

Early Onset Neonatal Sepsis In Developing Countries: Listeria Hysteria And More

Lizel G Lloyd

Neonatologist

Tygerberg Hospital, Stellenbosch University

Cape Town, South Africa



DECLARATION OF INTERESTS

- Nothing to declare

Antibiotic overuse and infections caused by antibiotic resistant pathogens is a worldwide problem that threatens the achievements of modern medicine

WHO REPORT 2014

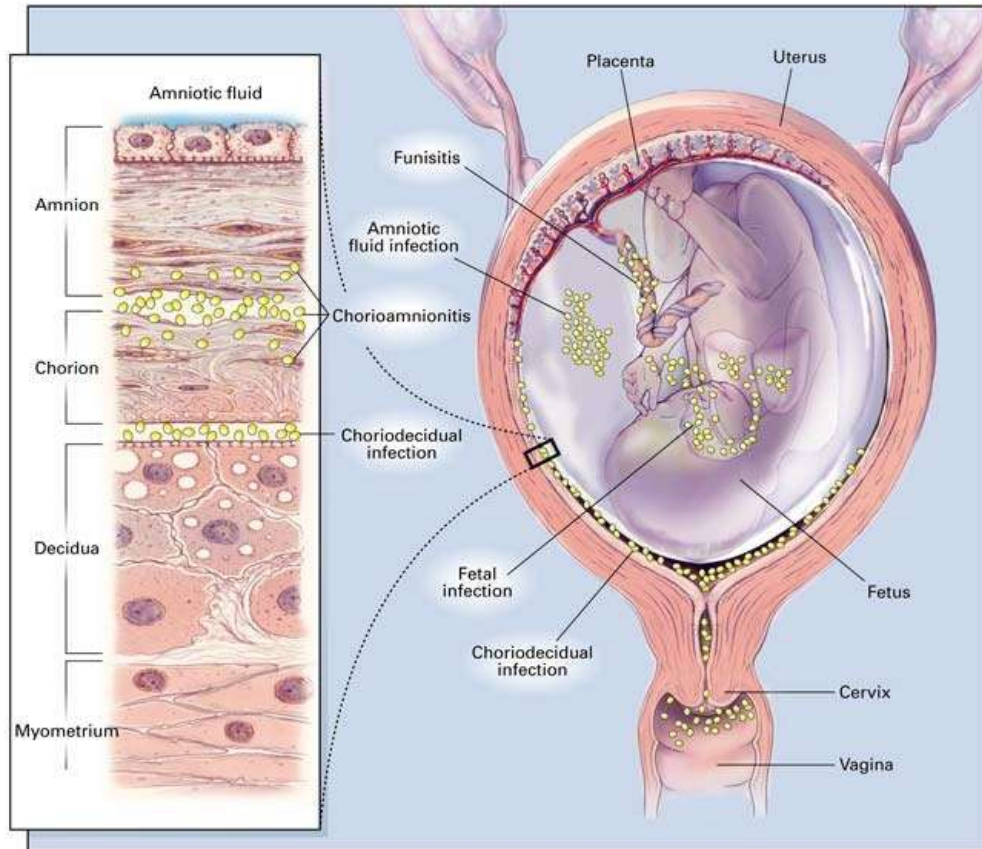


OUTLINE

1. Defining early onset neonatal sepsis (EOS)
2. Incidence
3. Etiology
4. Prevention
5. Identifying at risk patients
6. Diagnosis
7. Antibiotics
8. Outcomes

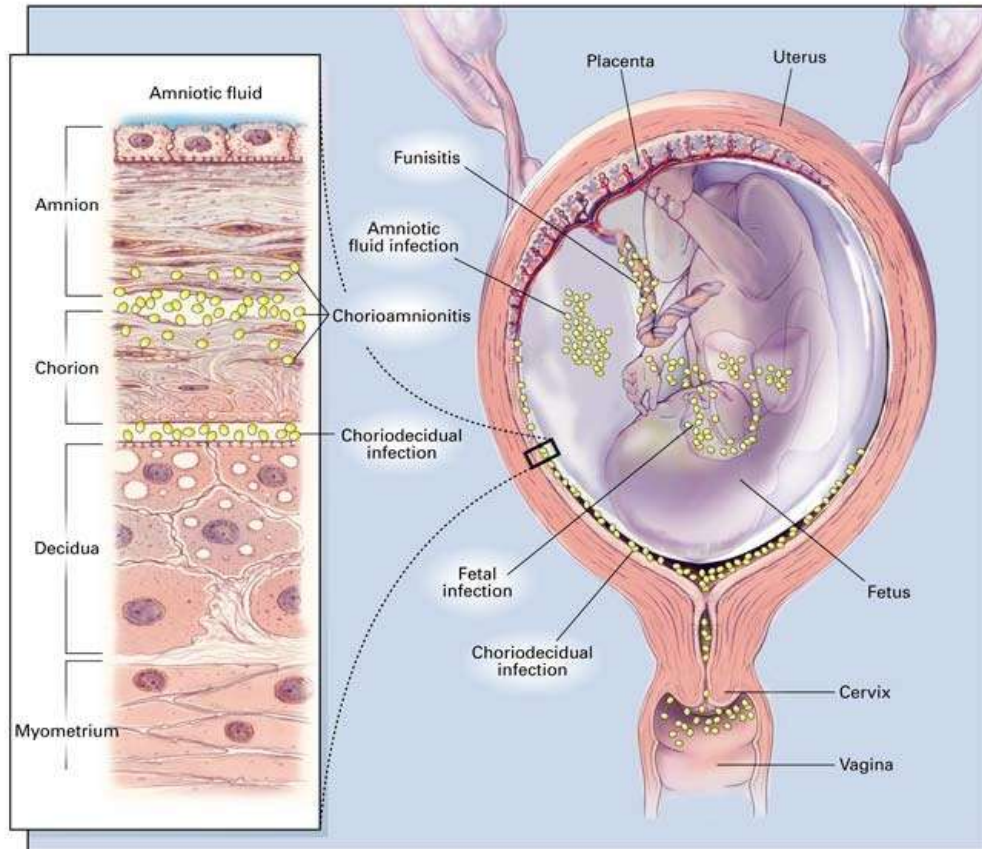
1. DEFINING EOS

- MODE



1. DEFINING EOS: LACK OF CONSENSUS

- MODE



- AGE LIMIT

<48 hours



neonIN
Surveillance
network

<72 hours

NICE
National Institute for
Health and Care Excellence

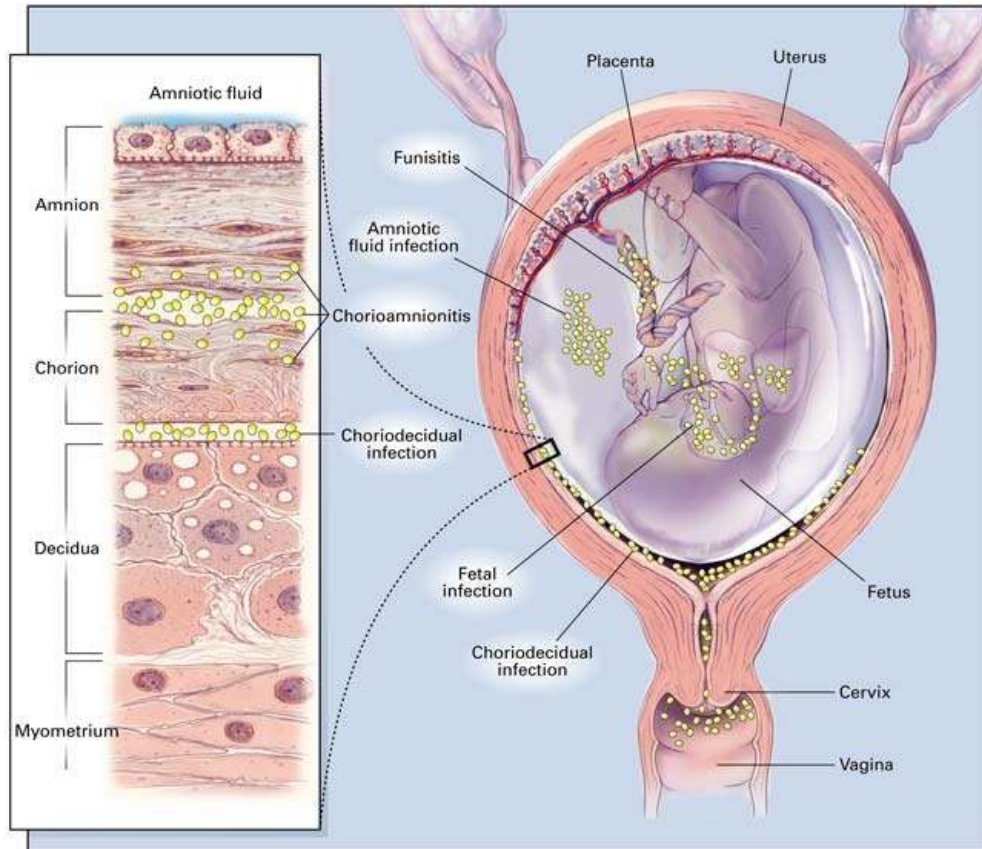
NIH
NICHD

<7 days



1. DEFINING EOS: LACK OF CONSENSUS

- MODE



- AGE LIMIT or not?

