Neonatal meningitis and sepsis: what happens to survivors?

Meningitis & septicaemia | November 5th - 6th 2019

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#MRFConf2019

Thanks to many exceptional women!

Prof Kim Mullholand
according to on line programme!!

Uduak Okomo

Anna Seale

Kate Milner

Maya Kohli-Lynch

Cally Tann

Proma Paul

Jaya Chandna

World you are born into determines your survival… and of disability

High income countries
~12 million births

Upper middle income countries
~39 million births

140 million births per year

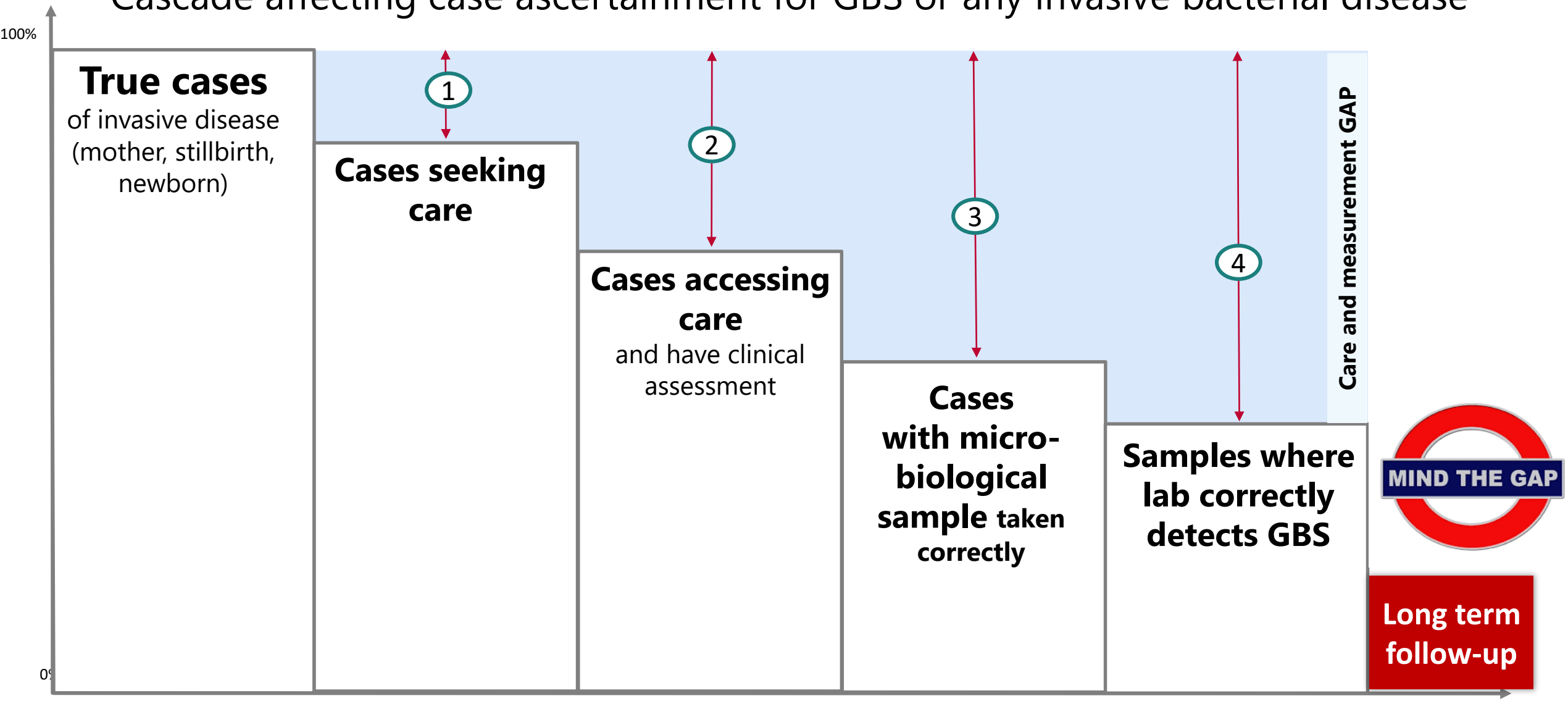
Low and middle income countries

Low and middle income countries

And the chance of being counted correctly - highest risk, least data (“Inverse data law”)

Data waterfall …

Cascade affecting case ascertainment for GBS or any invasive bacterial disease

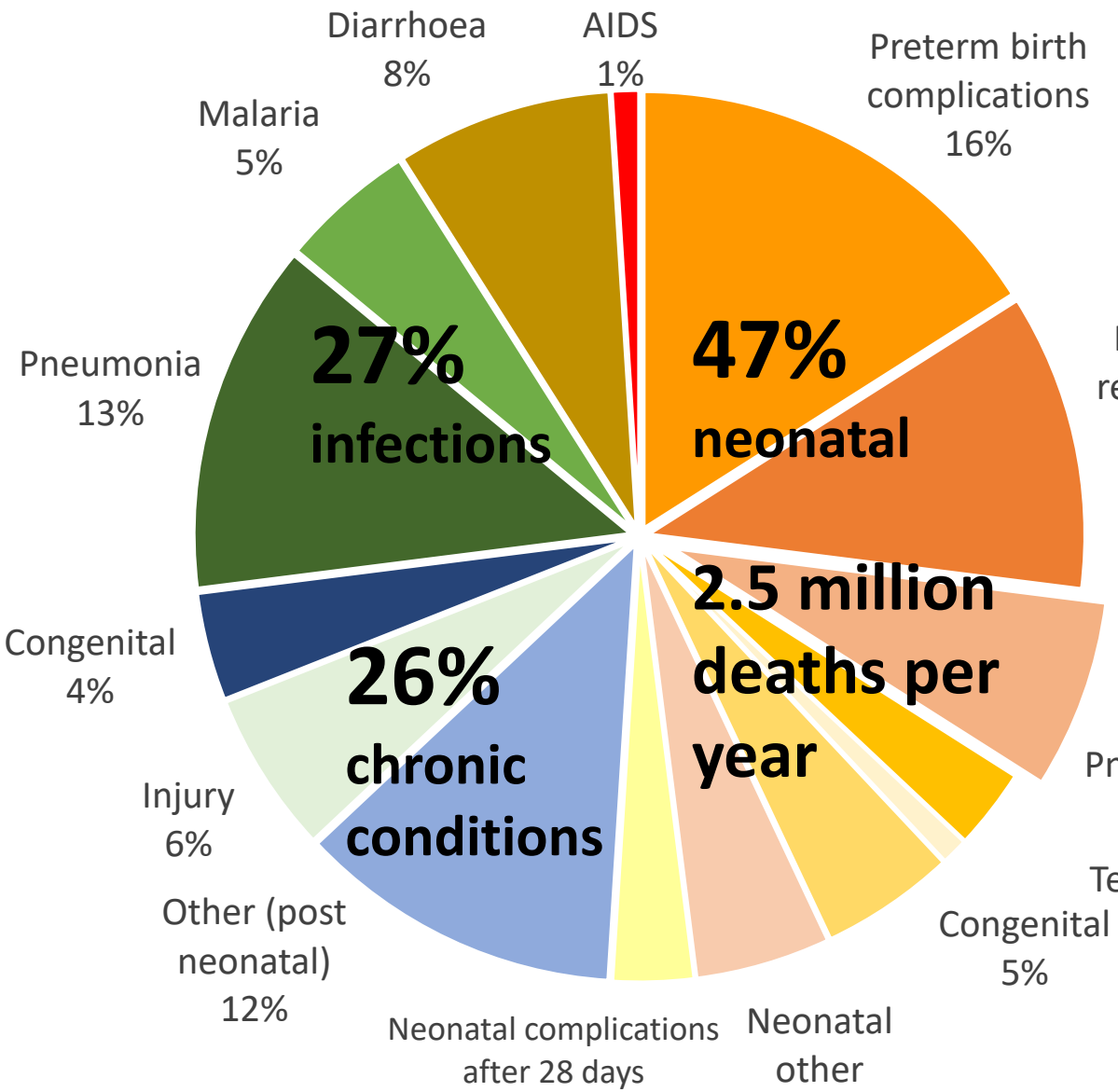


Lawn JE, et al Clinical Infectious Diseases. 2017;65(S2):S89-99

5.3 million deaths

WHY do children die?

