Public Health Ontario | Santé publique Ontario

To view an archived recording of this presentation please click the following link:

https://youtu.be/0lB9HrGcat4

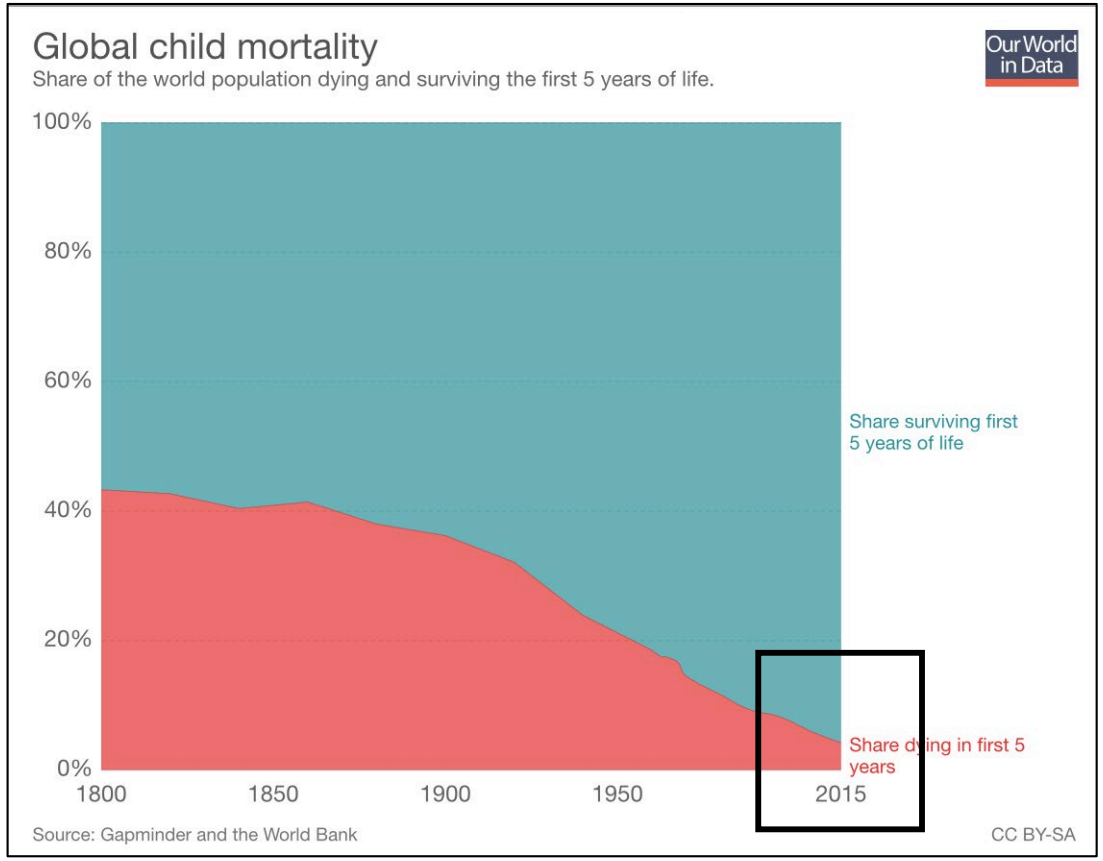
Please scroll down this file to view a copy of the slides from the session.

Neonatal Sepsis in Low-resource Settings:

what's the problem??