LMIC: Community acquired infection

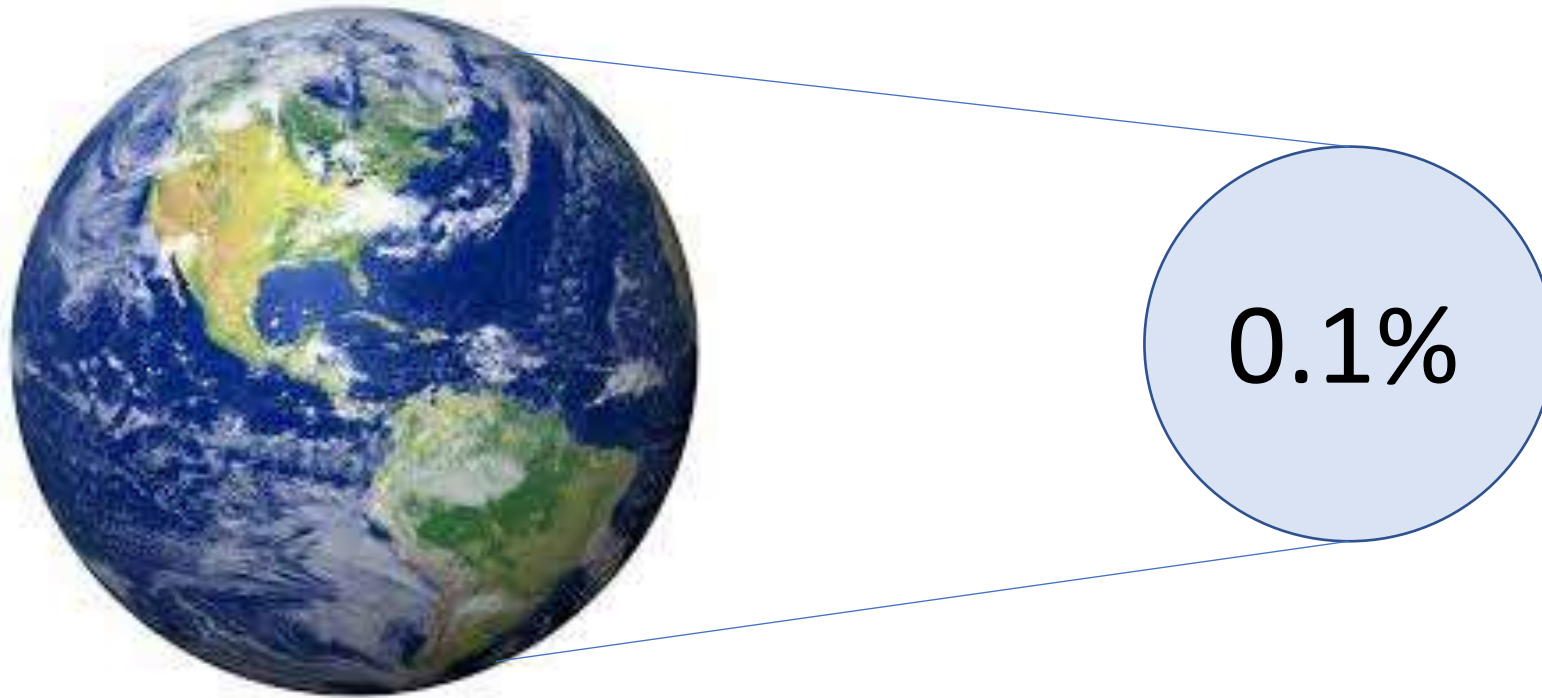
**HIC:
<72 hours - VLBW**



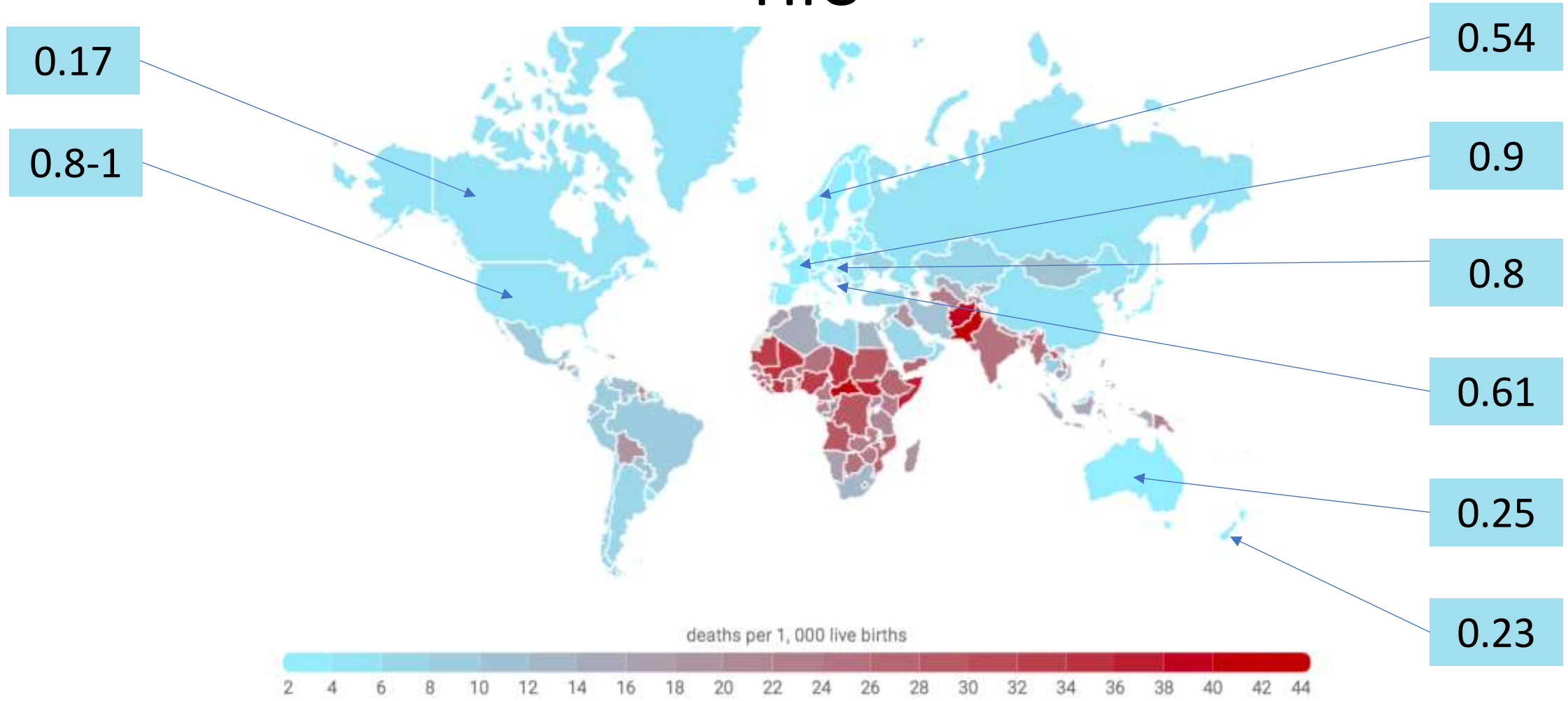
<7 days- Term



2. GEOGRAPHY OF INCIDENCE



EOS rates per 1000 live births superimposed on NNMR: HIC

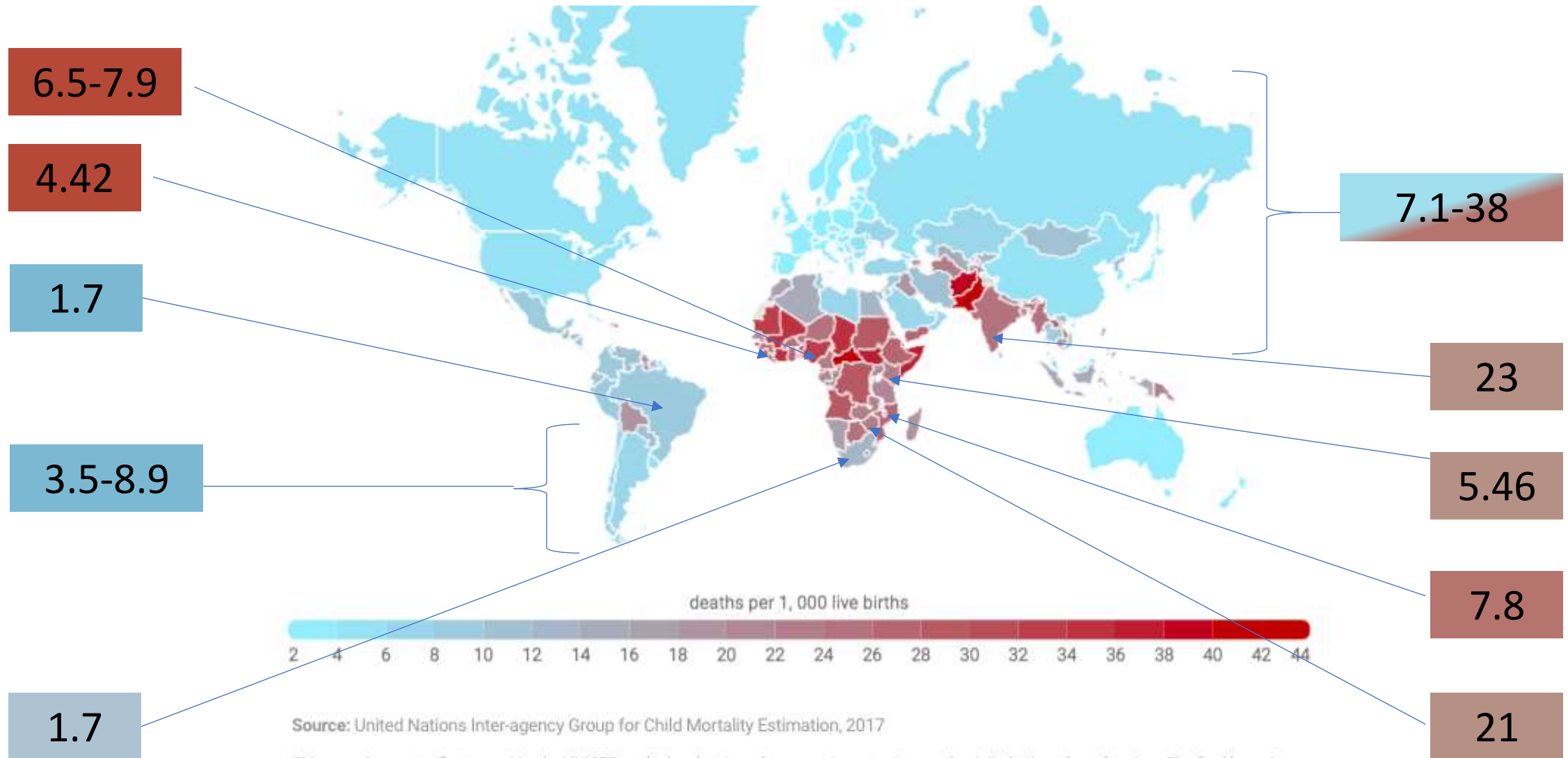


Source: United Nations Inter-agency Group for Child Mortality Estimation, 2017

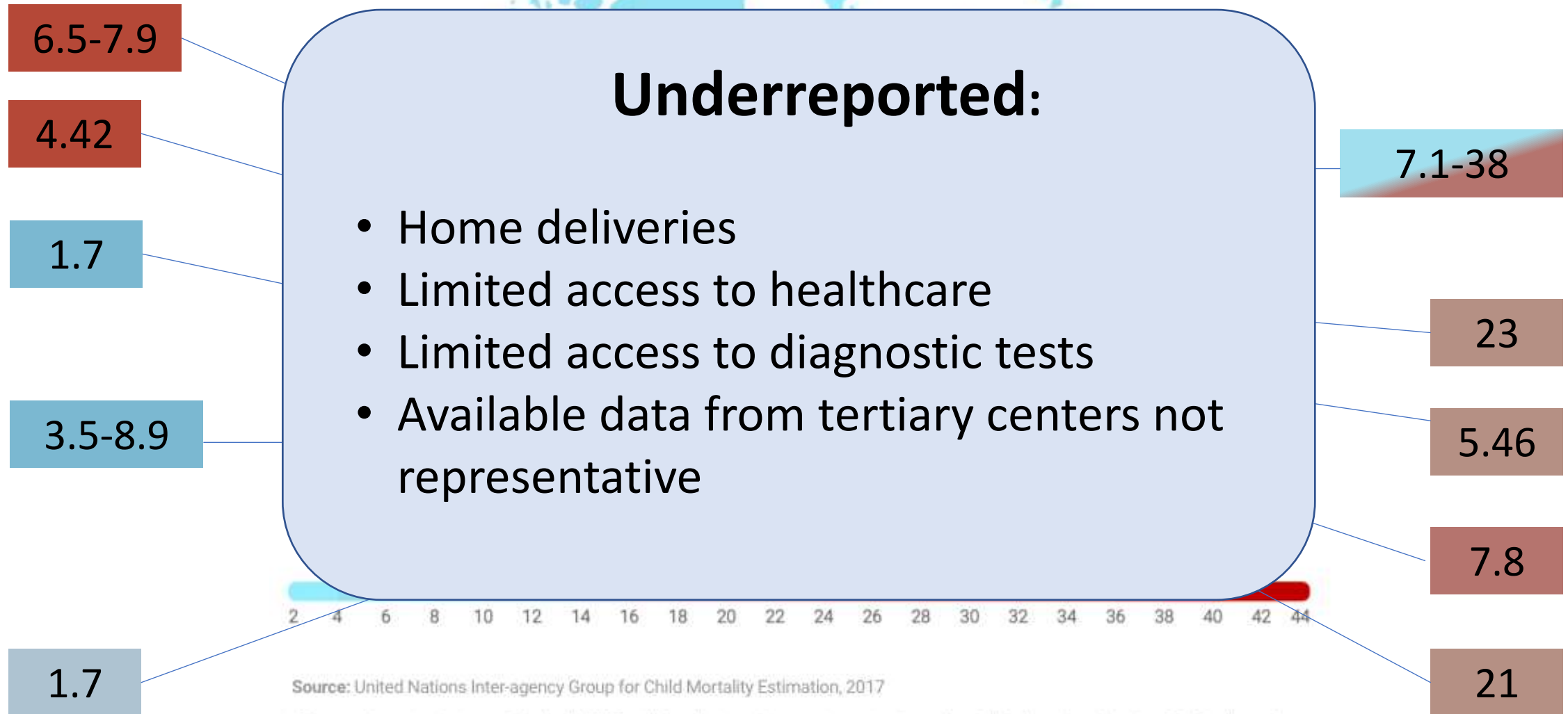
This map does not reflect a position by UNICEF on the legal status of any country or territory or the delimitation of any frontiers. The final boundary between the Sudan and South Sudan has not yet been determined. The final status of Jammu and Kashmir has not yet been agreed upon by the

