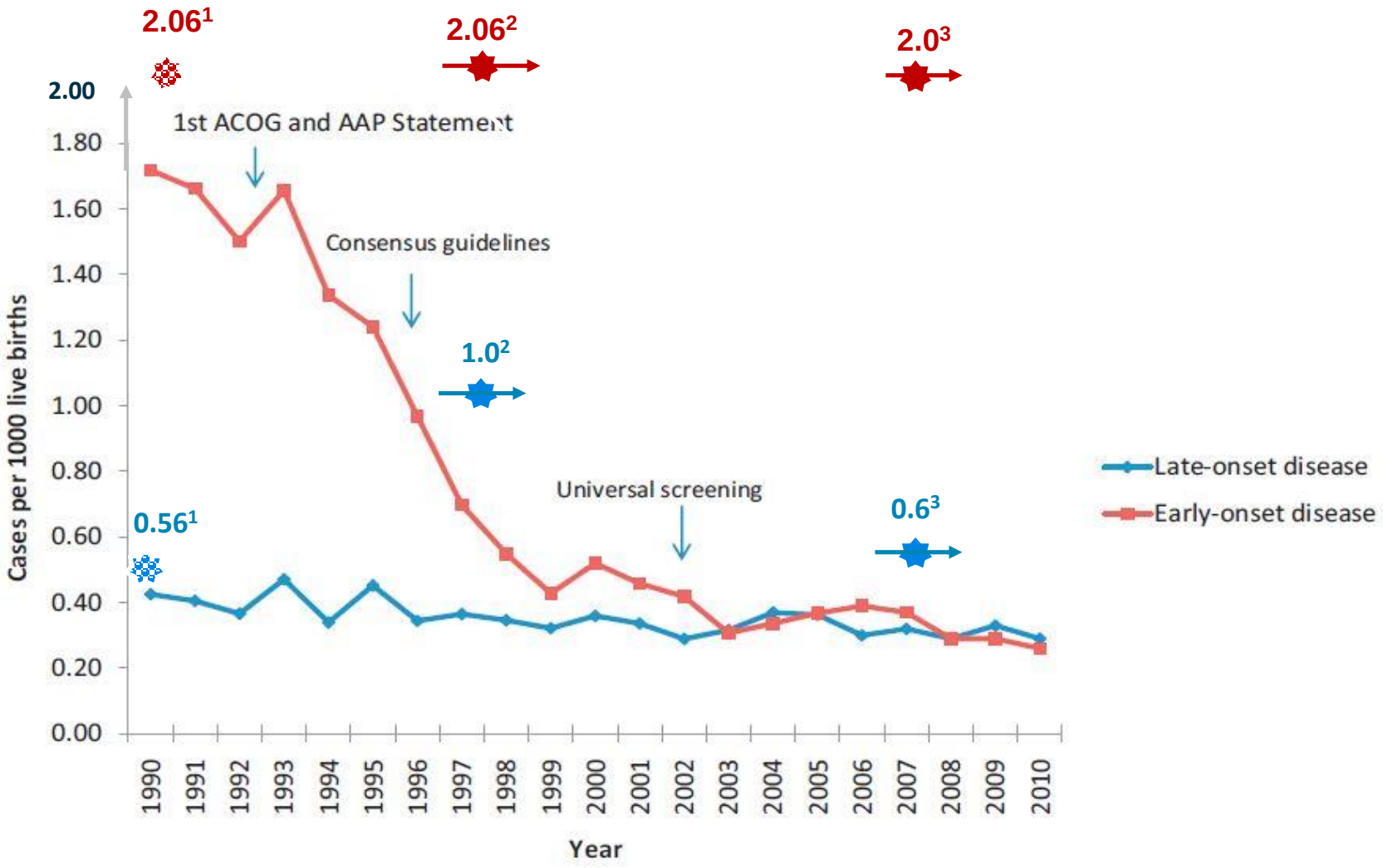
Invasive Group B Streptococcal Disease in USA and South Africa.



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

Possible reasons for difference between expected and observed incidence rates of early-onset invasive GBS disease

- Screening for GBS colonization 34-37 weeks GA, coupled with intra-partum or risk-based antibiotic prophylaxis.
- Differences in serotype (including strain virulence) associated with colonization and invasive potential between regions.
- Ethnic/genetic/host/enviromental differences in susceptibility to colonization and/or invasive disease.
- Differences in maternal anti-capsular antibody levels and transplacental transfer to their newborns.
- Biases in case detection, due to differences in health care access.

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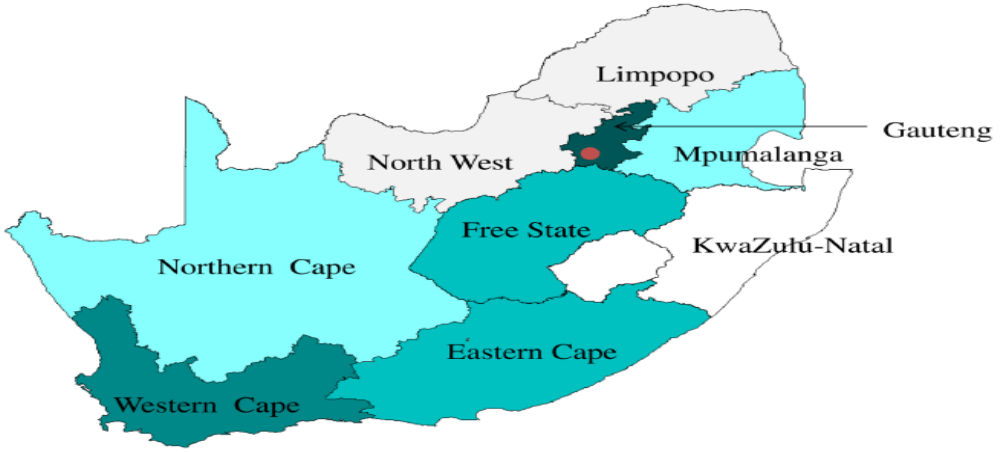
Passive Laboratory-based Surveillance: Variability in Incidence of Invasive GBS Disease in South Africa.