Susan Coffin, MD, MPH
UPenn School of Medicine
Children's Hospital of Philadelphia
October 2023

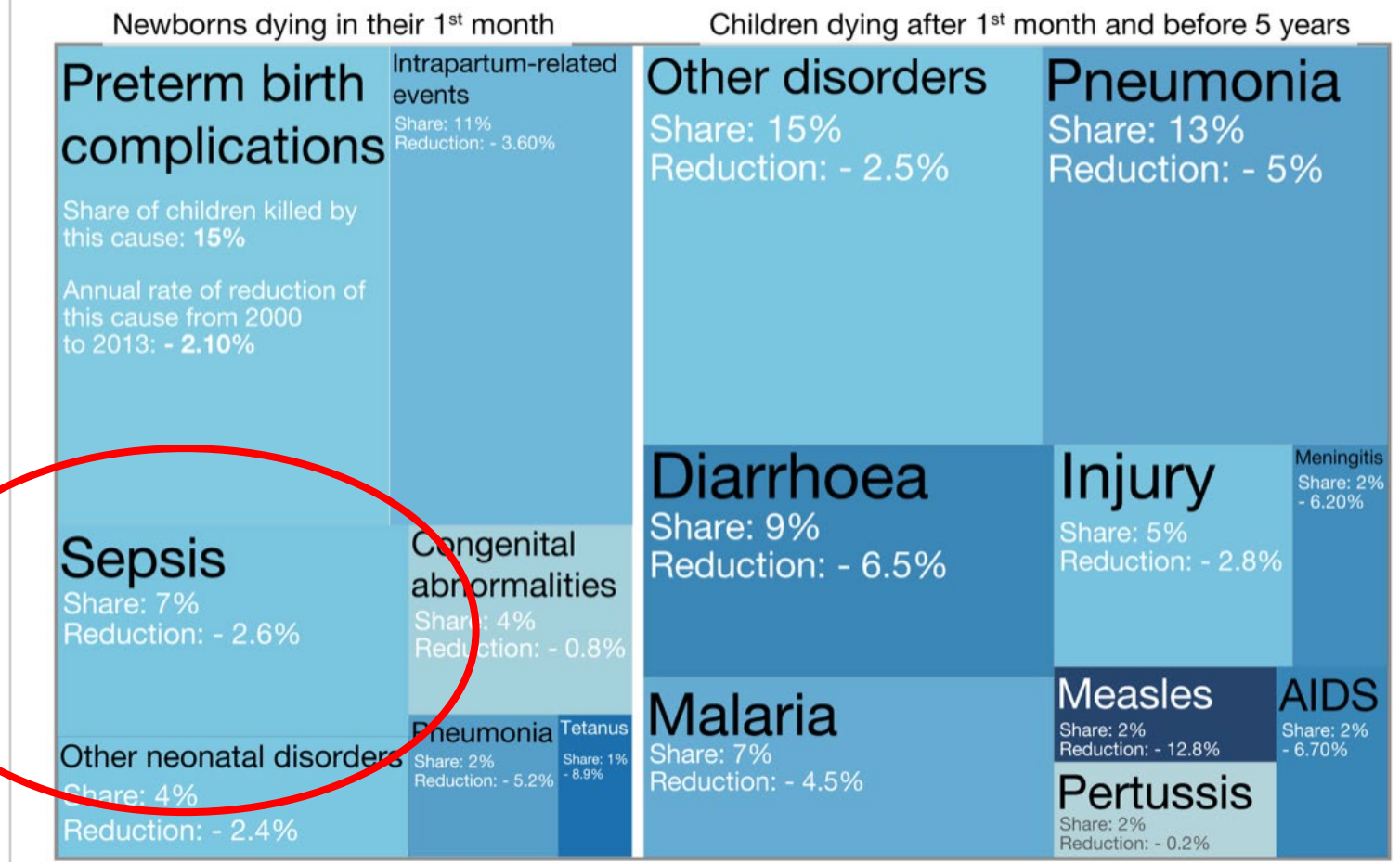
Steady Improvements in Child Survival



Causes of Child Mortality, 2013 (annual rate of reduction 2000-2013)

Sepsis + other infections
= 1/3 neonatal deaths

<3% reduction over 13 yrs



Liu, Lancet, vol 385; 2015.