*Sgro et al, *Paediatrics & Child Health* 2018 ; Schrag et al *Pediatrics* 2016; Singh et al *ADC Fetal and Neonatal Edition* 2018

EOS rates per 1000 live births superimposed on NNMR: LMIC



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Tygerberg Hospital: 2017

- 124 neonatal beds
 - 8 NICU beds
 - 4 High Care beds
-
- Total deliveries region 33 360
 - Total institutional deliveries 7986
-
- EOS **1.9/1000** live births
 - GBS **0.5/1000** live births
 - Excluding Listeria outbreak **0.9/1000** live births





Tygerberg Hospital: 2017

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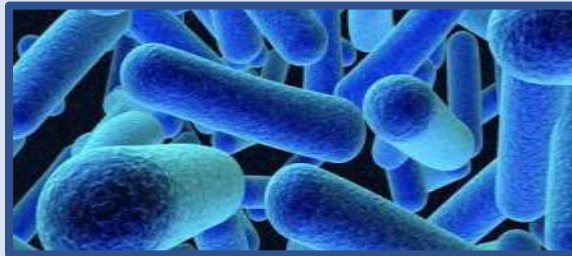


Not representative of South Africa

3. ETIOLOGIES: HIC



1. Group B *streptococcus*



2. *Escherichia coli*



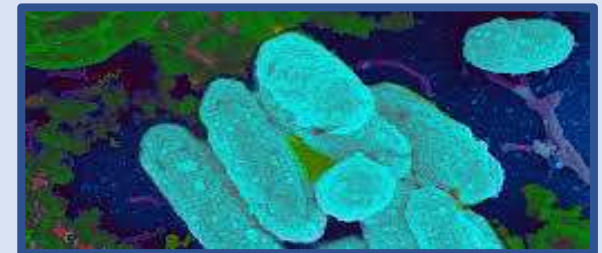
3. *Listeria monocytogenes*



4. CoNS



5. *S. aureus*

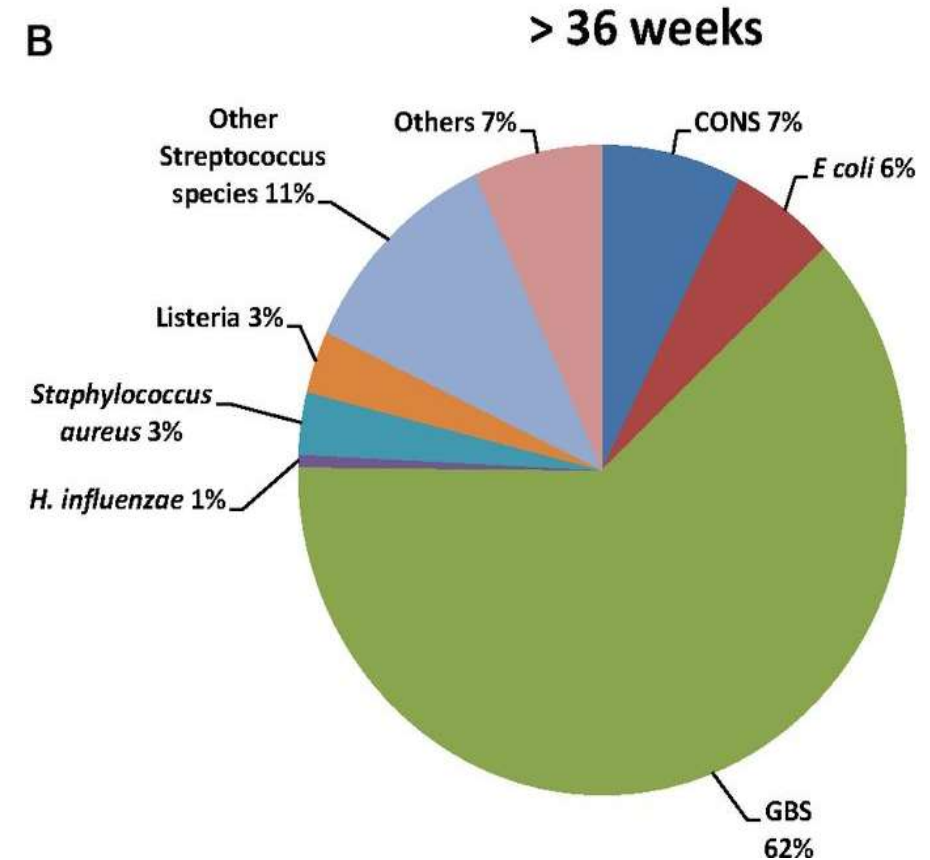
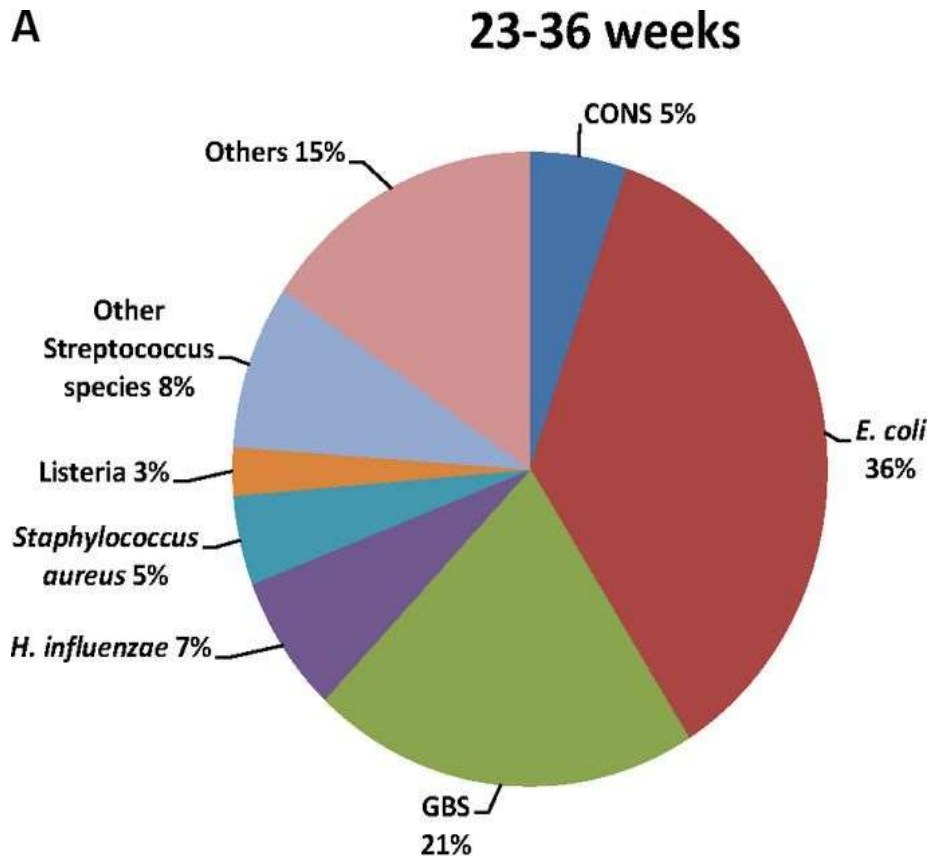


6. *H. influenzae*

Early-onset neonatal infections in Australia and New Zealand, 2002-2012

Tarun Singh, Elizabeth H Barnes, David Isaacs, Australian Study Group for Neonatal Infections

Archives of Disease in Childhood – Fetal and Neonatal Edition Published Online First: 27 March 2018



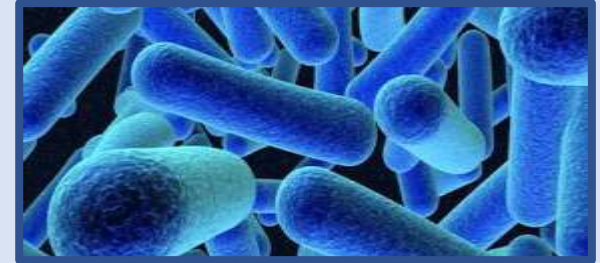
3. ETIOLOGIES: LMIC



1. *Klebsiella* spp.



2. *S. aureus*



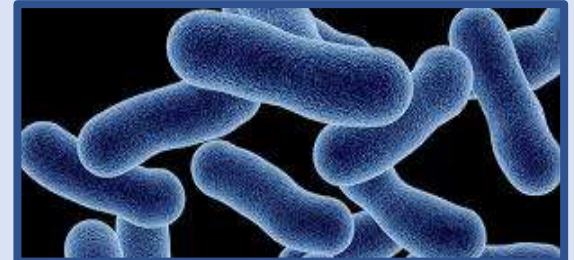
3. *Escherichia coli*



4. Group B streptococcus



5. *S. pneumoniae*



6. *Salmonella* spp.