- Differences in threshold for investigating for sepsis.
- Imbalance across country of births occurring in midwife-operated units vs. hospitals with laboratory facilities.
- Empiric antibiotic treatment before referral to hospital in distressed newborn.
- Home based versus facility based births, and resultant deaths prior to hospital evaluation.

Quan V et al PLoSOne Apr. 2016

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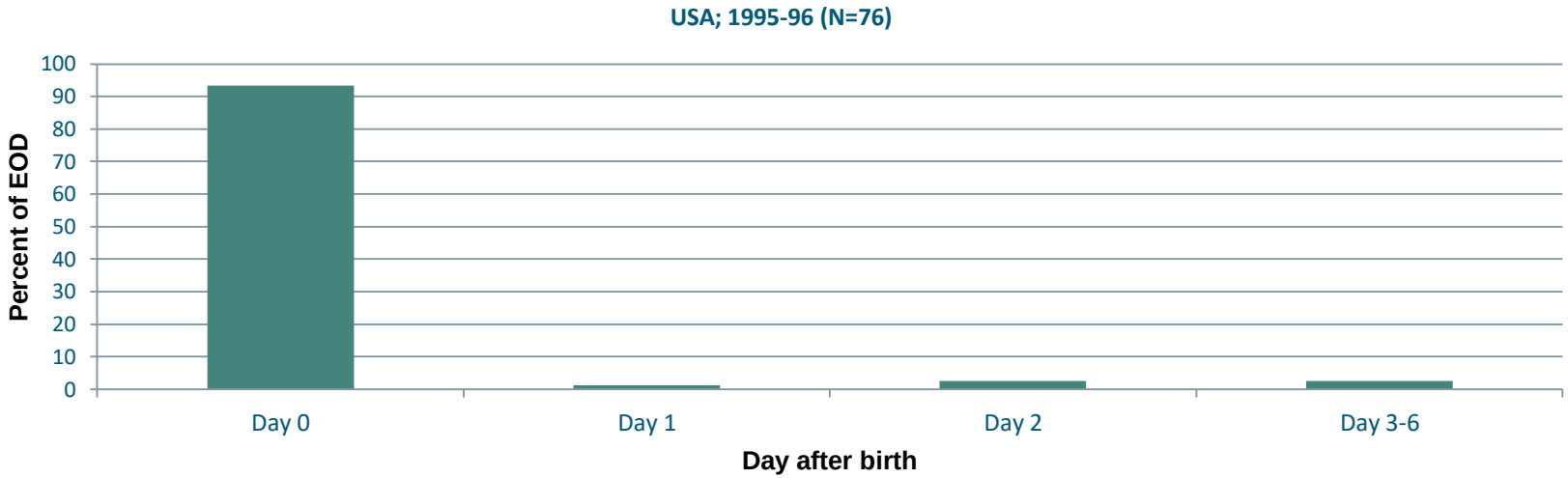
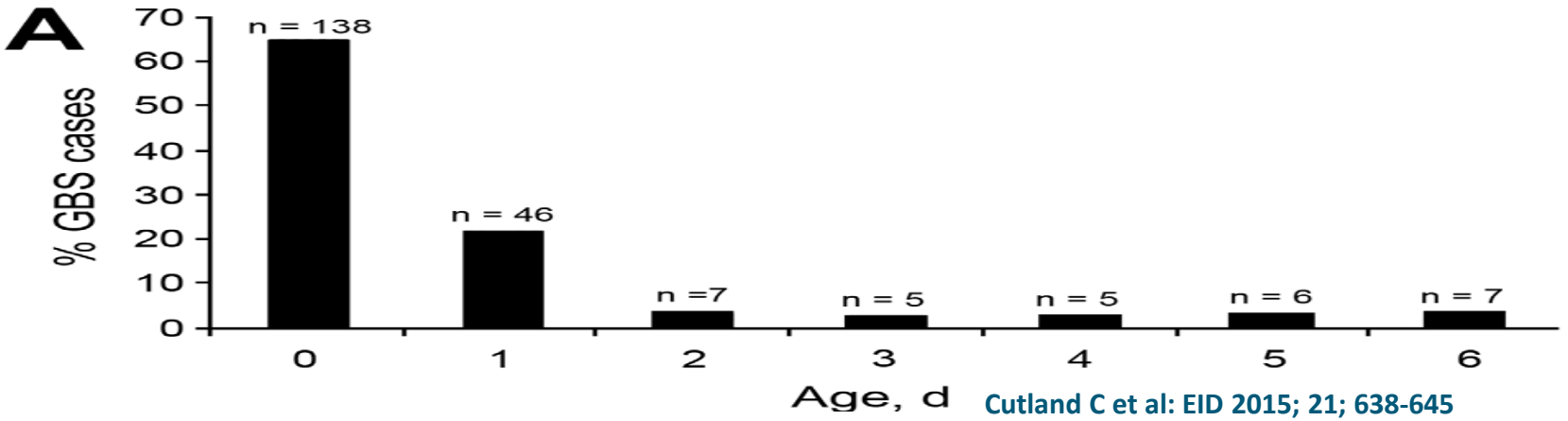
Age Distribution of Young Infants With Invasive GBS Disease.



Schuchat A. Pediatrics 2000: 105:21-6



Cutland C et al: EID 2015; 21; 638-645

- 95.5% EOD in South Africa (2012-2014) culture at <24 hours age

  Dangor Z et al: PlosOne 2015; 10, e0123014

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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 proportion	Estimated annual deaths nationally
Influenza virus[1]	412 (325-515)	4/54 (4.5%)	190
RSV[1]	3,282 (3,028-3,553)	10/841 (1.2%)	390
Pertussis[1]	202 (152- 266)	2/40 (5%)	120
Group B streptococcus[2]	272 (262-281) (?>x2-3)	16/372 (17%)	550 (?>x2-3)

[1]SARI and Pertussis surevillance database- Unpublished.
[2]Cutland C/Madhi SA et al Emerg Infect Dis. 2015