Global causes of child deaths under 5 years of age in 2017



1. Preterm birth top cause of CHILD deaths + important cause of disability and loss of human capital

2. Birth complications

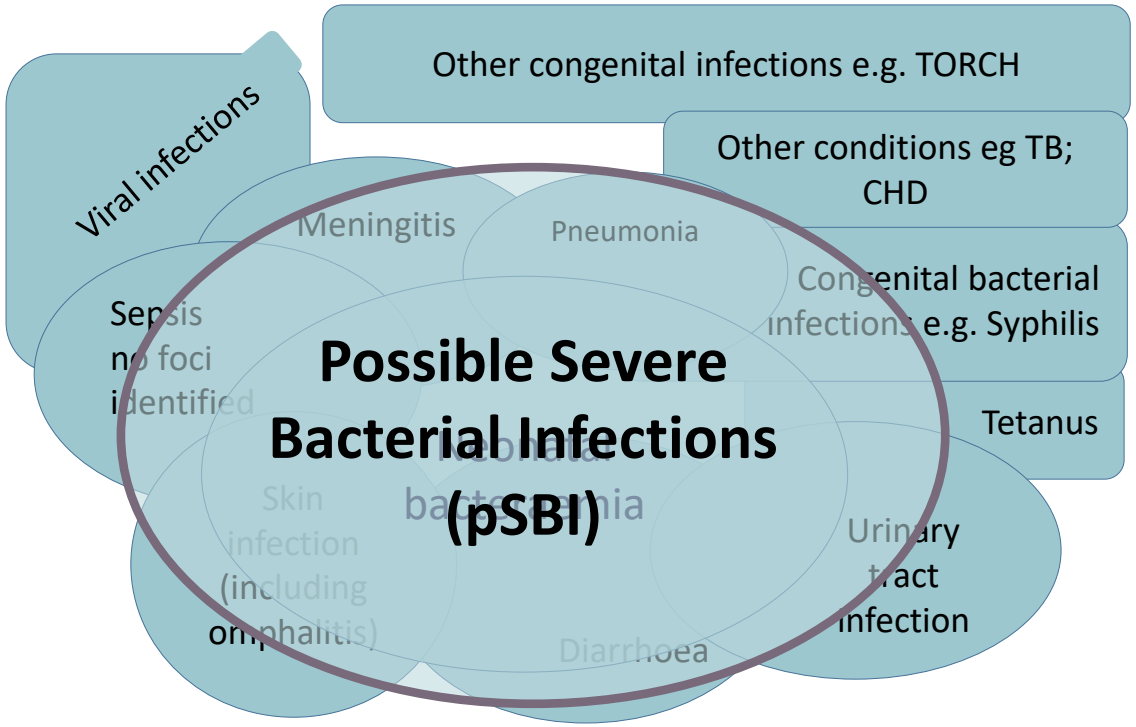
3. Neonatal infections:

"Black box" for aetiological data regarding 600,000 deaths due to neonatal infections.

WHO and UNICEF, 2018, From Li Liu, *et al*. Lancet, 2016

Cases - clinical syndromes

Cases clinically assessed



Meningitis
Invasive CSF infection

Sepsis
Invasive blood stream

Pneumonia
Invasive respiratory infection

Increasing complexity for clinical & lab diagnosis

WHO definition for Possible Severe Bacterial Infection (pSBI):

The presence of **any one** of the following six signs :

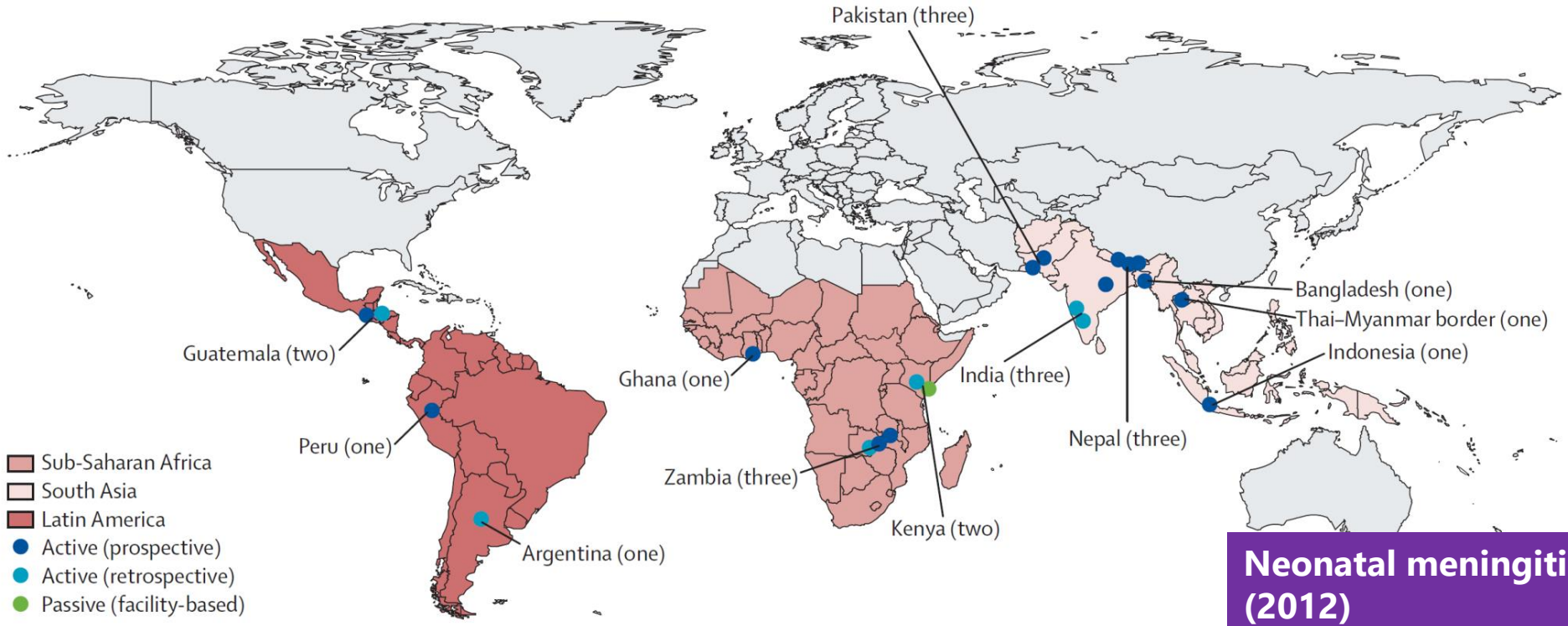
(1) a history of difficulty feeding, (2) history of convulsions, (3) movement only when stimulated, (4) respiratory rate of 60 breaths per minute or more, (5) severe chest in-drawing, (6) temperature $\geq 37{\cdot}5\ ^0C$, or $\leq 35{\cdot}5^0C$*

*Young Infants Clinical Signs Study Group. Clinical signs that predict severe illness in children under age 2 months: a multicentre study. *Lancet* 2008; 371(9607): 135-4

Figure adapted from Seale … Lawn Lancet ID 2013

Cases clinically assessed

Neonatal pSBI estimates
Geographic distribution of data included



Neonatal meningitis cases (2012) **~200,000**

Source: Lancet ID, Seale … Lawn JE, 2014

Articles

Estimates of possible severe bacterial infection in neonates in sub-Saharan Africa, south Asia, and Latin America for 2012: a systematic review and meta-analysis

Anna C Seale, Hannah Blencowe, Alexander A Manu, Harish Nair, Rajiv Bahl, Shamim A Qazi, Anita K Zaidi, James A Berkley, Simon N Cousens, Joy E Lawn, for the pSBI Investigator Group*

Summary

Estimated total cases of pSBI

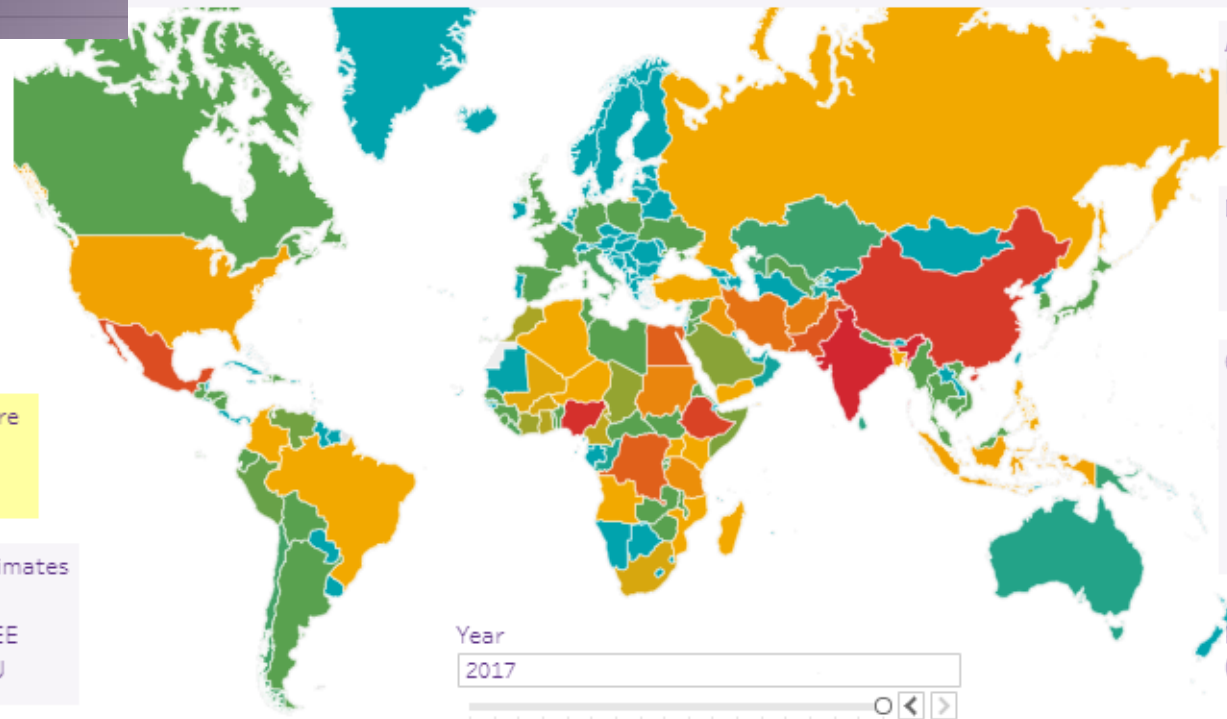
6·9 million per year (5.5-8.3)