Challenges in the diagnosis and management of neonatal sepsis

Alonzo Zea-Vera, Theresa J. Ochoa

Journal of Tropical Pediatrics, Volume 61, Issue 1, 1 February 2015

Developing countries

<i>Klebsiella</i> spp.	14-21%
<i>S. aureus</i>	13-26%
<i>E. coli</i>	8-18%
GBS	2-8%
<i>S. pneumoniae</i>	2-5%
<i>Salmonella</i> spp.	1-5%

Developed countries

GBS	43-58%
<i>E. coli</i>	18-29%
Other GNB	7-8%
<i>S. aureus</i>	2-7%
CoNS	1-5%
<i>L. monocytogenes</i>	0.5-6%

Challenges in the diagnosis and management of neonatal sepsis

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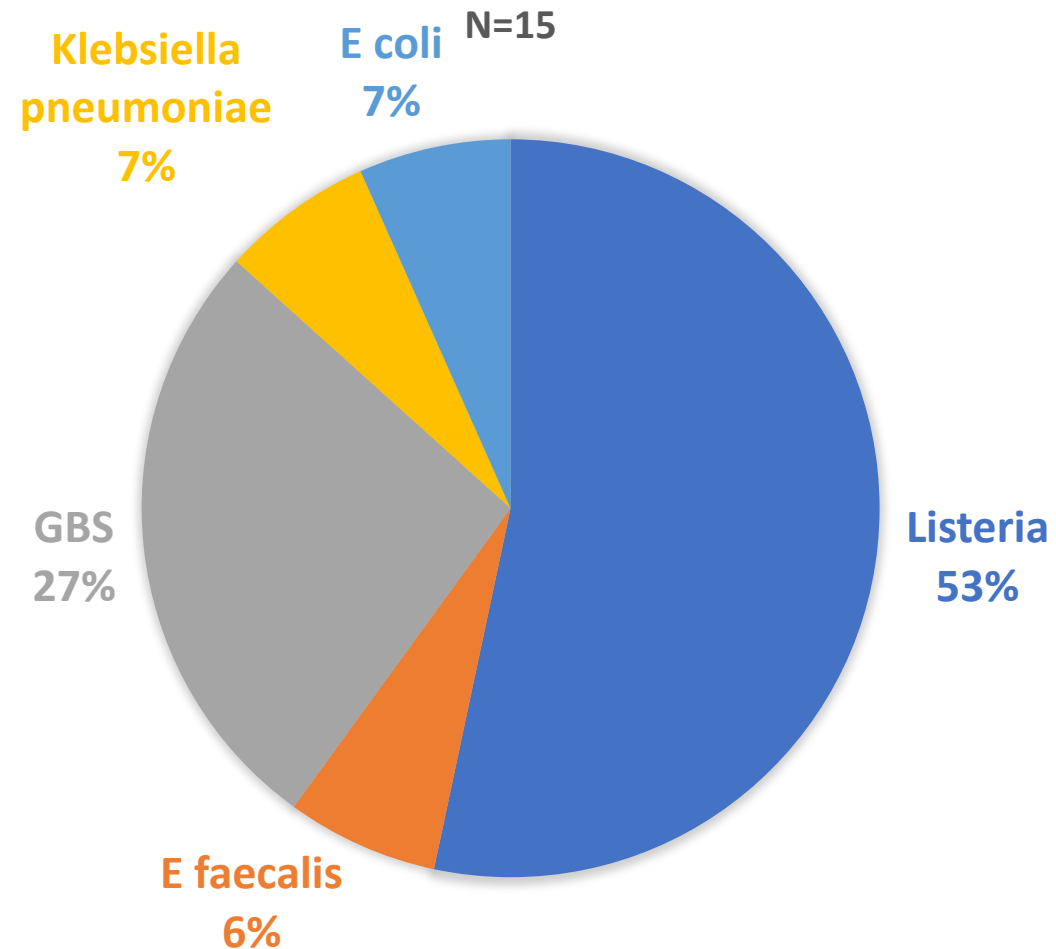
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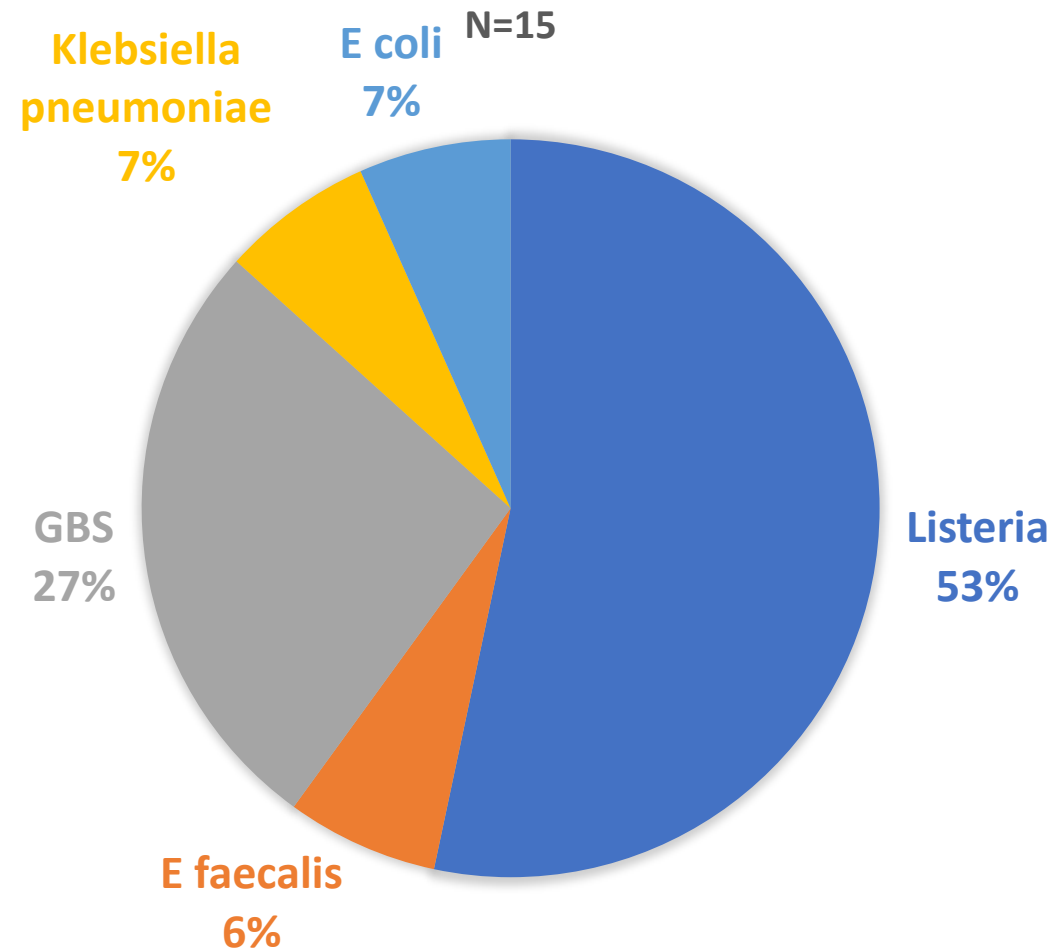
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TYGERBERG: ETIOLOGY OF EOS 2017



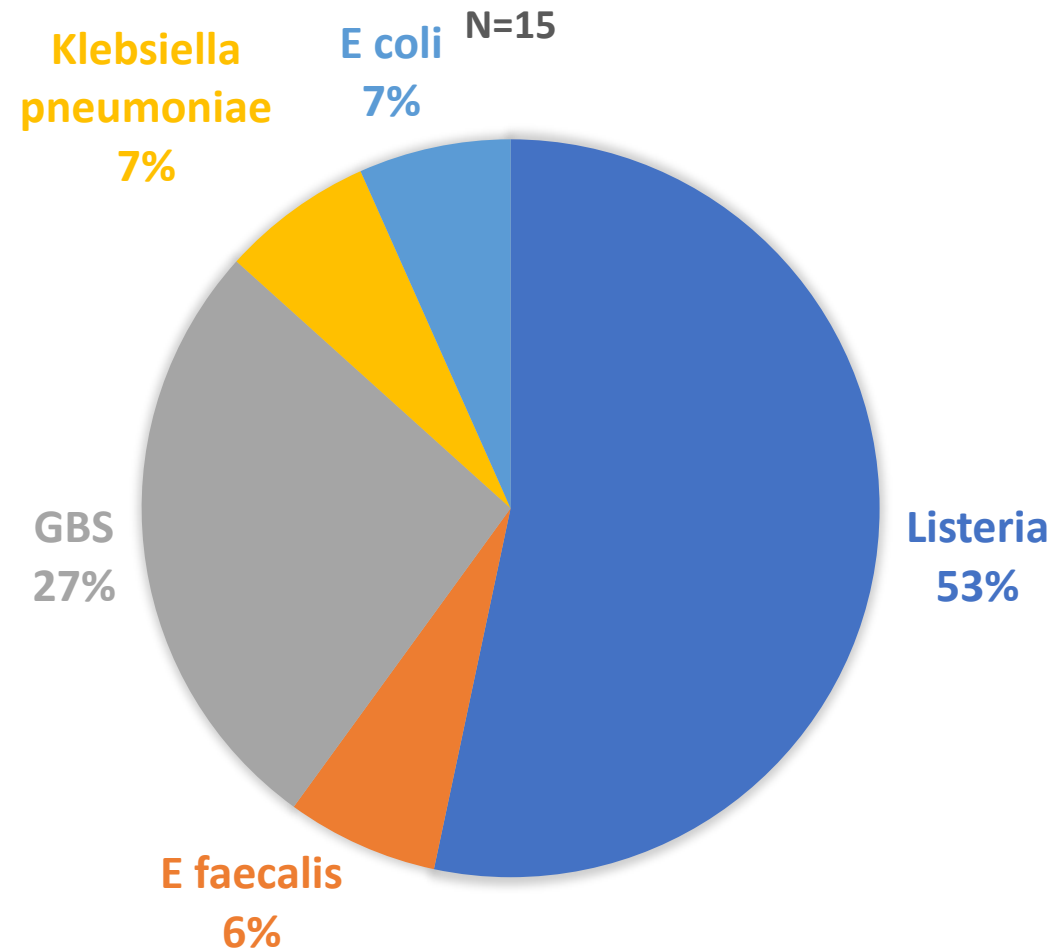
TYGERBERG: ETIOLOGY OF EOS 2017

Combination of
HIC and LMIC
etiologies



TYGERBERG: ETIOLOGY OF EOS 2017

Combination of
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Listeria outbreak



WORLD'S LARGEST LISTERIA OUTBREAK

BBC

NEWS

South Africa listeria: Source of 'world's worst outbreak' found

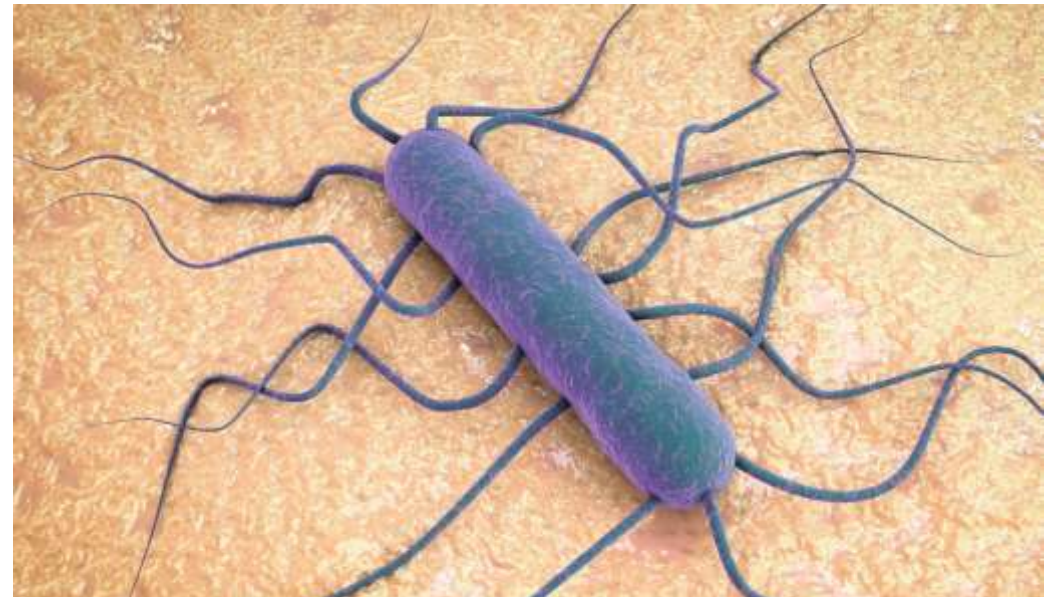
South Africa says it has finally traced the source of a listeria outbreak that has killed 180 people in the past year - said to make it the worst in history.