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Overview

- Defining the burden of vaccine preventable GBS disease in neonates and young infants.
- Maternal GBS infection and adverse fetal outcomes (stillbirths and preterm births).
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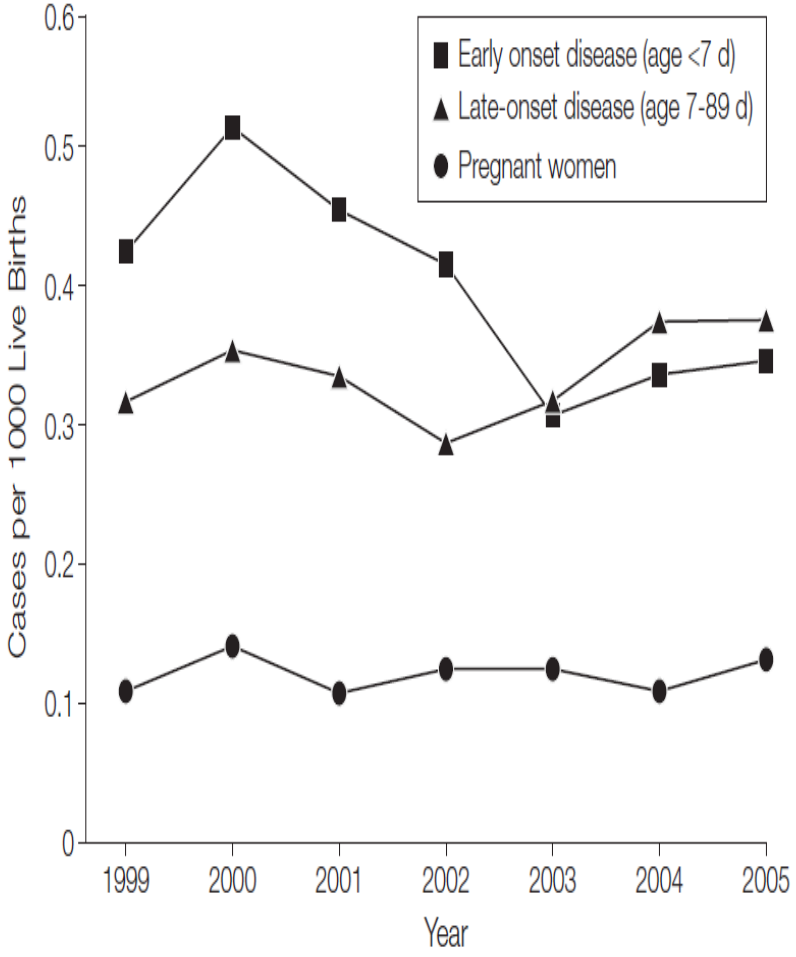
Invasive GBS Disease in Pregnant Women



Pregnancy outcome in women with invasive GBS disease

- 61% spontaneous miscarriage/stillbirth
- 5% infant with clinical infection
- 4% induced abortion
- 30% health infant

Phares CR; JAMA 2008; 299: 2056-2065

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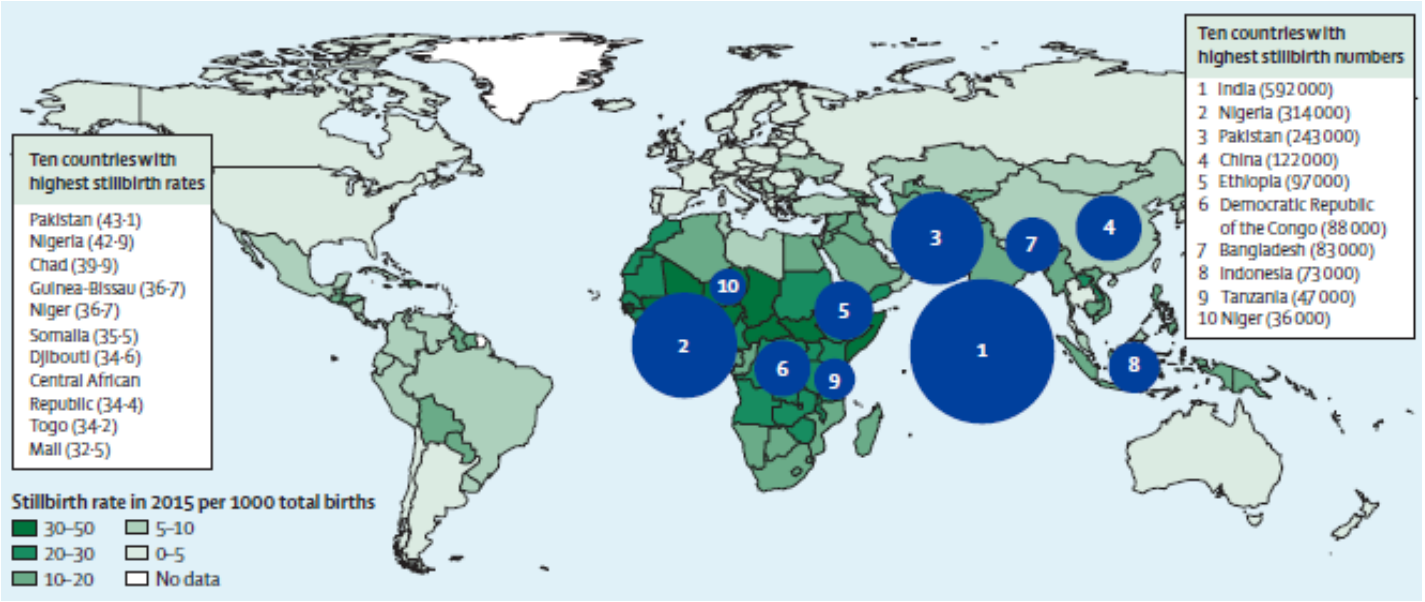
Estimated Country-level Stillbirth Rates, 2015.