Overall incidence risk 7.6% (95%CI 6.1-9.2%)

Input data 259 944 neonates, 20 196 pSBI cases

evention | Surveillance | Diagnosis and Treatment | Support and Aftercare | Tracking Progress | Sources of Data

Meningitis and Neonatal Sepsis in Children Under 5



Select Measure
- Deaths
- Cases

Source of Estimates
- IHME
- WHO-MCEE
- MCEE/JHU

© 2019 Mapbox © OpenStreetMap

Year
2017

Age Range
- 1 to 59 Months
- Neonatal

Diseases
- Meningitis
- Neonatal sepsis

Cause
- Hib meningitis
- Meningococcal meningitis
- Pneumococcal meningitis
- Other meningitis
- Neonatal sepsis

Rank of country by deaths (highest to lowest)
1 — 195

Countries in the Meningitis Belt
- N
- Y

WHO Region
- Africa
- Americas
- Eastern Mediterranean
- Europe
- South-East Asia
- Western Pacific

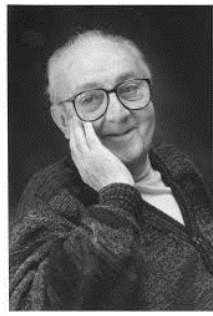
Income Level
- High income
- Upper middle income
- Lower middle income
- Low income

Reset

Estimates suggest that meningitis and neonatal sepsis combined are the second largest infectious killers of children aged under five. There has been some success in reducing cases and deaths over time, but progress still lags behind other infectious diseases.

Estimated Total Deaths 210,090 | Estimated Total Cases 1,477,260

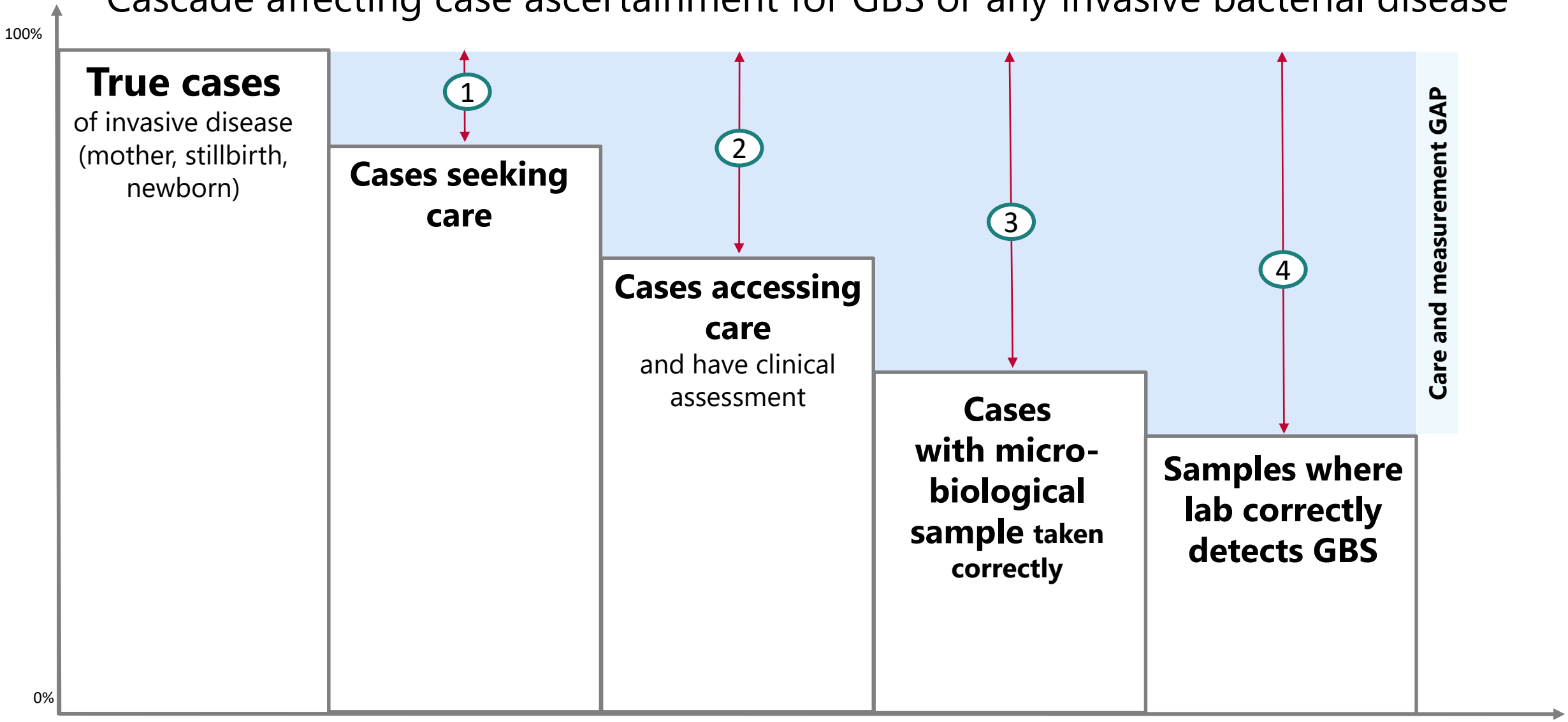
Neonatal meningitis deaths 19,530 | **CFR 13% ?** | **Neonatal meningitis cases 153 240**



"All models are wrong but some are useful!!" Lord Box

Data waterfall …

Cascade affecting case ascertainment for GBS or any invasive bacterial disease



Lawn JE, et al Clinical Infectious Diseases. 2017;65(S2):S89-99

Cases micro-biologically assessed

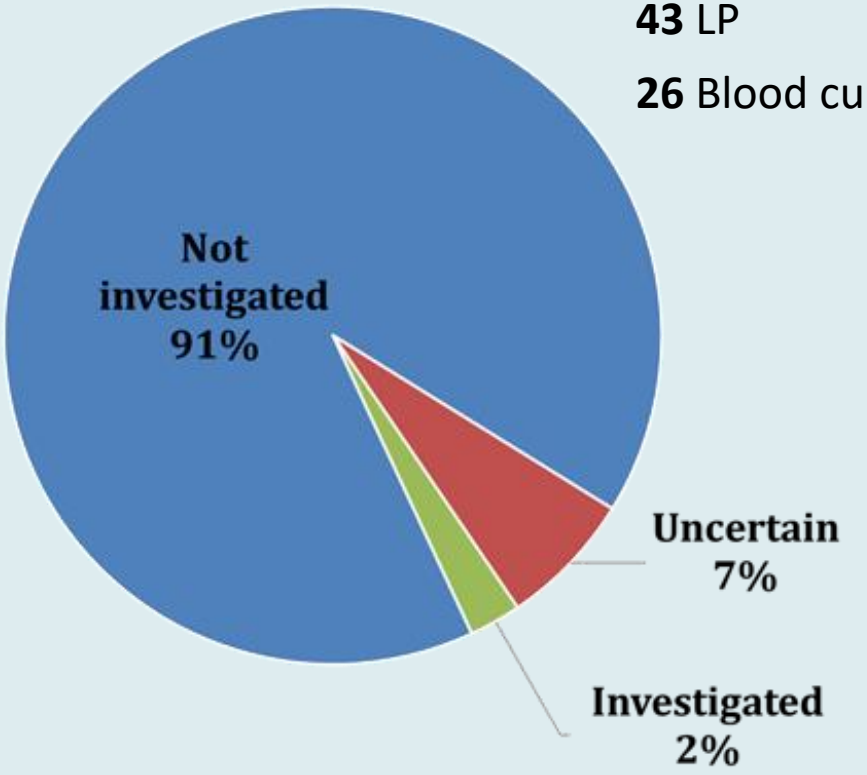
Cases with laboratory investigation

Mismatch of investigation *vs* antibiotics use in a Gambian Teaching Hospital (N=4999)