The Telegraph

News

News

Listeria contaminated food kills 200 in South Africa, including 80 babies



WORLD'S LARGEST LISTERIA OUTBREAK

- 1034 cases
- 13% in Western Cape
- 43% in neonates
- 28% mortality



news24
Breaking News. First

WHO: South Africa's listeriosis outbreak 'largest ever'

The second largest outbreak of listeriosis was in 2011, when the United States had a total of 147 reported cases. Prior to that, Italy had a large occurrence in 1997.

Lindmeier said the three-week incubation period makes it difficult to establish the source and thus, tough to prevent.

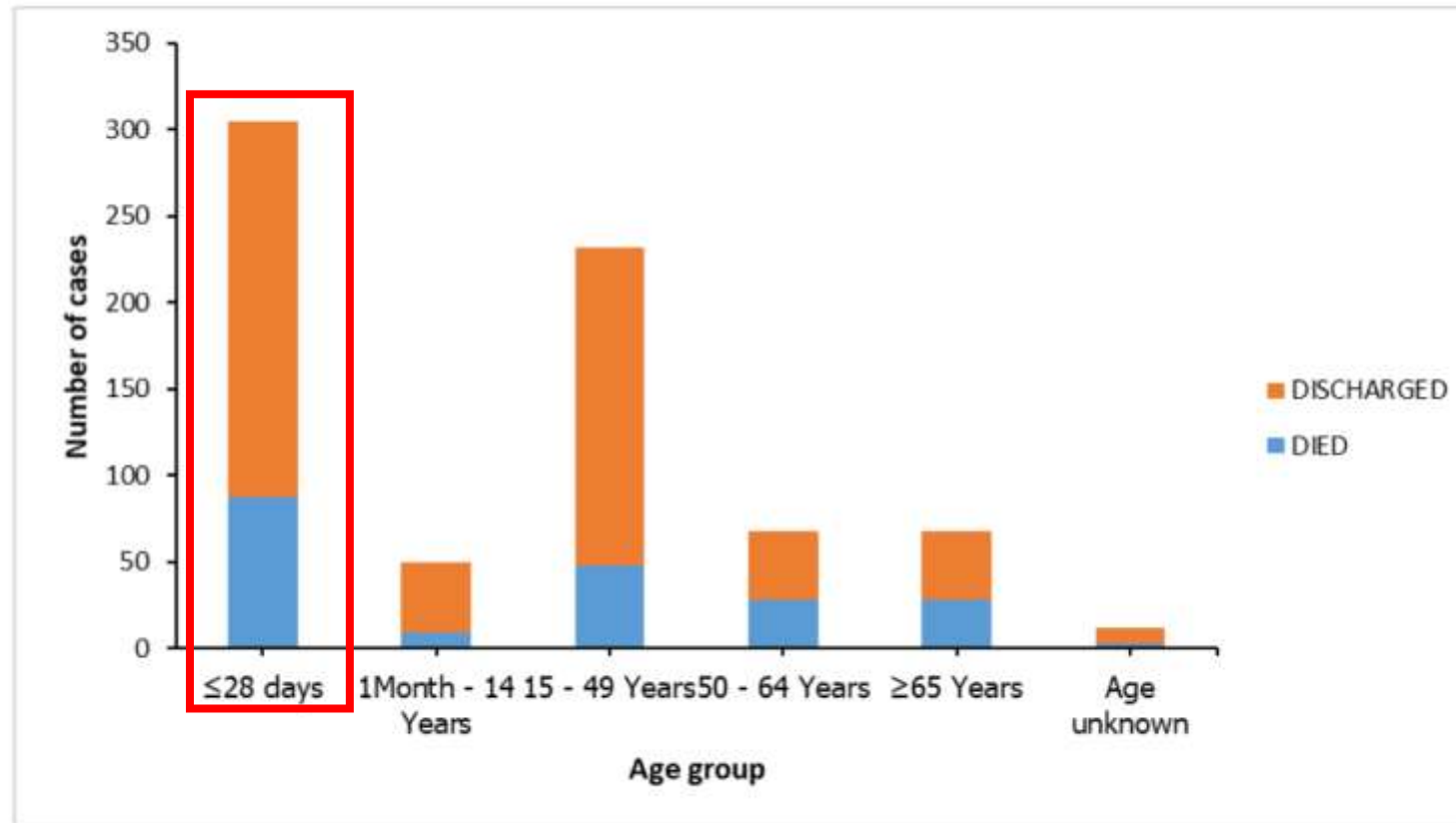


Figure 2: Outcome of laboratory-confirmed listeriosis cases by age group, South Africa, 01 January 2017 to 17 May 2018 (n=735, where outcome is known)