	2000		2015		Annual rate of reduction in stillbirth rate 2000–15
	Stillbirth rate per 1000 total births (uncertainty range)	Number of stillbirths (uncertainty range)	Stillbirth rate per 1000 total births (uncertainty range)	Number of stillbirths (uncertainty range)	
Developed region	4·5 (4·4–4·6)	59 000 (58 000–61 000)	3·4 (3·4–3·5)	47 000 (46 000–48 000)	1·8
Southern Asia	35·5 (31·3–41·2)	1 443 000 (1 266 000–1 684 000)	25·5 (22·5–29·1)	967 000 (847 000–1 104 000)	2·2
Caucasus and Central Asia	16·8 (13·9–23·6)	23 000 (19 000–33 000)	11·9 (9·8–15·6)	23 000 (19 000–31 000)	2·3
Eastern Asia	14·3 (10·6–19·6)	240 000 (177 000–331 000)	7·2 (5·6–9·7)	129 000 (100 000–175 000)	4·5
Latin America	11·3 (10·3–12·8)	135 000 (123 000–153 000)	8·2 (7·5–9·2)	91 000 (83 000–103 000)	2·1
North Africa and Middle East	19·9 (17·7–23·6)	156 000 (139 000–185 000)	14·5 (12·9–17·5)	148 000 (131 000–180 000)	2·1
Southeastern Asia	17·0 (14·6–21·5)	194 000 (166 000–246 000)	12·2 (10·7–14·6)	155 000 (135 000–186 000)	2·2
Sub-Saharan Africa	35·6 (31·4–42·2)	1 000 000 (879 000–1 194 000)	28·7 (25·1–34·2)	1 060 000 (923 000–1 271 000)	1·4
Worldwide	24·7 (22·4–28·4)	3 250 000 (2 931 000–3 740 000)	18·4 (16·6–21·0)	2 620 000 (2 359 000–2 984 000)	2·0

See appendix p 3 for details.

Blencowe et al. Lancet Global Health; 2016; 4: e98-108.

Systematic Review on Contribution of GBS to All-cause Stillbirths.

Author (year) (reference)	Study period	Proportion of stillbirth		Proportion GBS-related stillbirth		Among infection-related stillbirth (%)
		In cohort (per 1000 births)	National rate in study period (per 1000 births) **	In total cohort (per 1000 births)	Among stillbirths (%)	
Sweden						
Bergqvist et al. (1978)[22]	1970 - 1975	117/17638 (6.0)	7.2 – 5.9[a]	5/17638 (0.3)	5/117 (4.3)	5/24 (20.8)
Berg et al. (1977)[21]	1971 - 1974	n/a	7.2 – 6.7[a]	2/10422 (0.2)	n/a	2/21 (9.5)
Christensen (1982)[24]	1979 - 1980	20/4130 (5.0)	4.4 – 4.3	1/4130 (0.2)	1/20 (5.0)	1/2 (50.0)
Tolockiene et al. (2001)[35]	1985 - 1994	n/a	3.6 – 3.2	n/a	2/117 (1.7)	2/32 (6.3)
Ahlenius et al. (1995)[19]	1987 - 1989	66/10707 (6.0)	3.8 – 3.7	2/10707 (0.2)	2/66 (3.0)	2/8 (25.0)
Lithuania						
M						
B						
B						
I						
M						
United States						
Hood et al. (1961)[29]	1958 - 1959	n/a	n/a	n/a	11/113 (9.7)	11/66 (16.7)
Singer et al. (1986)[34]	1975 - 1982	620***/38492 (16.0)	7.8[d]	5/38492 (0.1)	5/620 (0.8)	n/a
Katz et al. (1988)[30]	1982 - 1985	n/a	7.8[d]	6/6363 (0.9)	n/a	n/a
Blackwell et al. (2003)[23]	2000 - 2002	n/a	6.6 – 6.4	n/a	1/44 (2.3)	n/a
Canada						
Davies et al. (2001)[25]	1995 - 1999	n/a	n/a	13/262398 (0.05)	n/a[f]	n/a
Zimbabwe						
Moyo et al. (1996)[33]	1989 - 1991	n/a	21.0[e]	n/a	8/66 (12.1)	8/43 (18.6)
Mozambique						
Folgosa et al. (1997)[28]	1990 - 1991	n/a	31.0[e]	n/a	0/58 (0.0)	0/41 (0.0)

*Authors reported # GBS-positive isolates from different sites, we assumed there were 4 individual cases. **Annualized rates in study start and end years. ***Reported number (N=620) is for total autopsies on fetuses and infants.

[a]Data from 1973 onward. [b]Data from 1998 only. [c]Data from 2009 only. [d]Data from 1985 only. [e]Data from 1995 only. [f]Only cases with confirmed GBS were included, therefore not possible to calculate GBS stillbirth rate among stillbirths in study cohort.

- Proportion of stillbirths associated with GBS range from 0 to 12.1%.
- Incidence of GBS-related stillbirths vary from 0.04 to 0.9 per 1,000 births
- Approximately 15% of infection related stillbirths due to GBS.

Nan C et al. B J Obs Gynec; 2015; 122:1437-45.