Objectives

- Describe the conspiracy of forces that drives neonatal sepsis in LMIC
- Examine the microbiology of neonatal sepsis in LMIC
- Review possible interventions

The Conspiracy that Drives Neonatal Sepsis

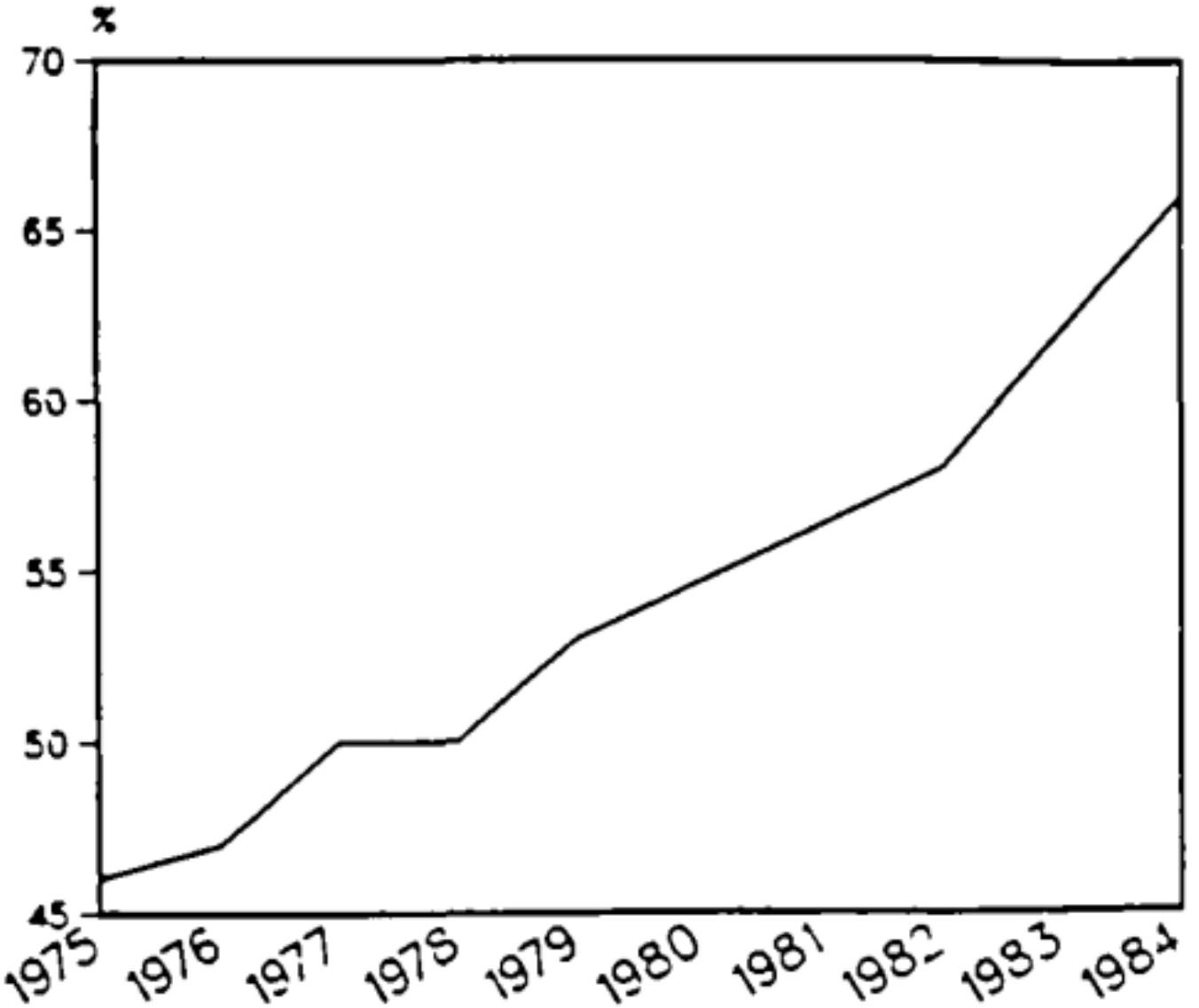


Figure 1. Percentage of supervised deliveries in Botswana from 1975–84 (*Source:* Botswana Ministry of Health, Family Health Division, 1985)