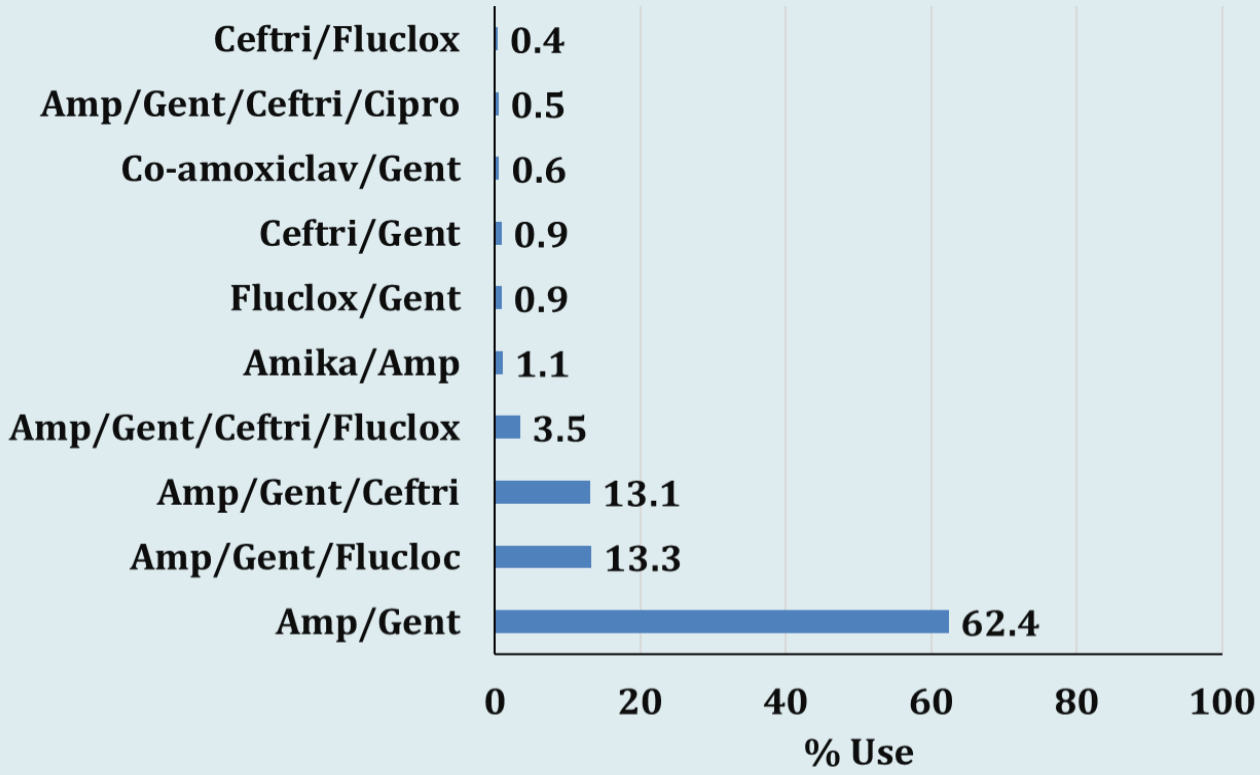
2% **Investigation results available**

43 LP

26 Blood cultures



94% **inpatient neonates given antibiotics**



Uduak Okomo et al Paediatrics and International Child Health 2015

Data waterfall …

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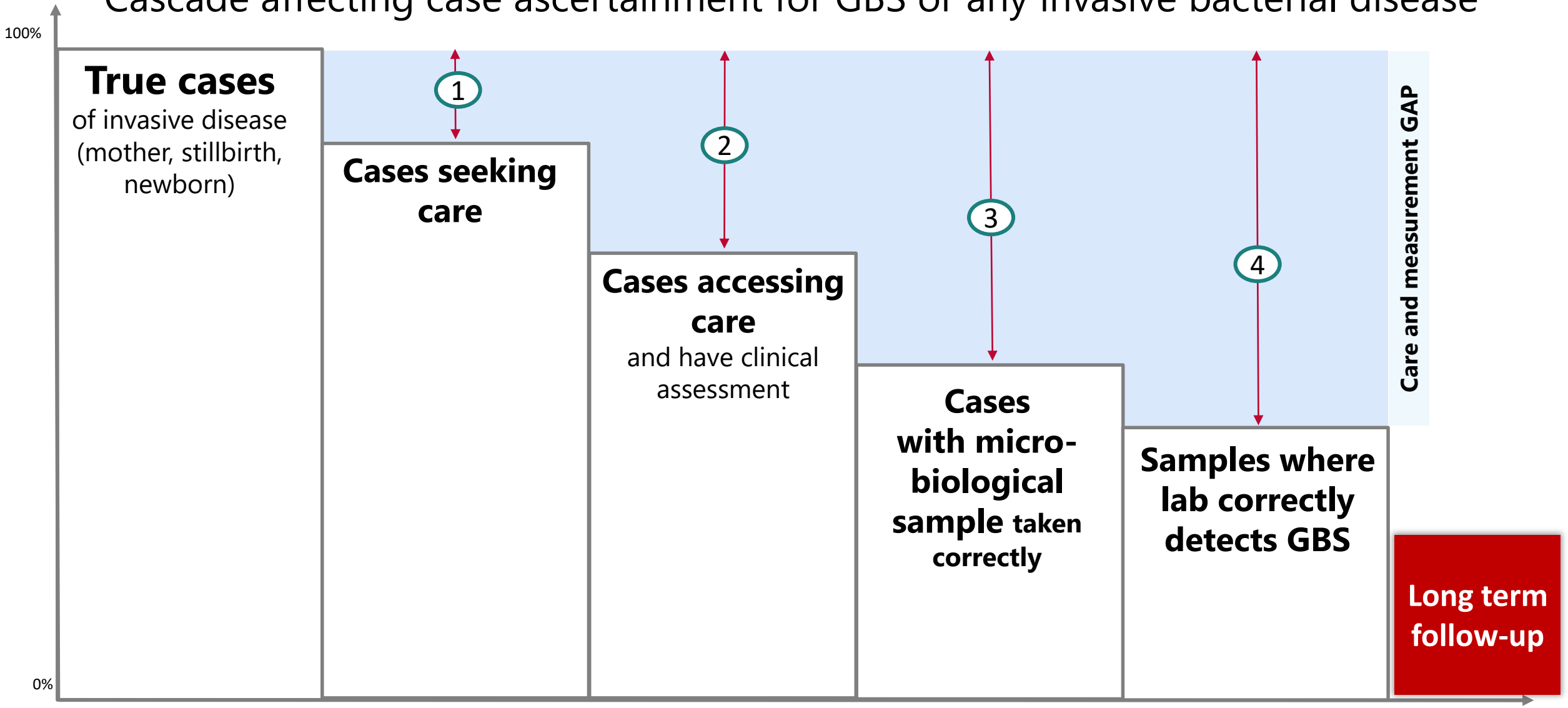

Lawn JE, et al Clinical Infectious Diseases. 2017;65(S2):S89-99

Beyond Neonatal Survival

Long term disability after neonatal conditions


Pediatric RESEARCH

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PEDIATRIC RESEARCH | EDITORIAL OPEN

Beyond newborn survival: the world you are born into determines your risk of disability-free survival

Joy E. Lawn, Hannah Blencowe, Gary L. Darmstadt & Zulfiqar A. Bhutta

Pediatric Research (2013) | doi:10.1038/pr.2013.202
Advance online publication 15 November 2013

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Every year, 135 million newborns enter the world, each arriving naked and apparently equal. Yet, their chances of surviving and thriving vary dramatically depending on which world these babies are born into—ranging from high-income countries with universal neonatal intensive care to the world of home births without midwives, medical supplies, or health system support (Figure 1).

http://www.nature.com/pr/journal/

NATURE PEDIATRIC RESEARCH

5 papers with first global estimates of incidence/prevalence & impairment:

- Preterm birth
- Retinopathy of Prematurity (ROP)
- Intrapartum-related neonatal encephalopathy
- Neonatal infections
- Neonatal jaundice

47 authors, 35 institutions led by LSHTM

Input to Global Burden of Disease with IHME

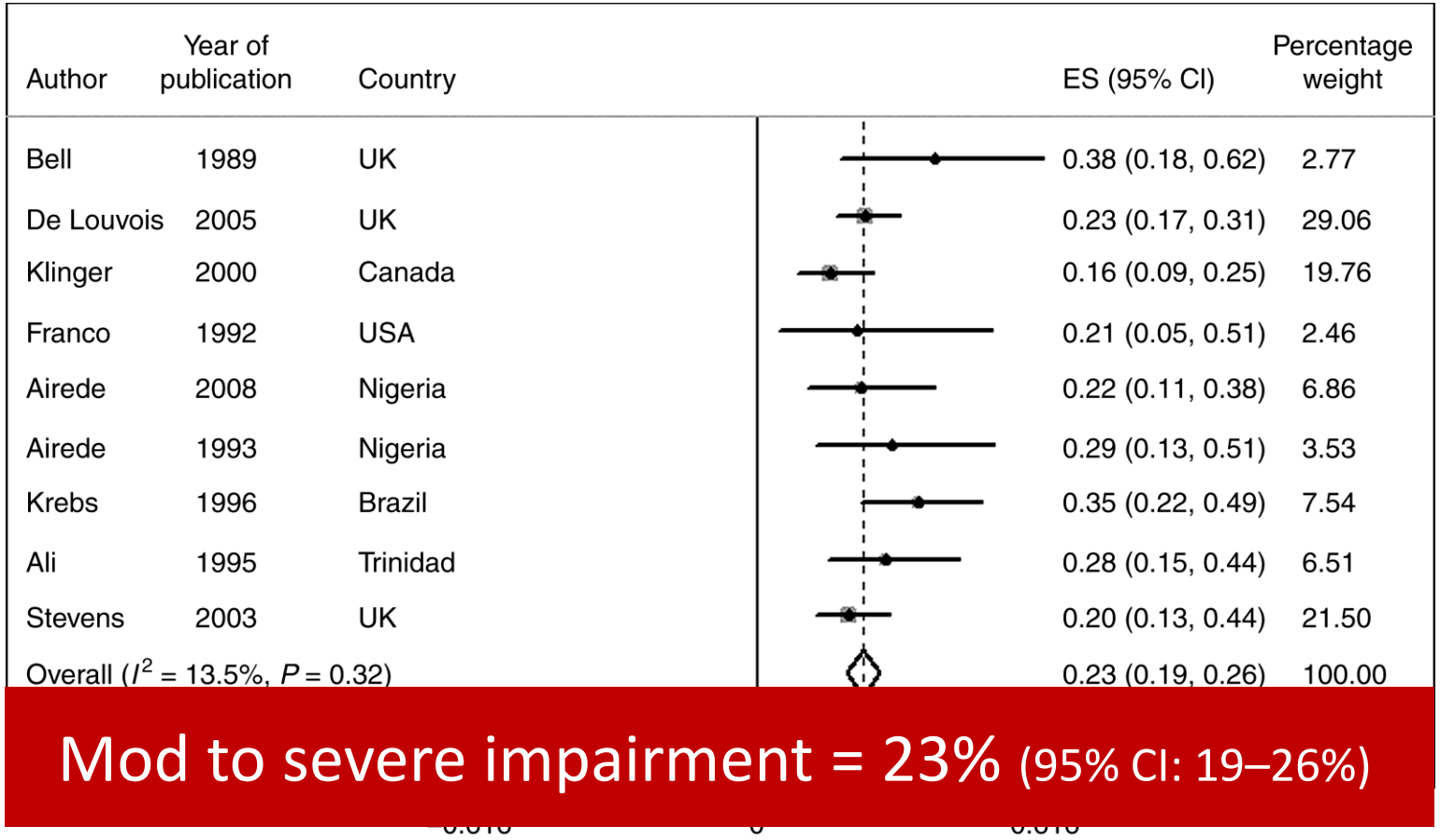
Neonatal conditions accounted for **7.5%** of worldwide DALYs in 2017