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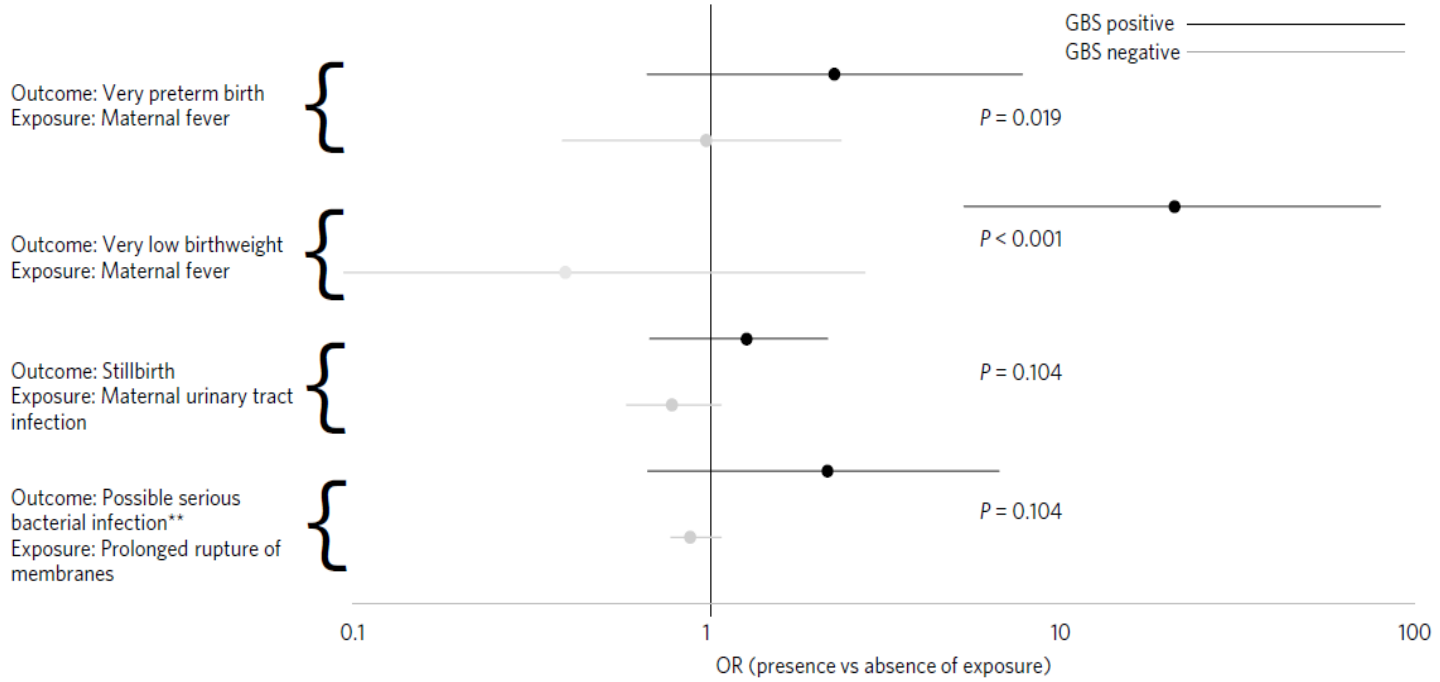
Interaction of Risk Factors at Delivery with Maternal GBS Colonization and Fetal and Neonatal Outcomes



- GBS isolated from 2.2% (95%CI: 0.6-5.5) of stillbirths.
- Incidence GBS associated stillbirths: 0.91 (95%CI: 0.25-2.3) per 1,000 births
- Incidence Invasive GBS Disease : 0.76 (95%CI: 0.25-1.77) per 1000 live births

Sealle A, et al. Nature Micro; 2016; DOI: 10.1038/NMICROBIOL2016.67

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Stillbirth Study Procedures (South Africa)

Type of Sample	Timing of sample	Test on sample
Cord/Heart blood	At delivery/within 12 hours	• Bacterial Culture (Bactec) • RPR/TPHA
Tracheal/Gastric aspirate	Within 12 hours of delivery	• Bacterial Culture
Stillbirth swab (axilla/umbilicus/groin)	At delivery	• Bacterial Culture
Placenta	At delivery	• Microscopy & Bacterial Culture (wedge resection) • Histology

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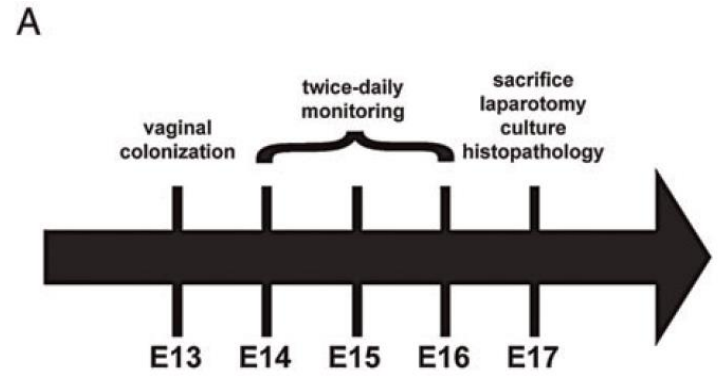
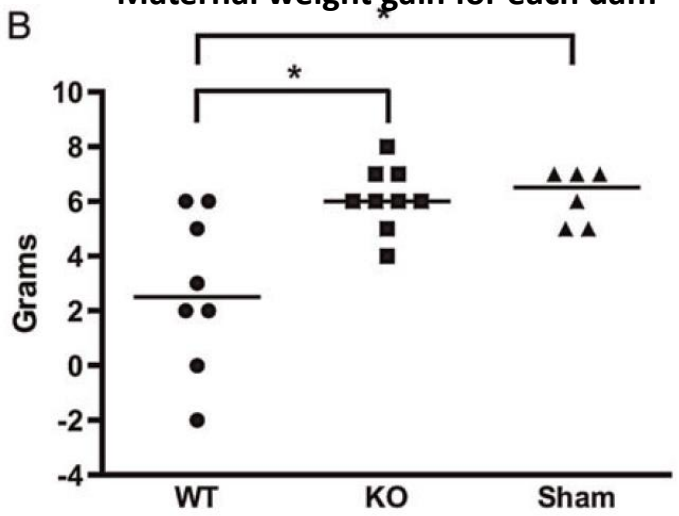
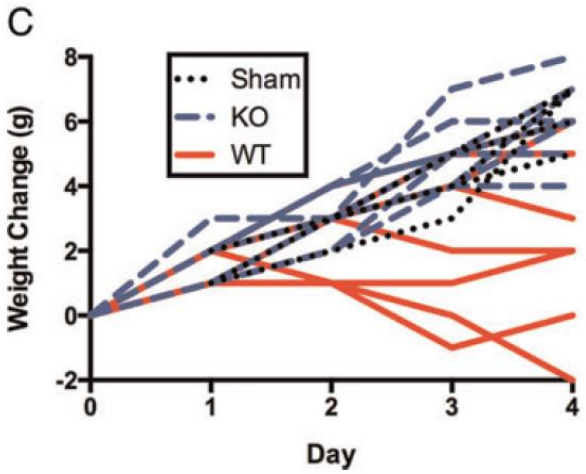
Role of Beta-hemolysin/Cytolosin Expressing GBS Colonising Strains on Preterm and Fetal Loss in Murine Model