Rising Proportion of Babies Born in Facilities

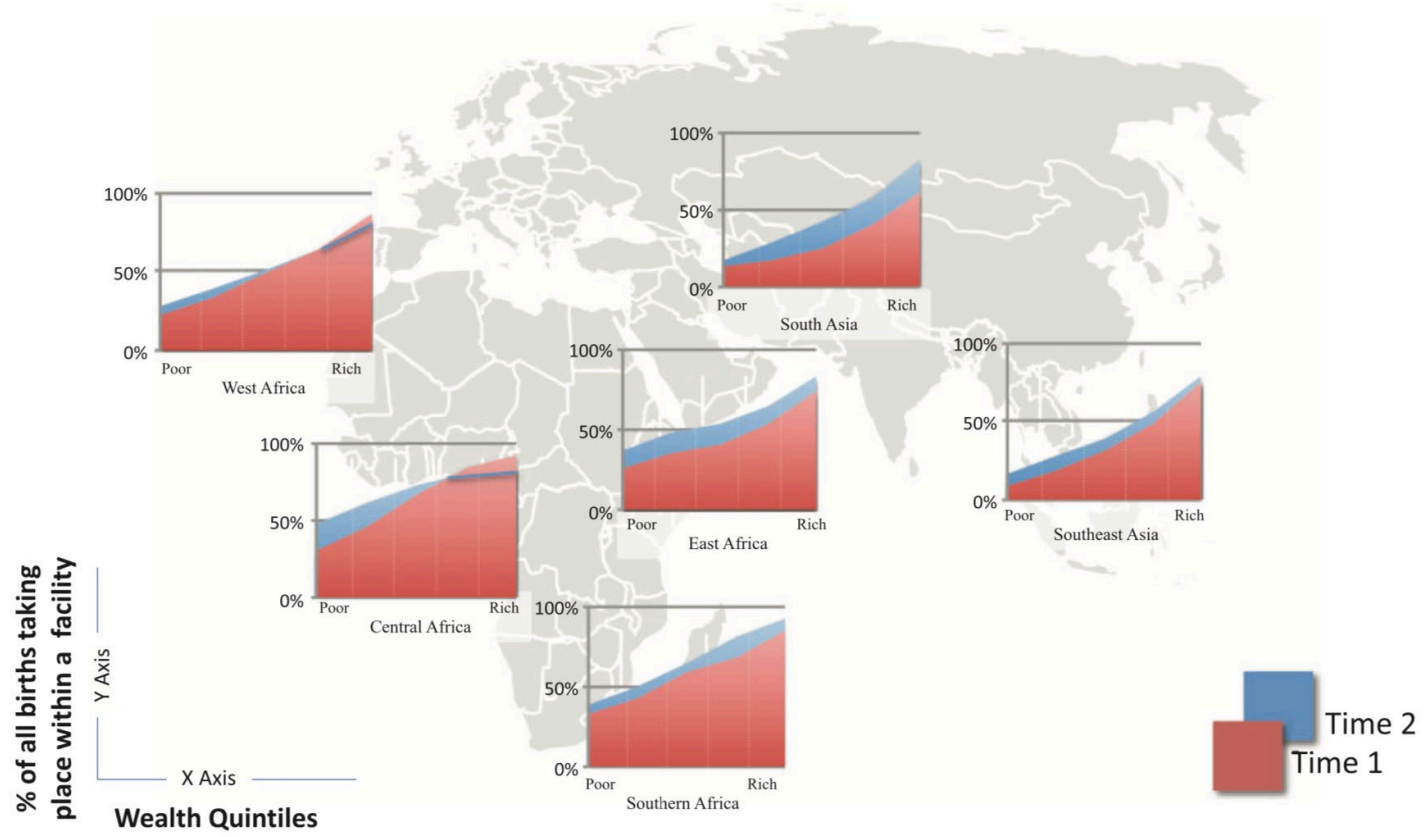


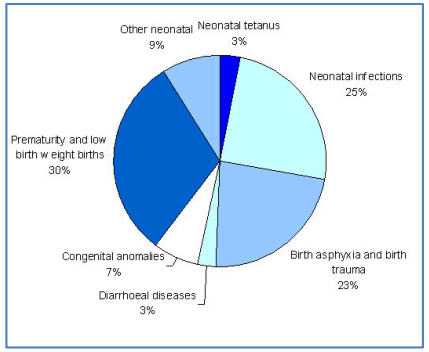
Figure 1. Trends in health facility deliveries across regions, by wealth quintiles (*Source*: Demographic and Health Surveys)

Montagu, Health Policy and Planning, 2017.

What's Going On…

- Initiatives to reduce maternal and neonatal mortality caused unique stresses
  - Majority of maternal mortality attributed to lack of skilled clinical care during and immediately after birth

➢**Solution: Facility births!**