Similar burden to all of Cardiovascular DALYS, 3 x HIV/AIDS

Mostly (>95%) attributed to mortality

Survivors of Neonatal Meningitis

Moderate to severe neurodevelopmental impairment (8 studies, N=451)



Author	Year of publication	Country	ES (95% CI)	Percentage weight
Bell	1989	UK	0.38 (0.18, 0.62)	2.77
De Louvois	2005	UK	0.23 (0.17, 0.31)	29.06
Klinger	2000	Canada	0.16 (0.09, 0.25)	19.76
Franco	1992	USA	0.21 (0.05, 0.51)	2.46
Airede	2008	Nigeria	0.22 (0.11, 0.38)	6.86
Airede	1993	Nigeria	0.29 (0.13, 0.51)	3.53
Krebs	1996	Brazil	0.35 (0.22, 0.49)	7.54
Ali	1995	Trinidad	0.28 (0.15, 0.44)	6.51
Stevens	2003	UK	0.20 (0.13, 0.44)	21.50
Overall (I^2 = 13.5%, P = 0.32)			0.23 (0.19, 0.26)	100.00

Mod to severe impairment = 23% (95% CI: 19–26%)

Mild impairment 12% (95% CI: 5–19%)

Hearing impairment 7% (95% CI: 3–12%)

Old, small, studies

Age of follow up
(aged 2 to 5 yrs)
Less likely to detect mild impairments

Measurement tools..
>100 child development assessment tools

Anna C. Seale et al 2013, Ped Res, Nature Publishing 2013

Survivors of Neonatal Sepsis

Neurological and developmental outcome of neonatal jaundice and sepsis in rural Kenya

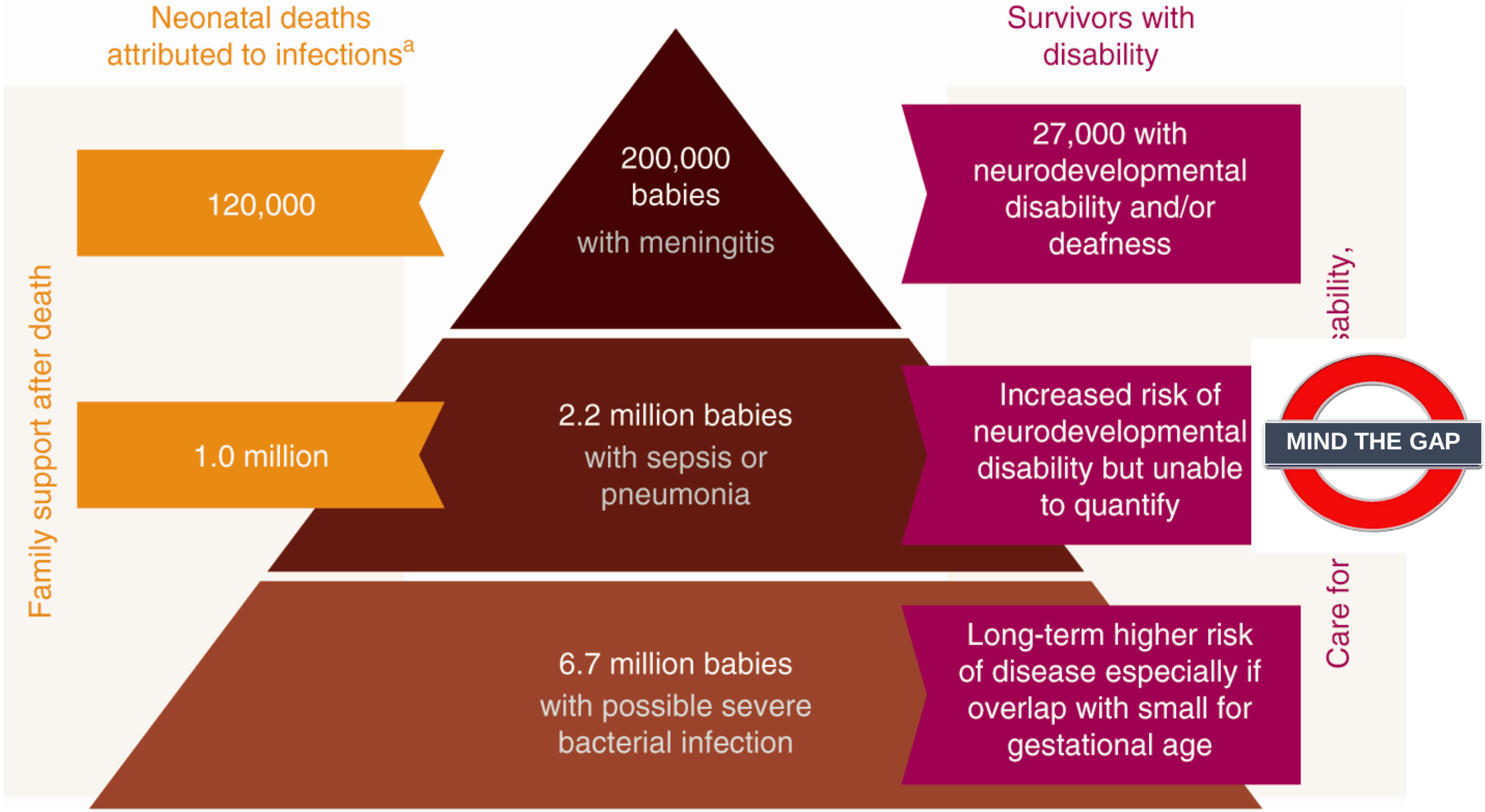
Anne L. Gordon[1,2], Michael English[1,3], J. Tumaini Dzombo[1], Mary Karisa[1] and Charles R. J. C. Newton[1,2]

1 *Centre for Geographic Medicine Research – Coast, KEMRI/Wellcome Trust Research Laboratories, Kilifi, Kenya*
2 *Neurosciences Unit, Institute of Child Health, University College London, UK*
3 *Departments of Paediatrics, University of Oxford, John Radcliffe Hospital, Oxford, UK*

Domain assessed	NJ ($n = 23$)	NS ($n = 24$)	CC ($n = 40$)	Comparison of NJ and CC groups	Comparison of NS and CC groups
Age (months) median (IQR)	23 (19, 27)	24 (19, 29)	27 (24, 30)	0.040	NS
Anthropometric data					
Weight (kg) mean (SD)	9.6 (2.0)	9.7 (1.6)	10.6 (1.3)	0.016	0.011
Height (cm) mean (SD)	78.4 (5.8)	79.5 (4.8)	81.5 (4.2)	0.011	NS
Head circumference (cm) mean (SD)	46.1 (1.7)	46.4 (2.5)	47.8 (1.4)	<0.001	0.007
Head circumference below second centile§ no. (%)	19 (83)	14 (58)	16 (40)	0.001†	NS
Eye signs no. (%)					
Unable to elicit horizontal optokinetic nystagmus	12 (52)	1 (4)	0 (0)	<0.001†	NS
Smooth pursuit disturbed	11 (48)	2 (8)	1 (3)	<0.001†	NS
Saccades disturbed	11 (48)	2 (8)	3 (8)	0.001†	NS
Neurological signs no. (%)					
Movement Disorder	11 (48)	0 (0)	3 (2)	0.001†	NS
Dystonia	8 (35)	0 (0)	0 (0)	<0.001†	NS
Motor signs no. (%)					
Posture and stability					
Unable to sit unsupported	8 (35)	0 (0)	0 (0)	<0.001†	NS
Unable to stand unsupported	10 (43)	4 (16)	0 (0)	<0.001†	0.008†
Locomotion					
Unable to walk independently	11 (48)	4 (16)	0 (0)	<0.001†	0.008†
Eye-hand and manipulation					
Unable to take lid off jar using two hands	11 (48)	5 (21)	0 (0)	<0.001†	0.009†
Unable to stack two blocks	10 (43)	5 (21)	0 (0)	<0.001†	0.009†
Unable to achieve pincer grasp with preferred hand	9 (38)	2 (9)	0 (0)	<0.001†	NS
Developmental scores median (range)					
Total score	37 (31, 42)	35 (32, 39)	42 (36, 48)	<0.001‡	0.002‡
Motor	11 (9, 13)	11 (10, 12)	12 (10, 14)	NS‡	NS‡
Hearing, speech and language	7 (5, 9)	6 (4, 8)	8 (5, 11)	0.001‡	0.005‡
Eye-hand co-ordination	20 (14, 26)	20 (14, 26)	23 (19, 27)	0.043‡	0.016‡