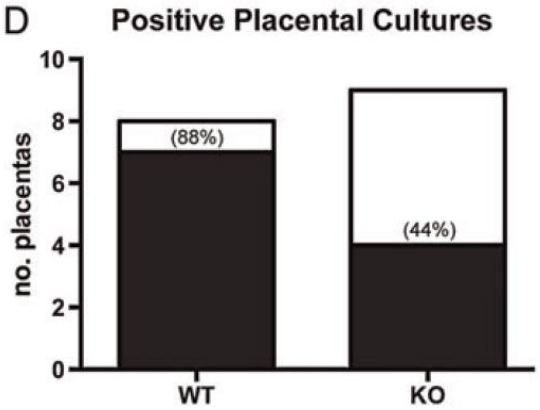


Maternal weight gain for each dam



Maternal weight gain following colonization





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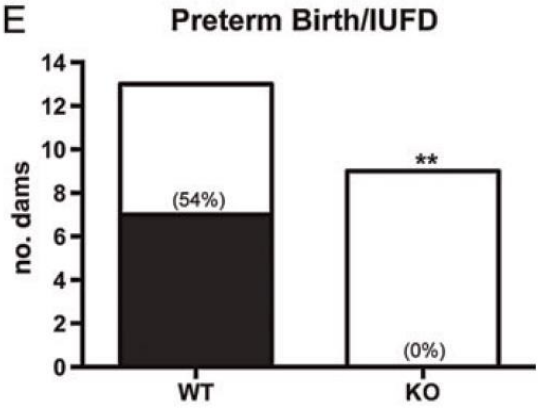

P=0.01

Randis TM et al. J Infect Dis; 2014

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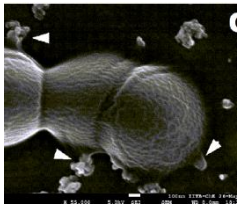
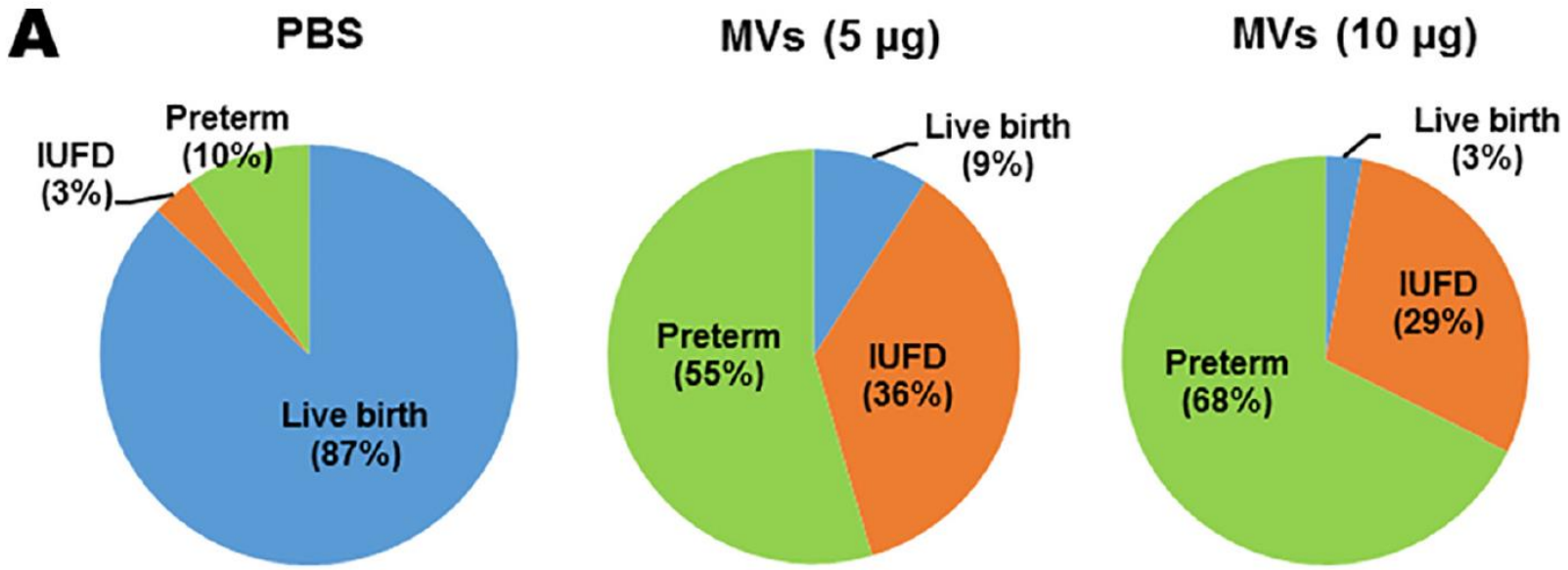
Intra-amniotic Injection of GBS Membrane Vesicles (MV) Cause Preterm and Fetal Death in Mice



- GBS produce MV containing extracellular matrix degrading proteases and pore forming toxins in a serotype independent manner.
- *Ex vivo,* MV cause collagen degradation of chorio-decidual membrane
- MV capable of anterograde transport in reproductive tract; up-regulation of pro-inflammatory cytokines and inflammation of placenta mimicking chorioamniotis and apoptosis of chorio-decidual membrane.



Surve MC et al. PLoSPathogens; 2016; e1005816

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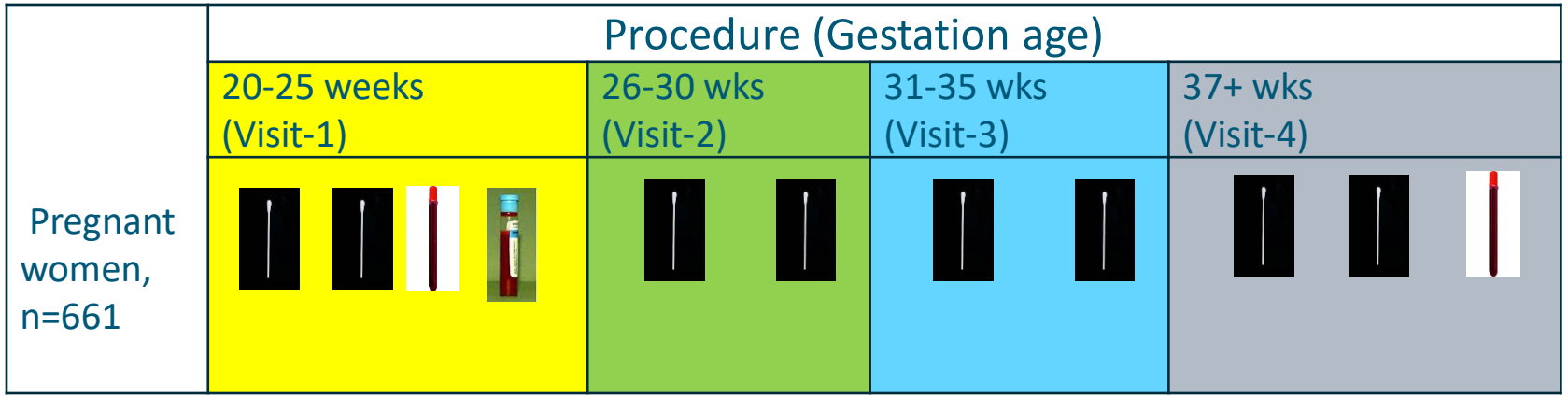
Longitudinal Cohort Study on Association of Humoral and Cellular Immunity on Dynamics of GBS Colonization during Pregnancy