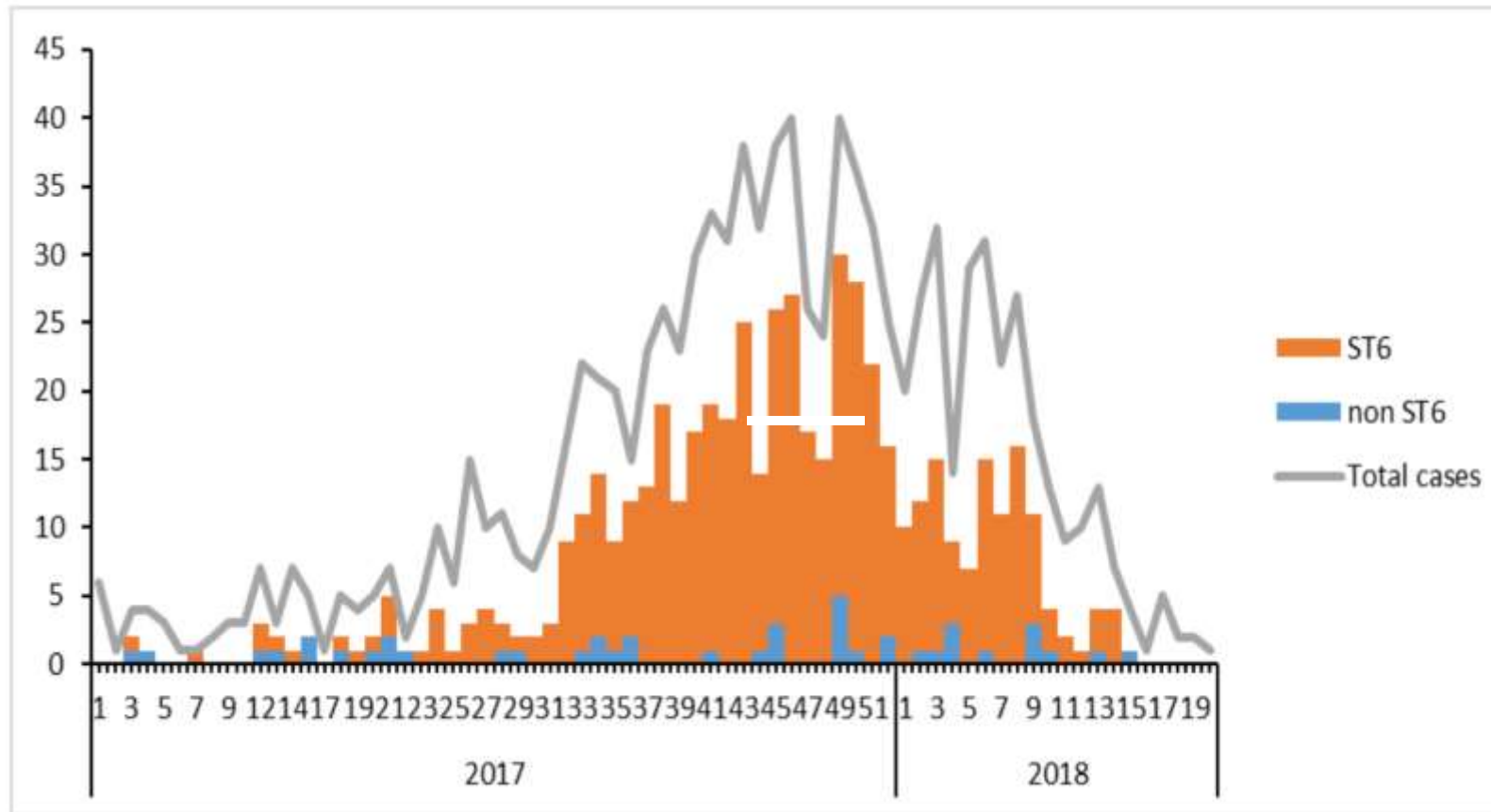


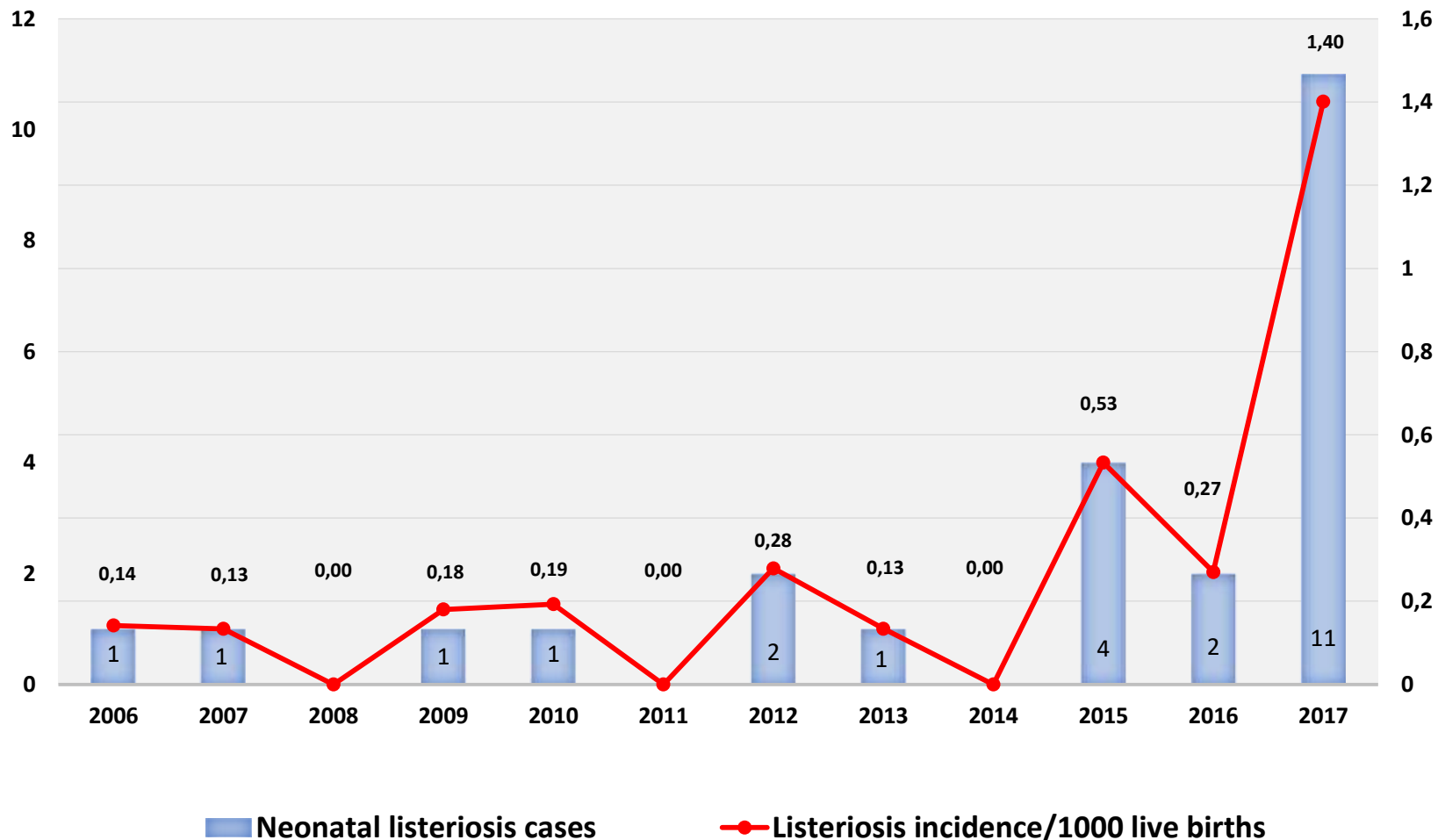
Figure 1: Epidemic curve of laboratory-confirmed listeriosis cases by date of clinical specimen collection (n= 1034) and sequence type (ST) (n-541), South Africa, 01 January 2017 to 17 May 2018

Neonatal listeriosis during a countrywide epidemic: a tertiary hospital's experience

Dramowski A, Lloyd LG, Bekker A, Holgate S, Reddy K, Aucamp M, Finlayson H

Accepted for publication: *South African Medical Journal* 23 April 2018

NEONATAL LISTERIOSIS ADMISSIONS (2006-2017)



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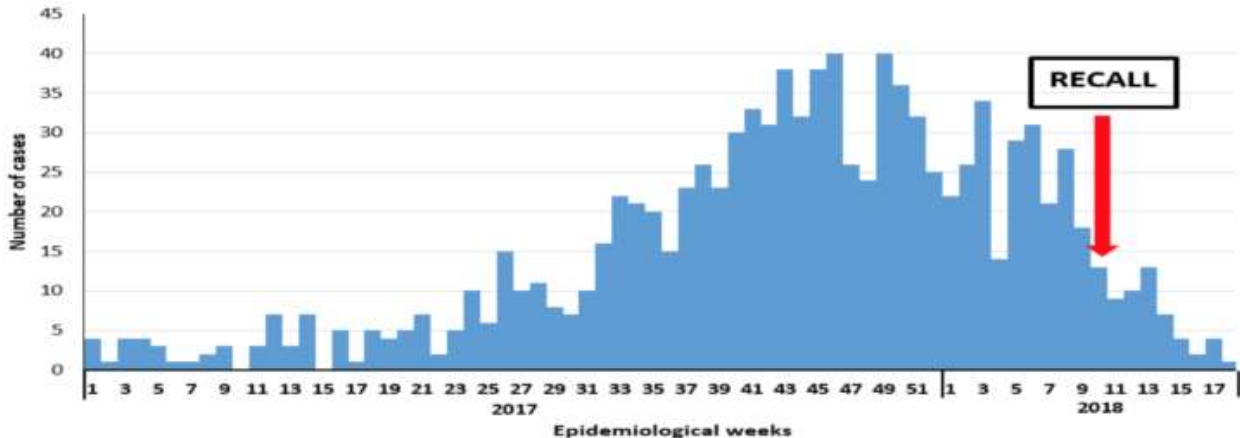
- **Listeria sequence type 4b** most common in outbreaks
- RSA outbreak – **Sequence type 6**
- Lower mortality during outbreak when compared to sporadic cases
- Higher mortality than global (25% vs 16%)
 - Reflects mortality at a tertiary center



WORLD'S LARGEST LISTERIA OUTBREAK: SOURCE IDENTIFIED

According to the Minister of Health, Dr. Aaron Motsoaledi:

THE CONCLUSION FROM THIS IS THAT THE SOURCE OF THE PRESENT OUTBREAK CAN BE CONFIRMED TO BE THE ENTERPRISE FOOD-PRODUCTION FACILITY IN POLOKWANE



HOME LEARN MORE ▾ RICHARD SPOOR INC. ATTORNEYS LHL CONTACT AN ATTORNEY

Listeria Class Action

From the office of Richard Spoor, South African activist and human rights attorney in partnership with LHL Attorneys Inc. and Markler Clark the United States' leading law firm representing victims of foodborne illness outbreaks.

4. PREVENTION PROGRAMS: GBS

USA

1.8/ 1000 LB

GBS prophylaxis



0.25/ 1000 LB

Sub-Saharan
Africa

- Poor identification previous baby with GBS
- Limited/No screening
- High maternal carriage (13-22%)
- High incidence 1.8-3.06/1000 LB

VACCINE VS INTRAPARTUM ANTIBIOTIC PROPHYLAXIS IN AFRICA



Vaccine

Volume 32, Issue 17, 7 April 2014, Pages 1954-1963



Cost-effectiveness of a potential group B streptococcal vaccine program for pregnant women in South Africa

Sun-Young Kim ^{a,✉}, Louise B. Russell ^b, Jeehyun Park ^b, Jennifer R. Verani ^c, Shabir A. Madhi ^d, Clare L. Cutland ^d, Stephanie J. Schrag ^c, Anushua Sinha ^a



Vaccine

Volume 33, Issue 47, 25 November 2015, Pages 6396-6400



Discussion

Ethical considerations for designing GBS maternal vaccine efficacy trials in low-middle income countries ☆

Amina White ^{a,✉}, Shabir A. Madhi ^{b, c}

If vaccine 50-90% effective



Vaccinate 75% women



Prevent 30-54% of invasive neonatal disease (Vs 10% with IAP)

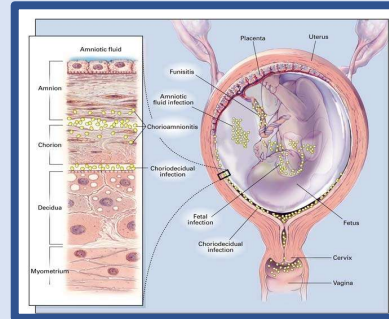
*Cortese et al *Ped & Neonatology* 2016; Heyderman et al *Lancet Inf Dis* 2016

5. WHO IS AT RISK?



<37 weeks

10 x increased risk
Poor immune defense



Chorioamnionitis

Fever
Fetal tachycardia
Uterine tenderness
Foul odor of amniotic fluid



Rupture of membranes

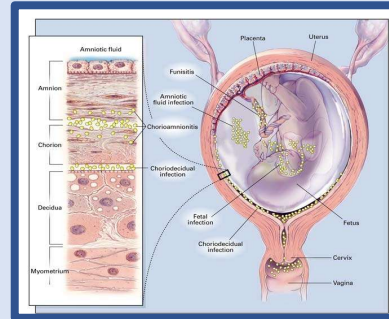
>18 hours –
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85% preterm births occur in Africa and Asia



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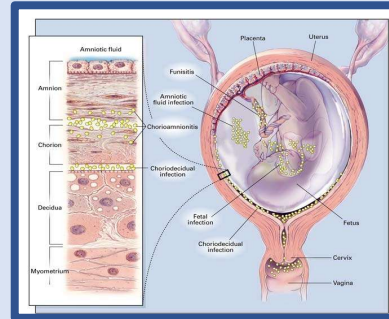
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Chorioamnionitis

17% get EOS
Undiagnosed
Untreated



**Rupture of
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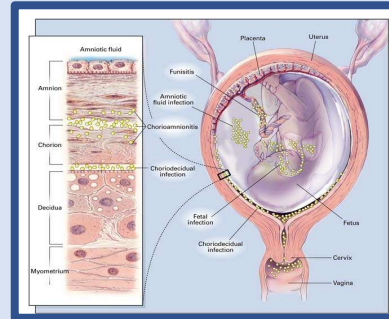
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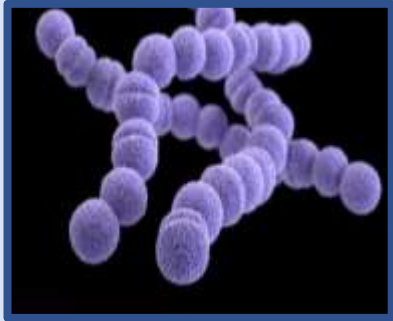
17% get EOS
Undiagnosed
Untreated



**Rupture of
membranes**

Poor transport
Home deliveries
Education ↓

5. WHO IS AT RISK?



GBS colonization

12-27% asymptomatic
colonization
50% perinatal
transmission
1-2% invasive disease



Maternal demographics

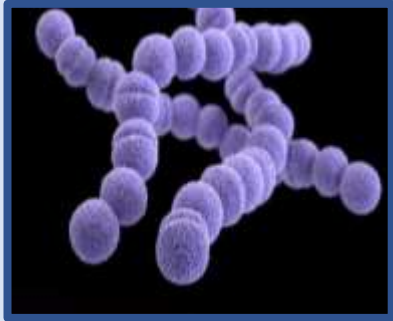
Ethnicity
Socio-economic status



Obstetric practices

Frequent vaginal exams
Invasive fetal
monitoring
Pharmacological
cervical ripening

5. WHO IS AT RISK?



GBS colonization

Poor antenatal
care
Limited IAP



Maternal demographics

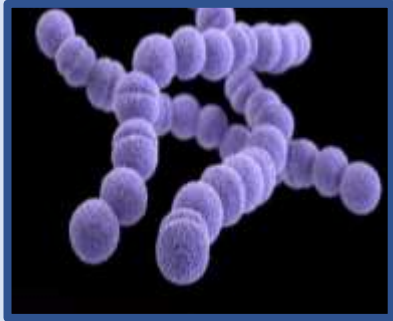
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5. WHO IS AT RISK?