One study of follow up after neonatal sepsis (average 2 yrs old)

Kilifi, Kenya – only 24 cases, ~17% "cerebral palsy"



Anna C. Seale et al 2013, Ped Res, Nature Publishing 2013

Group B Streptococcus

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*

upported by a grant to the London School of Hygiene & Tropical Medicine from the Bill & Melinda Gates Foundation.

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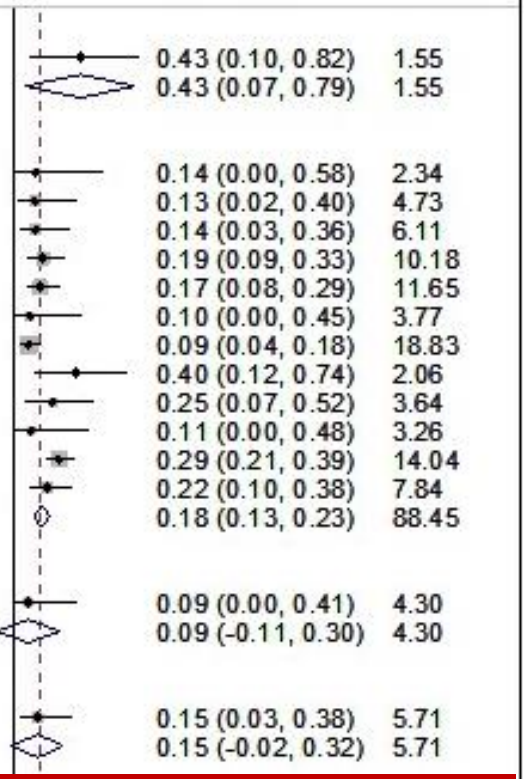
Imperial College London
UCL
ISGlobal Barcelona Institute for Global Health
DHAKA SHISHU(CHILDREN) HOSPITAL Pledged To protect Child Health
St George's University of London

Survivors of Group B Strep Meningitis

Mod to severe neurodevelopmental impairment (15 studies, N=453, to age of 18 months)

Author	Country	Year of Publication	Number of GBS meningitis survivors	Number of GBS meningitis survivors with moderate-severe NDI	ES (95% CI)	% Weight
Northern Africa						
Ben Hamouda	Tunisia	2013	7	3	0.43 (0.10, 0.82)	1.55
Subtotal (I-squared = .%, p = .)					0.43 (0.07, 0.79)	1.55
Developed						
Horn	USA	1974	7	1	0.14 (0.00, 0.58)	2.34
Haslam	USA	1977	15	2	0.13 (0.02, 0.40)	4.73
Chin	USA	1985	21	3	0.14 (0.03, 0.36)	6.11
Edwards	USA	1985	48	9	0.19 (0.09, 0.33)	10.18
Wald	USA	1986	54	9	0.17 (0.08, 0.29)	11.65
Franco	USA	1992	10	1	0.10 (0.00, 0.45)	3.77
Libster	USA	2012	85	8	0.09 (0.04, 0.18)	18.83
Schroder	Germany	1982	10	4	0.40 (0.12, 0.74)	2.06
Bennhagen	Sweden	1987	16	4	0.25 (0.07, 0.52)	3.64
Bennhagen	Sweden	1987	9	1	0.11 (0.00, 0.48)	3.26
Bedford	UK	2001	103	30	0.29 (0.21, 0.39)	14.04
Heath	UK	2017	37	8	0.22 (0.10, 0.38)	7.84
Subtotal (I-squared = 29.3%, p = 0.158)					0.18 (0.13, 0.23)	88.45
Eastern Asia						
Zhu	China	2014	11	1	0.09 (0.00, 0.41)	4.30
Subtotal (I-squared = .%, p = .)					0.09 (-0.11, 0.30)	4.30
Southeastern Asia						
Wee	Singapore	2016	20	3	0.15 (0.03, 0.38)	5.71
Subtotal (I-squared = .%, p = .)					0.15 (-0.02, 0.32)	5.71



Mod to severe impairment = 18% (95% CI: 13-22%)

13/15 studies more than 10 yrs ago

Age of follow up (aged 18 months) Less likely to detect mild impairments

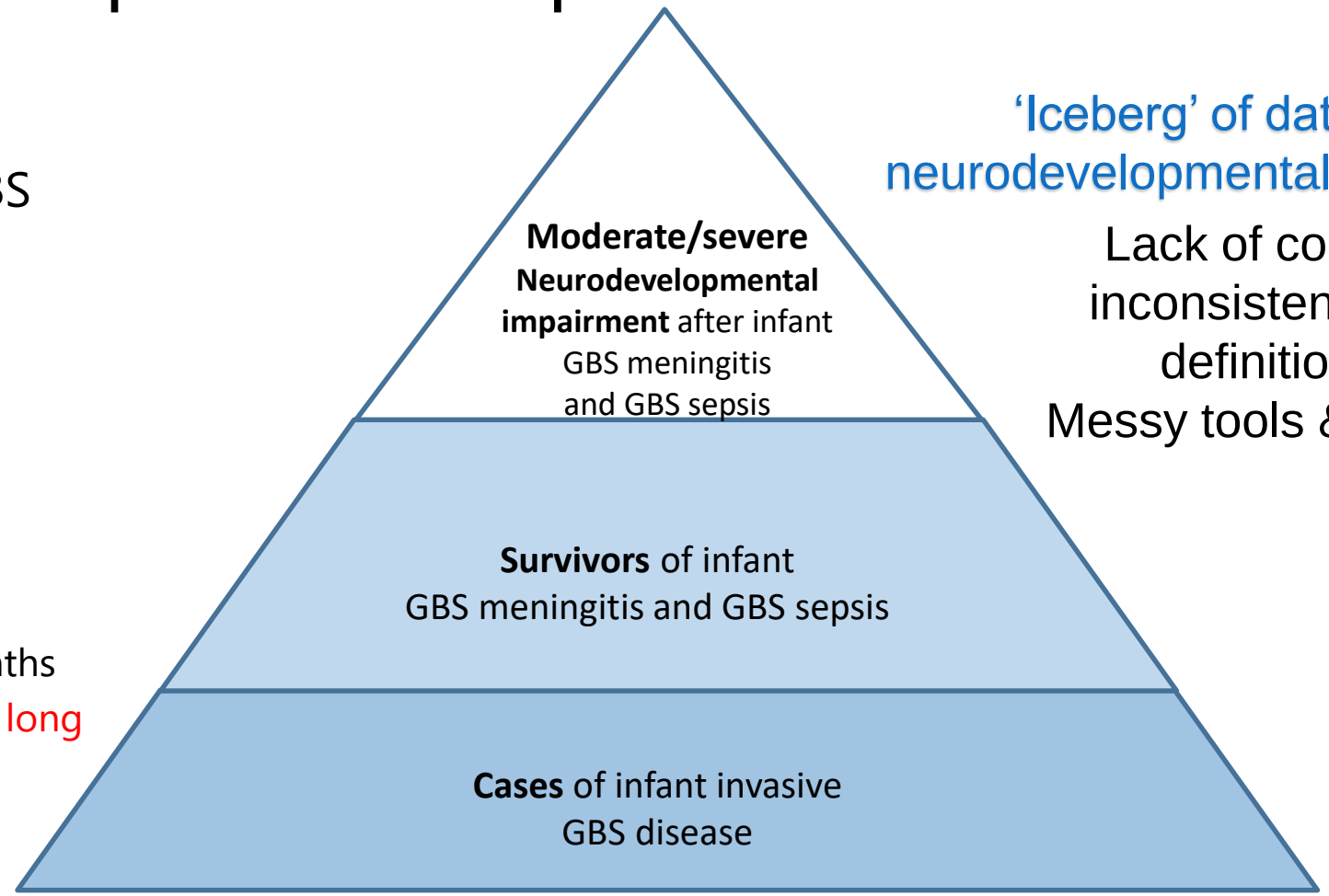
Measurement tools.. >100 child development assessment tools

Maya Kohli-Lynch et al , CID, 2017

Step 4. Neurodevelopmental impairment after GBS

- 229,000 survivors of infant GBS disease with
  - Sepsis: 171,000
  - Meningitis: 58,000

- Risk of neurodevelopmental impairment after
  - GBS Meningitis: 18% moderate/severe NDI at 18 months
  - GBS Sepsis: not able to quantify long term outcomes
  - Mild neurodevelopmental impairment not quantified



'Iceberg' of data on neurodevelopmental outcomes

Lack of cohorts, inconsistent case definitions, Messy tools & timing,

Kohli-Lynch, et al Clinical Infectious Diseases. 2017;65(S2):S190-99

Min est of 10,000 infants (3000-27,000) per year moderate-severe neurodevelopment impairment after GBS meningitis, and unknown after GBS sepsis

Finagel's laws of information

Pessimistic 20th century Scottish man

1. The information you have is not what you want
2. The information you want is not what you need
3. The information you need is not what you can obtain
4. The information you can obtain costs more than you want to pay

Laws to improve health information

Actionable 21st century Measurement improvement

1. The information we NEED
2. The information we have that we can USE now!
3. The information that we must OBTAIN!
4. The information system that would cost less if we INTEGRATED more!