Vaginal and rectal swab

Clotted blood
- Capsular antibody (Ia, Ib, III, V)
- OPA (Ia, III)

Heparinized blood
- CMI

1. Serum: Serotype Ia, III and V capsular IgG antibody (Luminex assay) and OPA for serotypes Ia and III
2. Heparinised blood: Capsular specific Elispot assays (interferon gamma) for GBS serotype Ia, III and V.
3. Vaginal and Rectal swabs was used to detect GBS colonization.

Kwatra et al Clin Micro Infect; April 2015; Kwatra G et al. J Infect Dis; 2016

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Dynamics of GBS colonization Between 20 weeks to 37+ Weeks of Gestational Age.

- Prevalence GBS colonization at 20-25 wks, 26-30 wk, 31-35 wk and 37+ wk gestational age were 33.0% , 32.7%, 28.7% and 28.4%, respectively.

- Of 507, who completed all visits, 50% (252) colonized at least once.
  - 28% (70/252) “persistently colonized” (i.e. from V1 to V4)
  - 39% (99/252) “cleared colonization”

Kwatra G et al. PlosOne; 2014, 9(6): e98778

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Higher capsular specific OPA GMTs associated with lower likelihood of serotype-specific recto-vaginal GBS Acquisition During Pregnancy.

Serotype	New-acquisition	Non-colonized	p-value [a]
IgG	GMC (95% CI)	GMC (95% CI)	
Ia	0.28 (0.17, 0.47); n=52	0.35 (0.27, 0.44); n=387	0.529
III	0.17 (0.11, 0.26); n=39	0.33 (0.28, 0.38); n=414	0.009
V	0.42 (0.26, 0.65); n=17	0.75 (0.66, 0.84); n=471	0.057
OPA	GMT[g] (95% CI)	GMT (95% CI)	
Ia	5 (4, 6); n=52	14 (11, 17); n=387	<0.001
III	20 (11, 36); n=39	132 (105, 164); n=414	<0.001

- Capsular antibody threshold ≥5 ug/ml for ST-Ia (aOR:0.37) and ≥3 ug/ml for ST-III (aOR: 0.11) associated with lower odds of acquisition of homotypic serotype.
- Serotype specific OPA titers ≥8 associated lower odds of serotype Ia (aOR 0.29) and III (aOR: 0.33) acquisition; with even lower odds at higher OPA titers (≥1:32: aOR 0.05 [Ia] and 0.23 [III]).

Neither serotype-specific antibody or OPA associated with clearance of existing colonization.

Kwatra G et al Clin Micro Infect; April 2015

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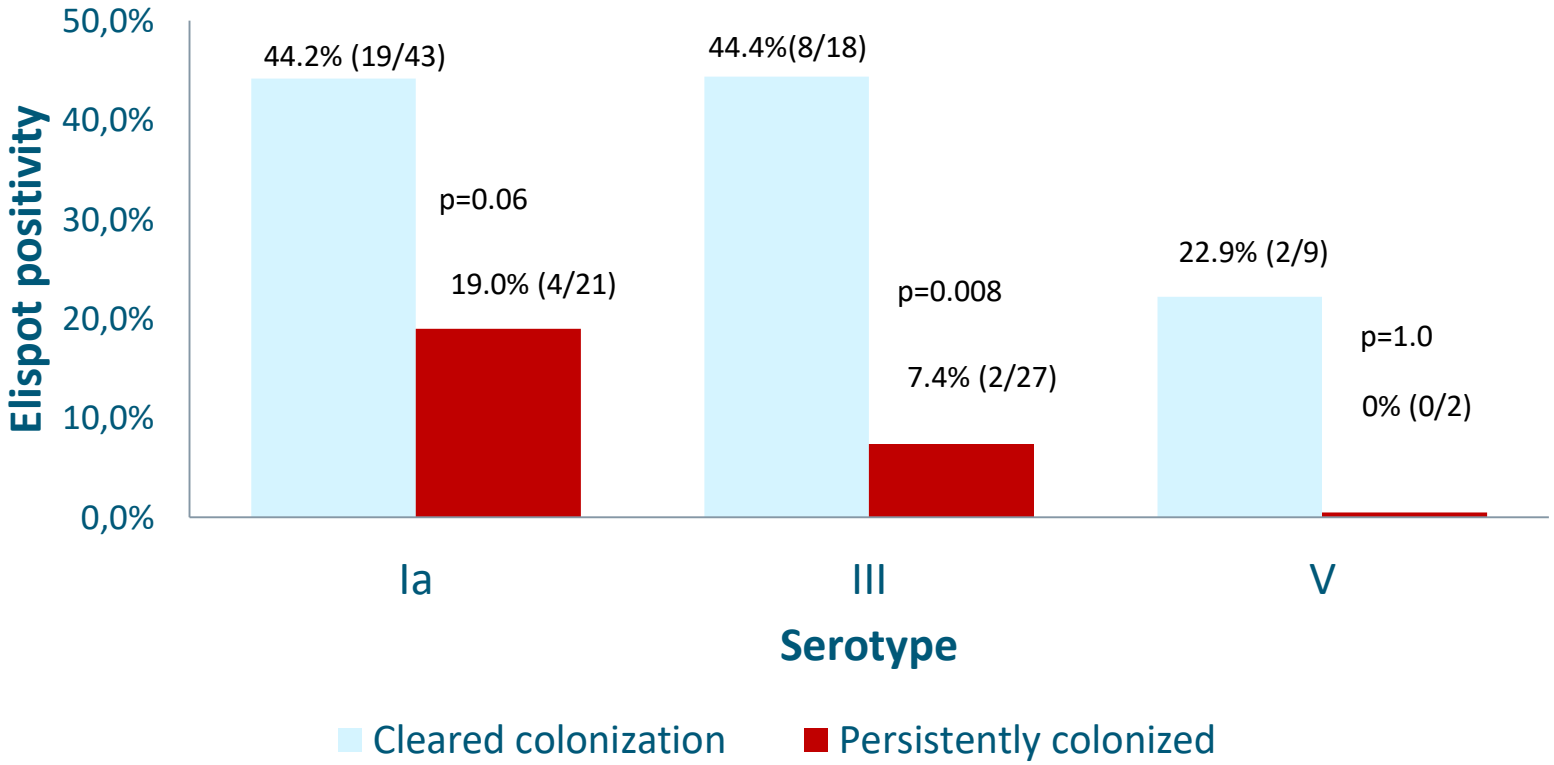
Clearance of GBS colonization and Cellular Immunity