GBS colonization

Poor antenatal care
Limited IAP



Maternal demographics

African
Poor socio-economic status
HIV



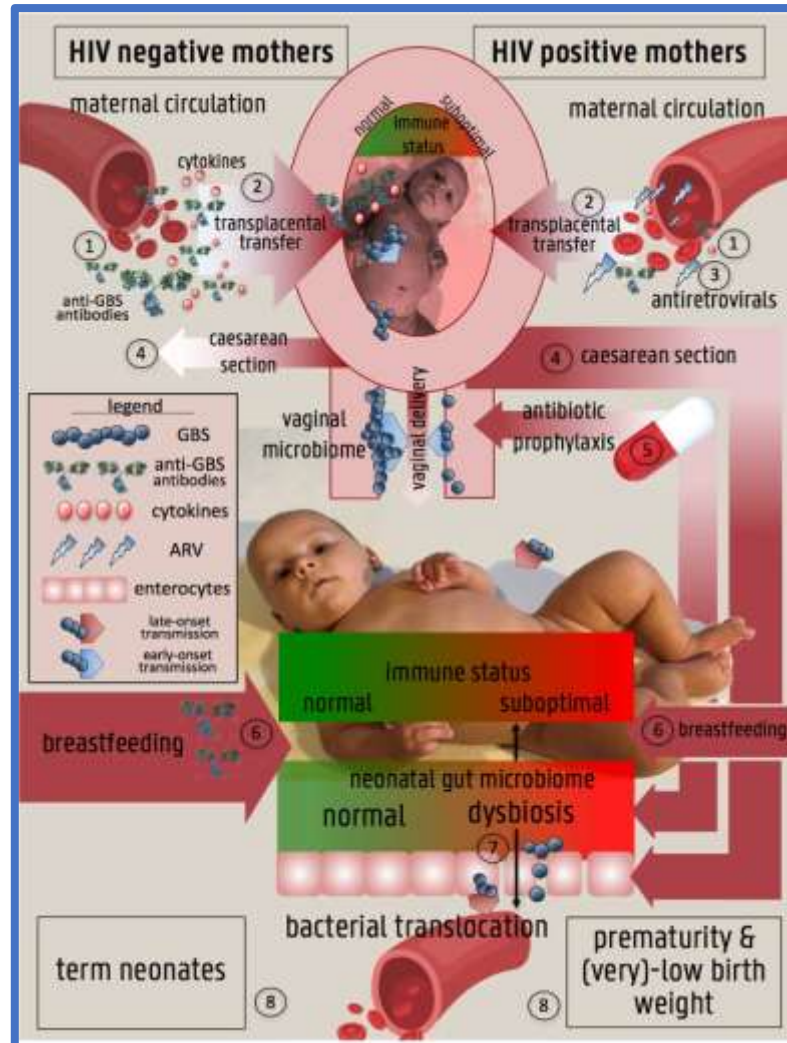
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Role of HIV exposure and infection in relation to neonatal GBS disease and rectovaginal GBS carriage: a systematic review and meta-analysis.

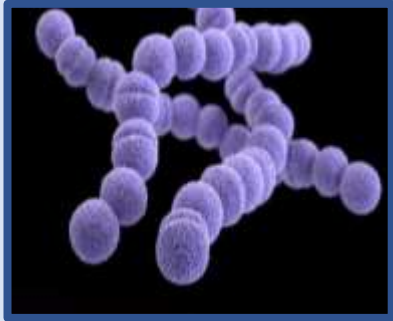
Cools P, van de Wijert JHJM, Jespers V, et al.

Scientific Reports. 2017;7:13820. doi:10.1038/s41598-017-13218-1



HIV-exposed neonates were **not at increased risk for early-onset neonatal disease**, but were 4.43 times more likely to have late-onset neonatal GBS disease

5. WHO IS AT RISK?



GBS colonization

Poor antenatal care
Limited IAP



Maternal demographics

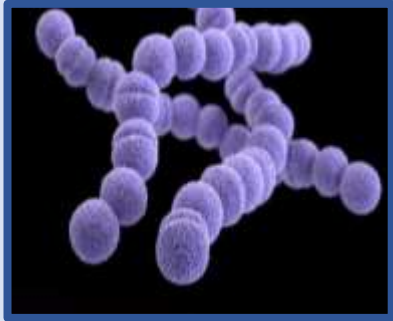
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HIV



Obstetric practices

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Pharmacological cervical ripening

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GBS colonization

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Limited IAP



Maternal demographics

African
Poor socio-
economic status
HIV



Obstetric practices

'Unclean'
practices
Home deliveries

AT RISK: TO TREAT OR NOT TO TREAT

Kaiser Permanente
Research

Neonatal Early-Onset Sepsis Calculator

Clinically symptomatic



Empirical antibiotics per
guideline



NICE
National Institute for
Health and Care Excellence

Well-appearing at risk newborns



Deciding who not to treat or
when to stop treatment

AT RISK: TO TREAT OR NOT TO TREAT

Kaiser Permanente
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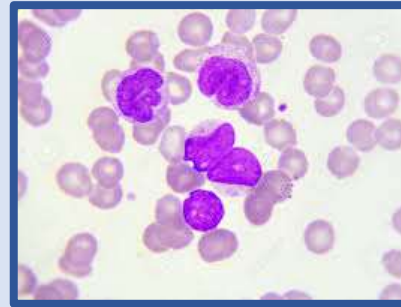
Deciding **WHO NOT TO TREAT** or
WHEN TO STOP treatment

6. THE DIAGNOSTIC DILEMMA



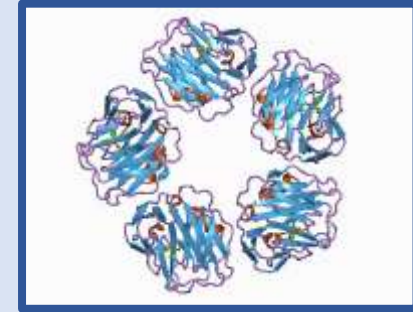
Blood culture

Gold standard



Complete blood count

Physiological
variation
I/T ratio



C-reactive protein

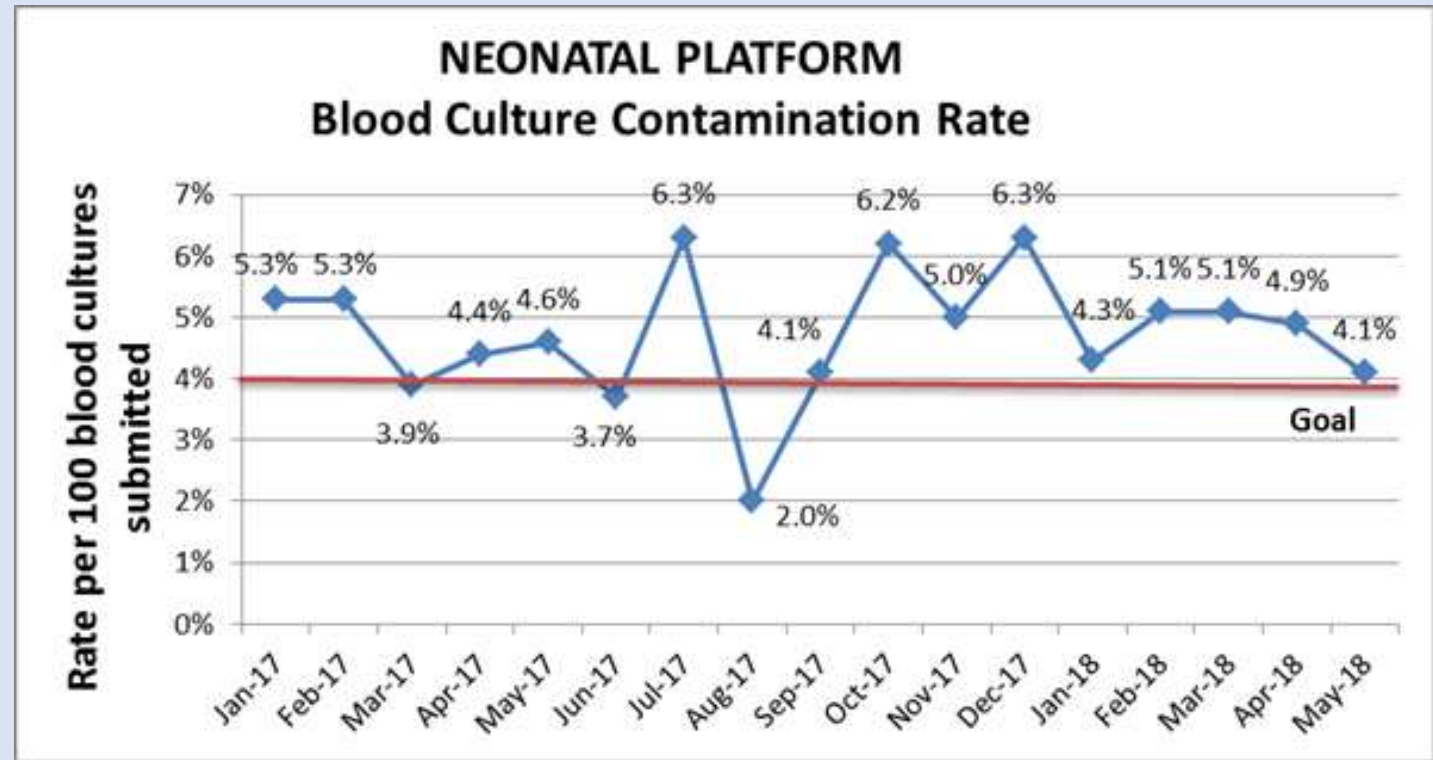
Serial
measurements

6. THE DIAGNOSTIC DILEMMA



Blood culture

'Flawed'
↓ yield
↑ contamination



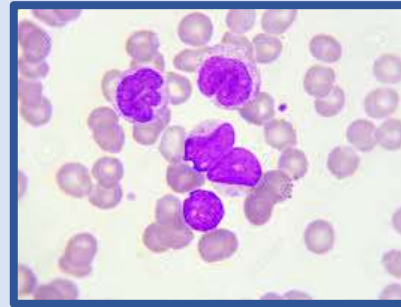
Tygerberg Hospital

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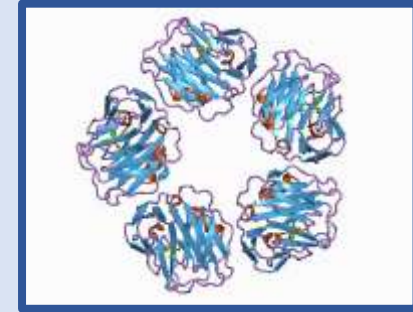
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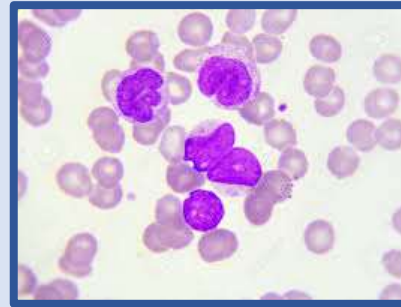
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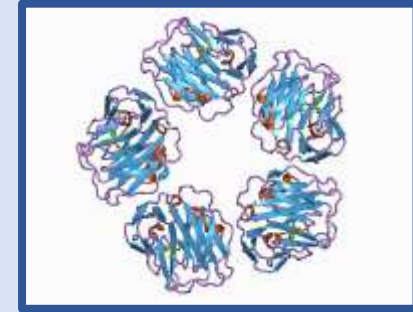
Blood culture