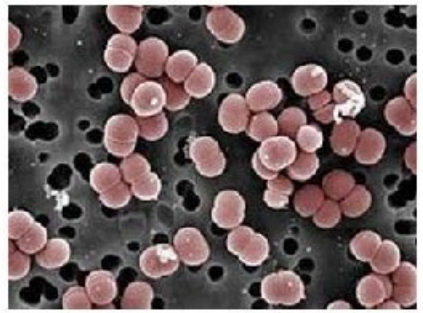
- But…
  - Insufficient resources to accommodate rapid increases in demand for hospital-based births

Related Stresses

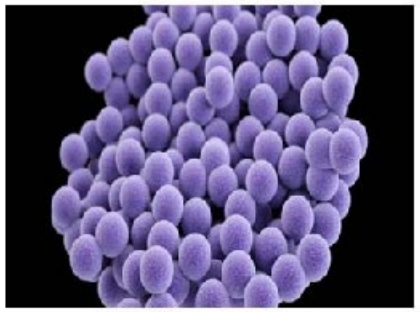
- “Neonatal intensive care units” in resource limited settings may have similar goals but lack similar resources as compared to high-resource settings

  Prematurity
  Perinatal injuries (birth asphyxia)
  Congenital anomalies

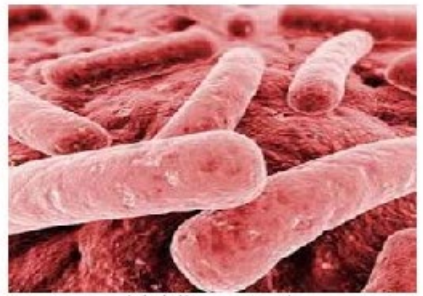
- Need for prolonged periods of in-hospital care exposes many more babies to complications of hospitalization