Multi-domain measurement = messy!

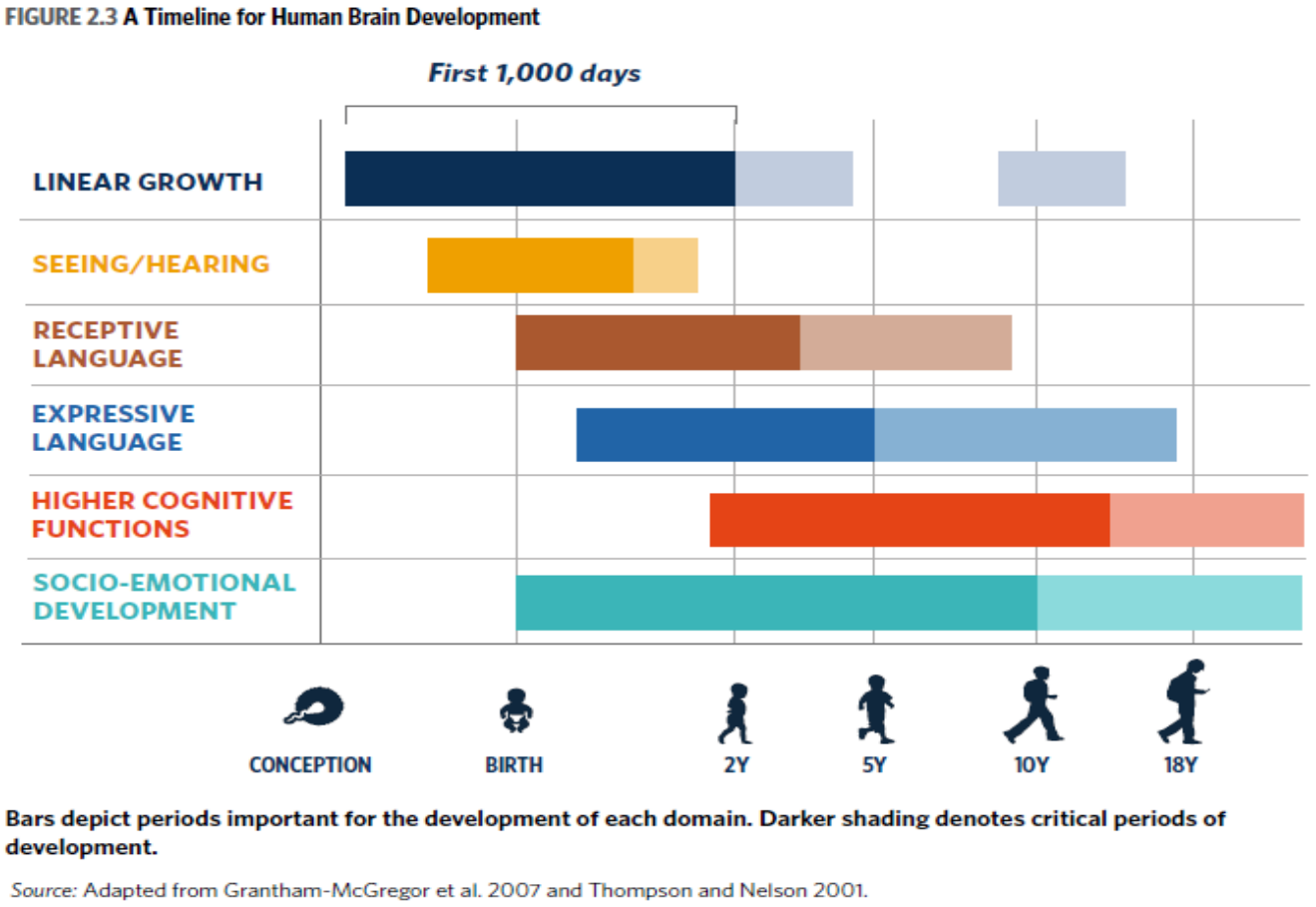


FIGURE 2.3 A Timeline for Human Brain Development

Bars depict periods important for the development of each domain. Darker shading denotes critical periods of development.

Source: Adapted from Grantham-McGregor et al. 2007 and Thompson and Nelson 2001.

Fernald LCH, Prado E, Kariger P, Raikes A, SIEF World Bank 2017

Archives of Disease in Childhood

Global child health: Design and implementation for early child development programmes P3

OPEN ACCESS

Rating early child development outcome measurement tools for routine health programme use

Dorothy Boggs,[1,2] Kate M Milner,[1,3] Jaya Chandna,[4] Maureen Black,[5,6] Vanessa Cavallera,[7] Tarun Dua,[7] Guenther Fink,[8] Ashish KC,[9] Sally Grantham-McGregor,[10] Jena Hamadani,[11] Rob Hughes,[12,13] Karim Manji,[14] Dana Charles McCoy,[15] Cally Tann,[1,16] Joy E Lawn[1]

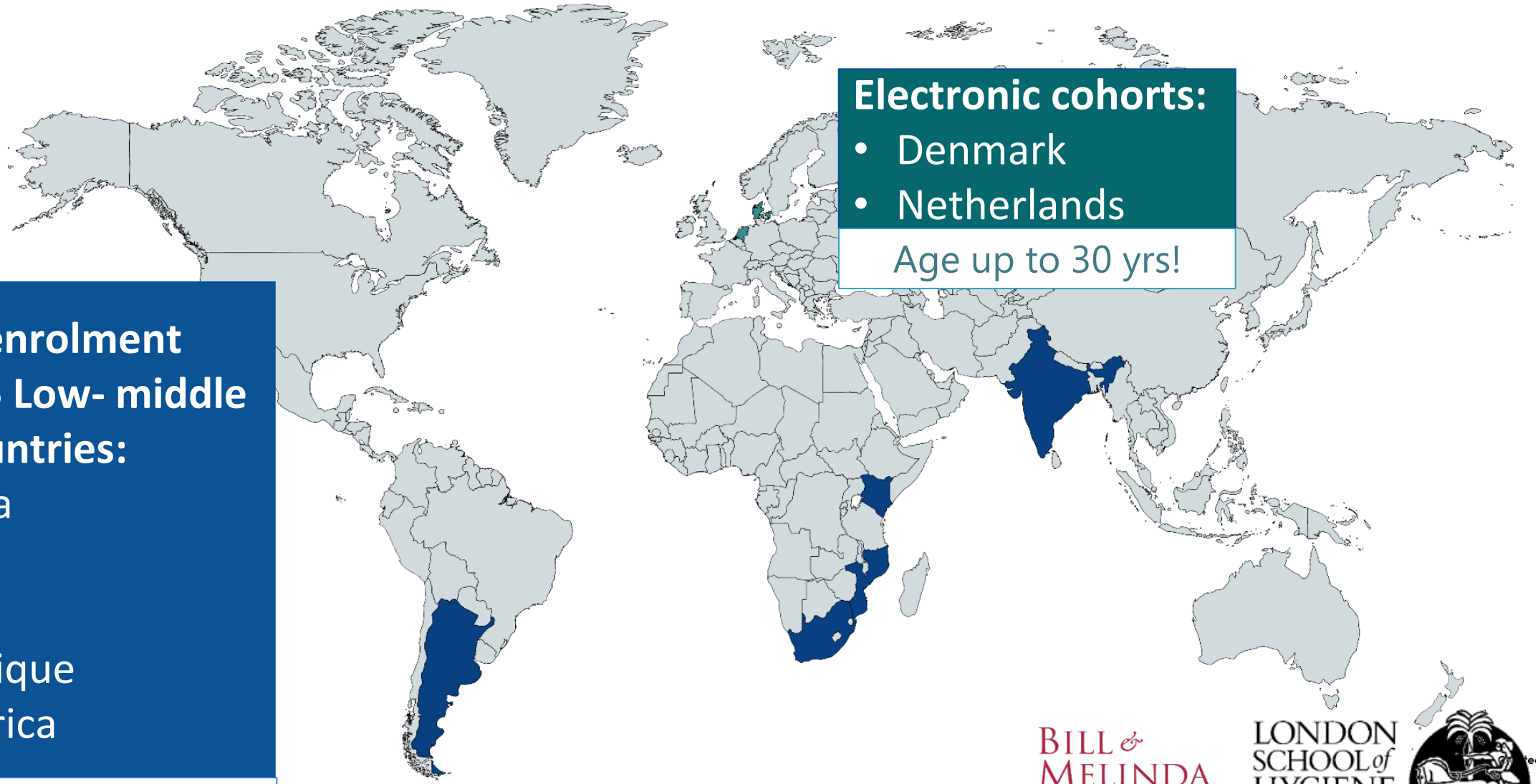
- Measuring neurodevelopment is multi-domain. Must include hearing and vision.
- Over 100 tools (mostly measure 6mnths-3years) but few meet accuracy and feasibility criteria
- Major challenges: cost, training requirements and adaptability
- Need for a simple, adaptable measurement that can be used across multiple LMICs

Boggs, Dorothy, et al. "Rating early child development outcome measurement tools for routine health programme use." *Archives of disease in childhood* 104.Suppl 1 (2019): S22-S33

WHO working on a new score (GSED) short and long form

Survivors of Group B Strep Meningitis and Sepsis

New data collection in progress



Electronic cohorts:

- Denmark
- Netherlands

Age up to 30 yrs!