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Complete blood count

Difficult to
interpret
I/T ratio
unavailable



C-reactive protein

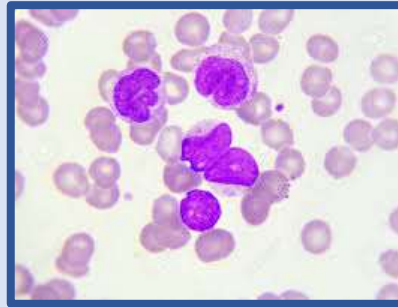
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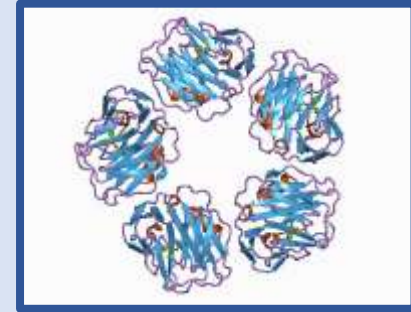
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Complete blood count

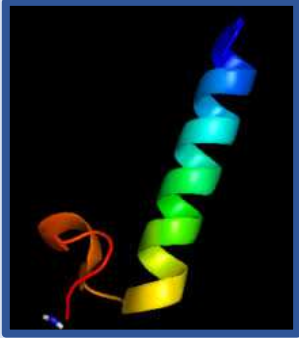
Difficult to
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I/T ratio
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C-reactive protein

Serial
measurements
Point-of-care

6. THE DIAGNOSTIC DILEMMA



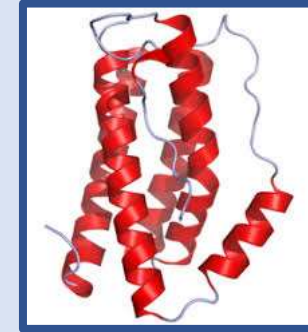
Procalcitonin

Diagnosis
Disease severity
De-escalation



Cord blood

'Less' invasive
Blood culture
CRP, PCT, IL-6
Hepcidin
CBC



New tests

CD64; TNF α ; presepsin
IL-6; IL-8, IL-35
16s rRNA
Proteomics/
Genomics

6. THE DIAGNOSTIC DILEMMA



Procalcitonin

Reduction antibiotic
use
Shorten hospital stay



Cord blood

'Less' invasive
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CRP, PCT, IL-6
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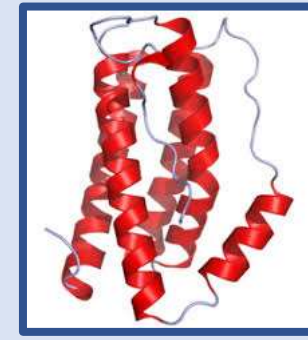
Procalcitonin

Serial
measurements
9.9 hours less
Expensive



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Procalcitonin

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Expensive



Cord blood

Hospital delivery
More research
needed



New tests

CD64; TNF α ; presepsin
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Genomics

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Cord blood

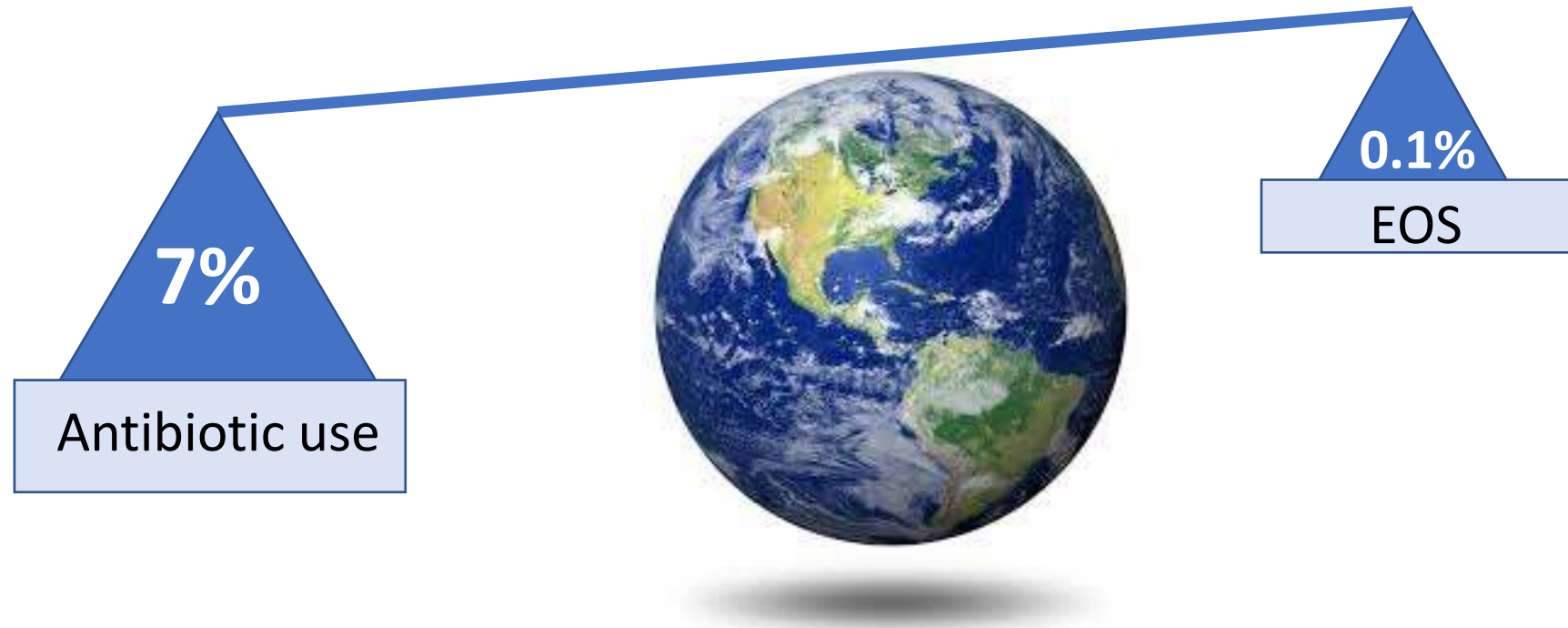
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More research
needed



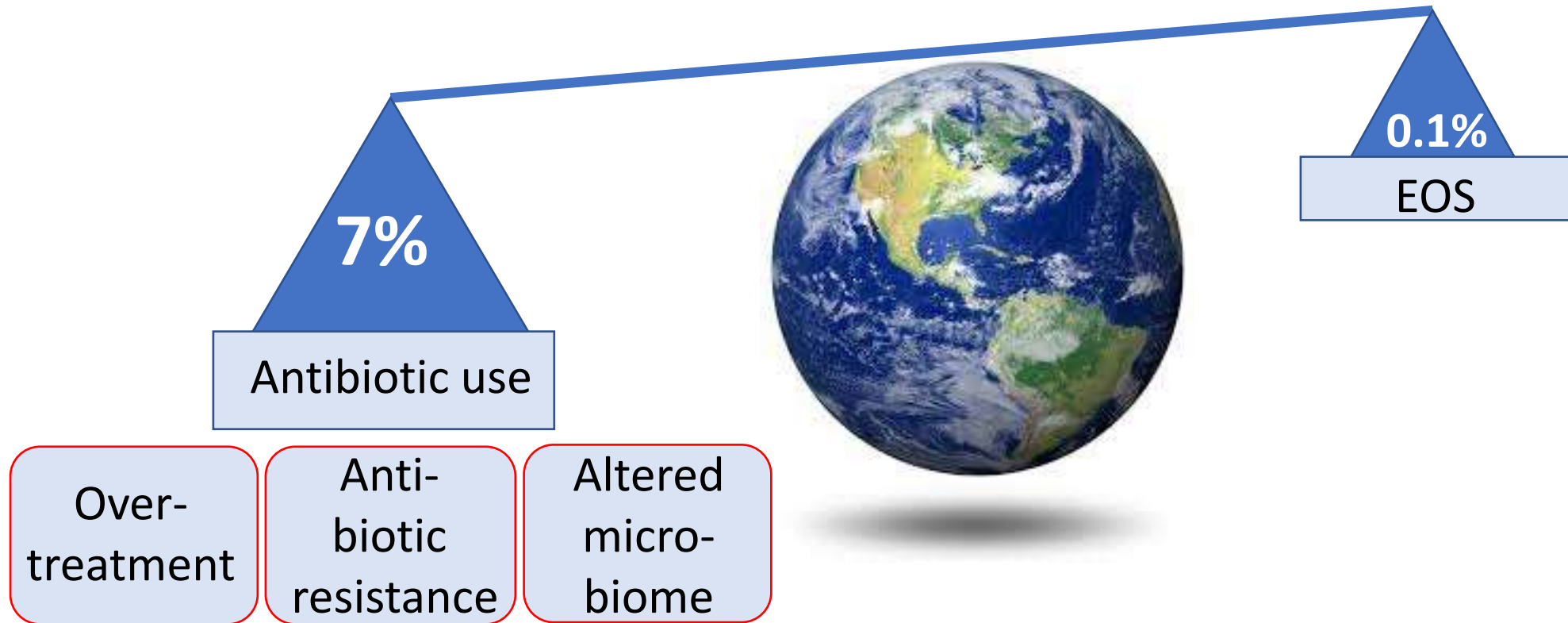
New tests

Expensive
Not available

7. EMPIRIC ANTIBIOTICS



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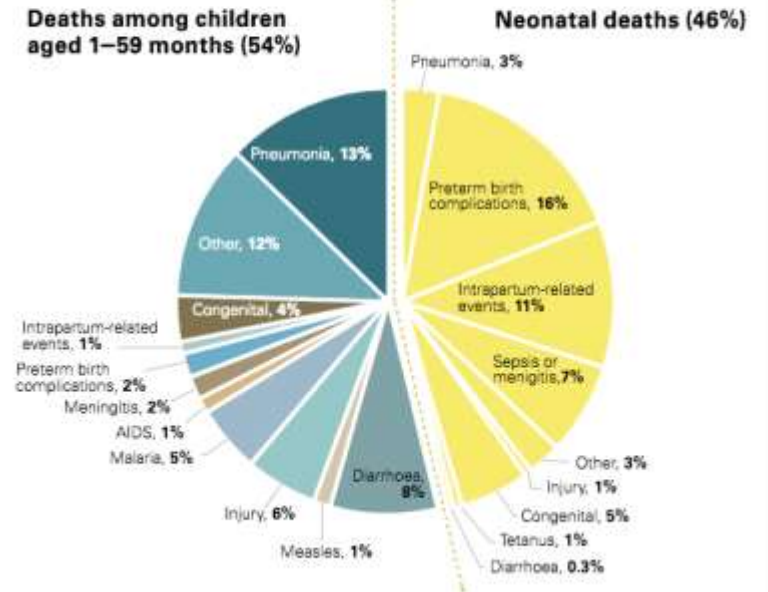


8. OUTCOME OF EOS

- Major contributor to neonatal mortality
 - 2-3% term infants
 - 20-30% preterm infants
- Long-term neurological deficit

FIGURE 4 Infectious diseases and neonatal complications are the leading causes of death among children under age 5

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



Nearly half of all deaths in children under age 5 are attributable to undernutrition

B. Global distribution of deaths among newborns, by cause, 2016



Note: Estimates are rounded and therefore may not sum up to 100%.

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

CONCLUDING REMARKS

Early onset neonatal sepsis is a
LOW INCIDENCE
HIGH CONSEQUENCE disease

Table Mountain