Presence of serotype-specific cellular immunity associated partially with clearance of existing colonization but did not reduce risk of GBS acquisition.



An ELISpot response was considered as positive if the number of antigen-specific spots was ≥7 SFU/10^6 PBMC and at least double the number of spots in the negative control well.

Kwatra G et al. J Infect Dis; 2016 ; 213: 1923-6

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Investigational GBS-TT vaccine Protects Against GBS Colonization in non-pregnant US Women

- GBS-TT serotype III, DBRCT: 650 USA non-pregnant women
- GBS-TT vaccination associated with longer time to acquire first serotype III GBS-positive swab (vaginal colonization efficacy 36% (p=0.044) and rectum 43% (p=0.015).
- Greater proportion of women in GBS vaccine group had persistently negative cultures (p=0.046).

Hiller et al; 47th IDSA Annual Meeting, Oct 2009; Abstract: 186

VPD Vaccine Preventable Diseases
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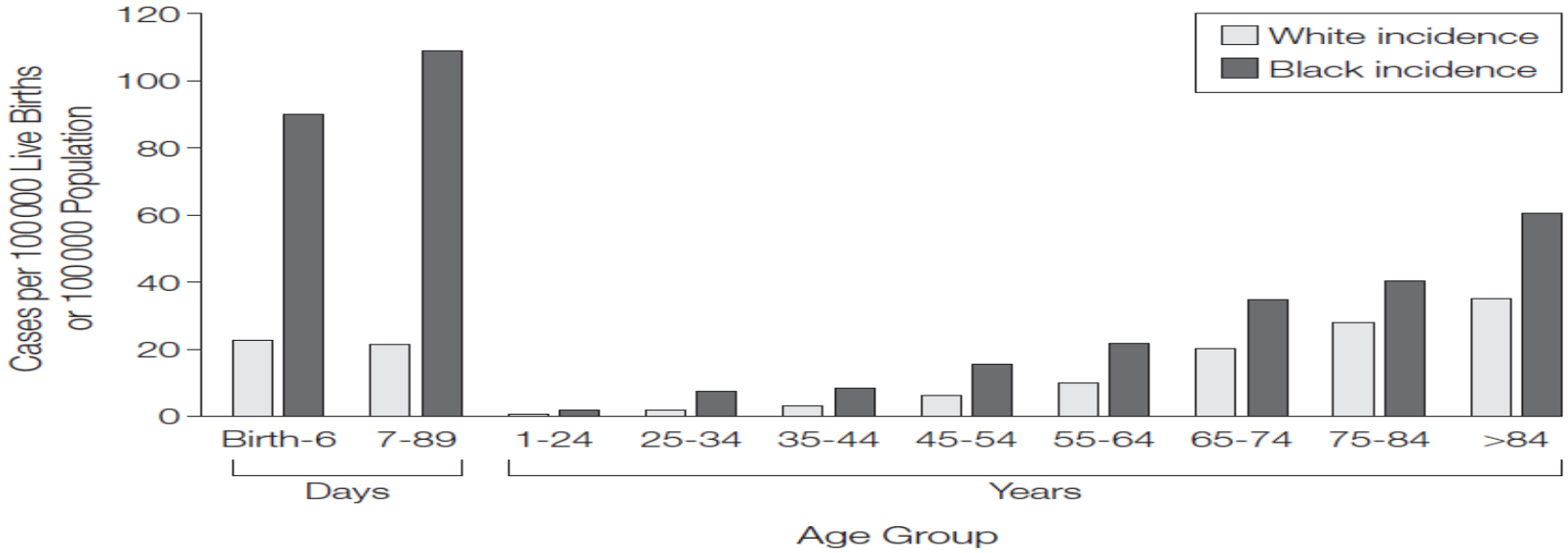
Incidence of Invasive GBS Disease and Estimated Deaths in USA, 2005.



	Age Group					
	Birth-6 d	7-89 d	1-14 y	15-64 y[a]	≥65 y	Total
Estimated incidence and projected counts for United States, 2005[e]						
Incidence	0.35/1000 live births	0.33/1000 live births	0.22/100 000 population	4.6/100 000 population	25.3/100 000 population	7.2/100 000 population
No. of cases	1425	1375	124	9207	9308	21 439
No. of deaths[c]	63	46	8	557	1067	1741

Phares CR; JAMA 2008; 299: 2056-2065

Discussion

- Challenges in characterizing burden of invasive GBS disease in LMIC.
- Culture-confirmed invasive GBS disease likely under-estimate the contribution of GBS to early-infancy morbidity and mortality.
- Maternal GBS colonisation associated with poor fetal outcome- including inducing preterm birth and stillbirths, which might exceed burden of invasive disease in neonates.
- GBS polysaccharide-protein conjugate vaccine has potential to reduce GBS recto-vaginal colonization in pregnant women.
- Vaccine-probe study likely to best characterize burden of GBS disease among women, effect on fetal outcomes and contribution to neonatal sepsis.

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