Cohort re-enrolment studies in 5 Low- middle income countries:

- Argentina
- India
- Kenya
- Mozambique
- South Africa

Age ~3-15!

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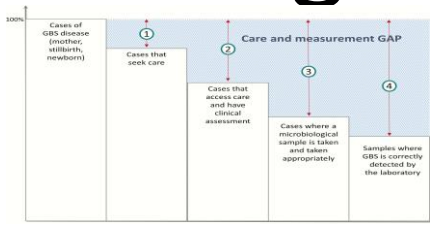
Closing data gaps



1. Careseeking and UHC (± active surveillance)
2. Clinical care improved quality
3. Lab investigations, LP to become the norm
4. Lab capacity strengthening (esp for GBS)

   Innovation – diagnostics, new interventions

- Follow up systems for at-risk newborns and COHORT studies to 5 years and beyond
- Improved measures/tools to detect multi-domain impairment, feasible in routine programmes

Closing care gap

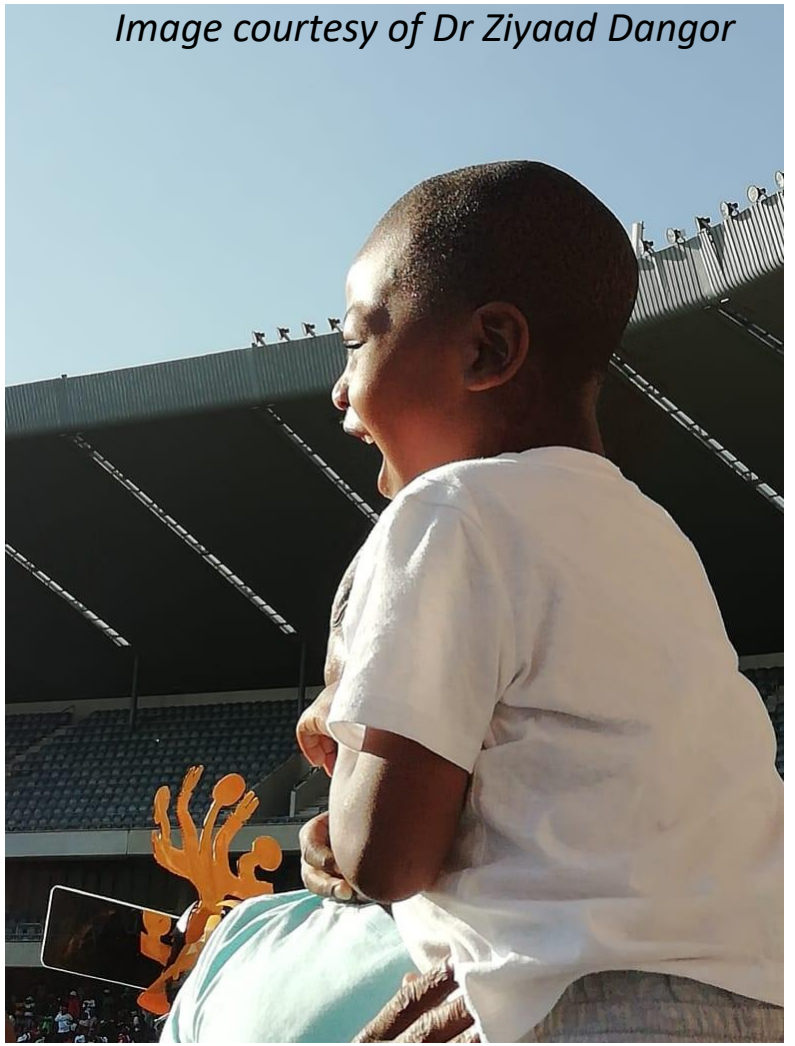


Image courtesy of Dr Ziyaad Dangor

Bad data will always be with us – but we need to smell it, improve it & use it!

Children, adults families affected need care, support and voice, not just a statistic

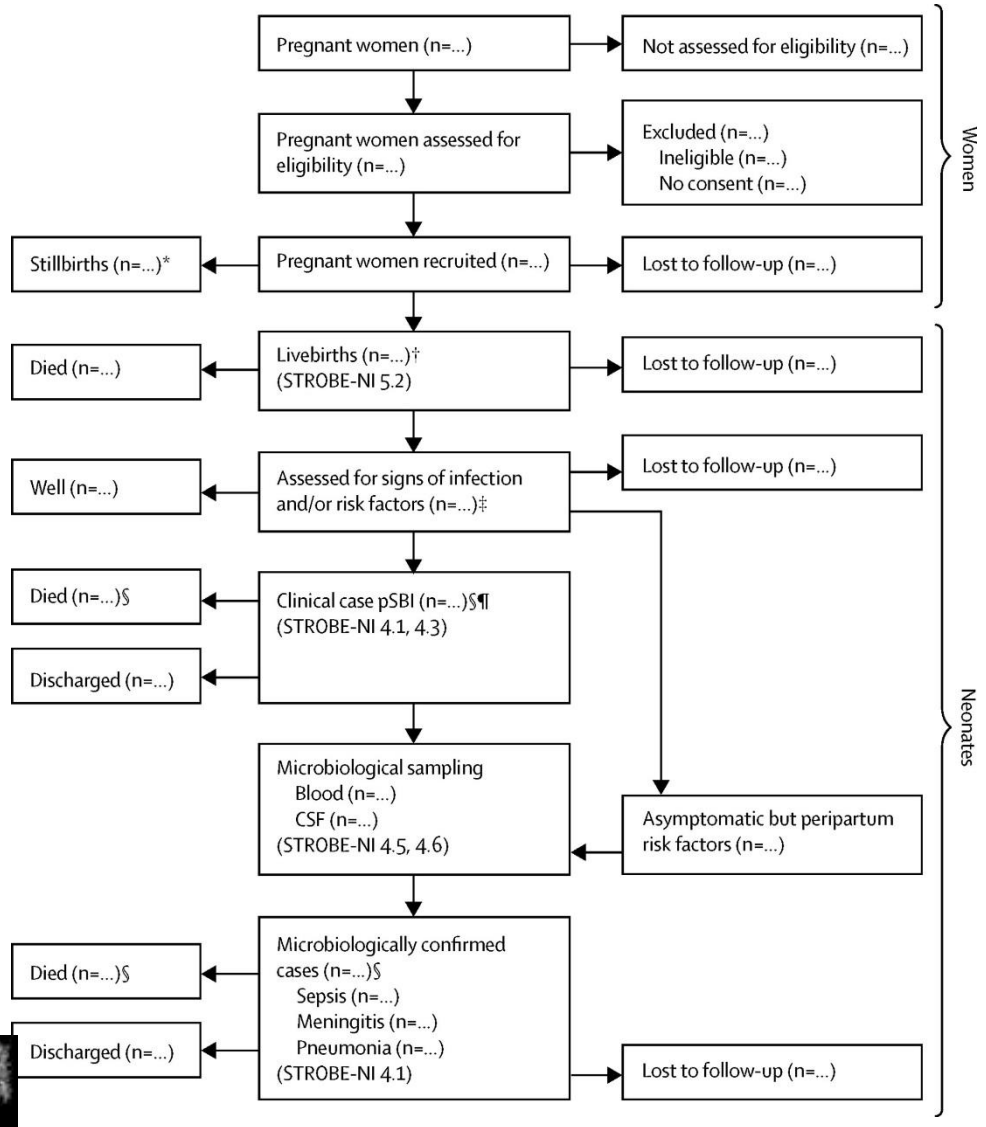
ADVANCE NOTICE
Group B Strep Global Conference
ISSAD 2021 in London

@joylawn

Image courtesy of Dr Cally Tann and Karen Martin

Challenge 1 – exposure and definitions

STROBE – Neonatal Infections



Review

Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection (STROBE-NI): an extension of the STROBE statement for neonatal infection research

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SPRINGuidance

ELSEVIER *The Lancet Infectious Diseases* 2016 16, e202-e213DOI: (10.1016/S1473-3099(16)30082-2)