Enterococcus Faecium



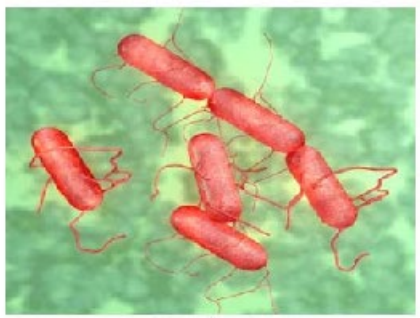
Staphylococcus aureus



Klebsiella pneumoniae

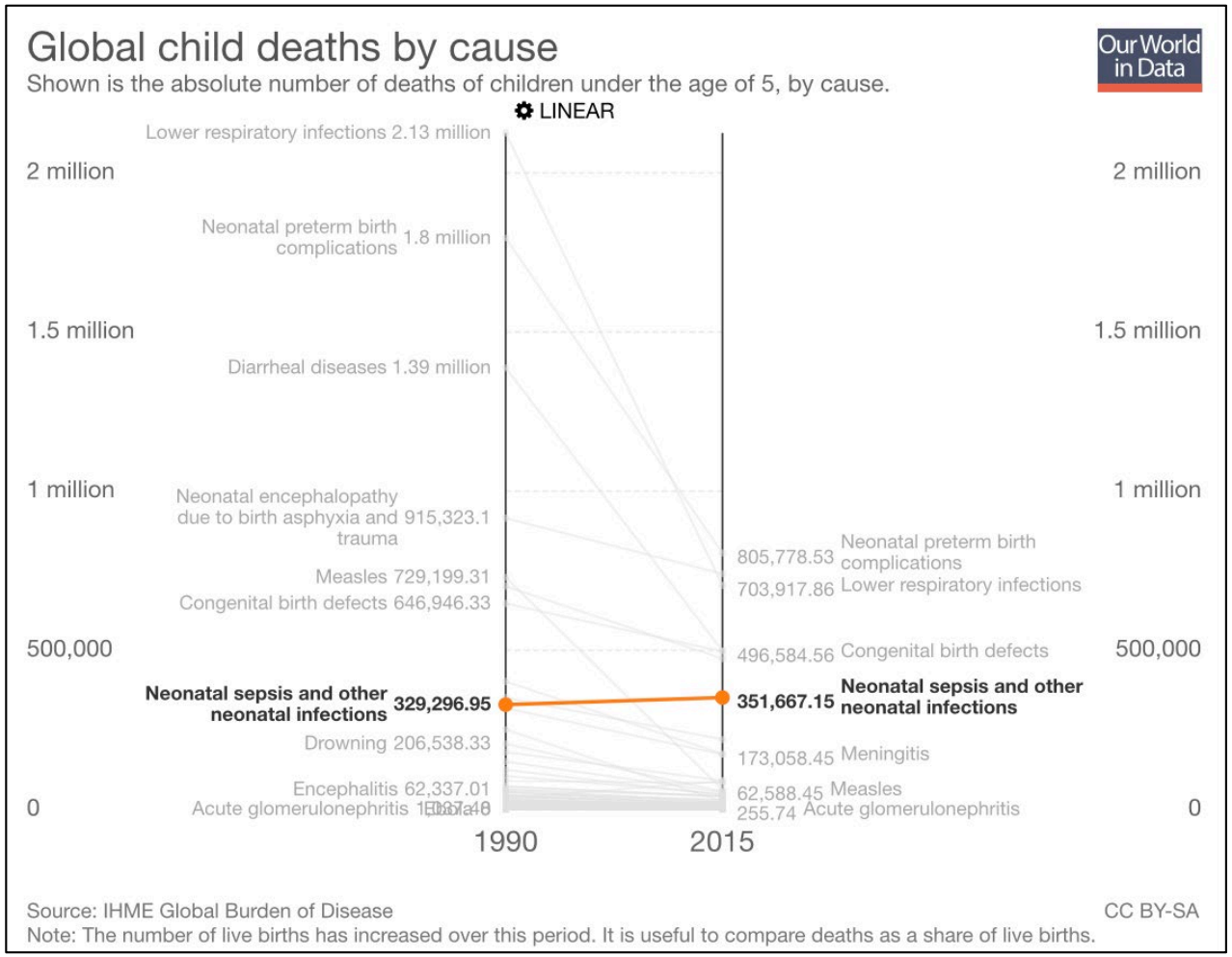
Acinetobacter baumannii

Pseudomonas aeruginosa



Enterobacter

More Babies Hospitalized → More Babies at Risk of Neonatal Sepsis



Bacteremia and lower respiratory tract infections account for >80% of neonatal sepsis

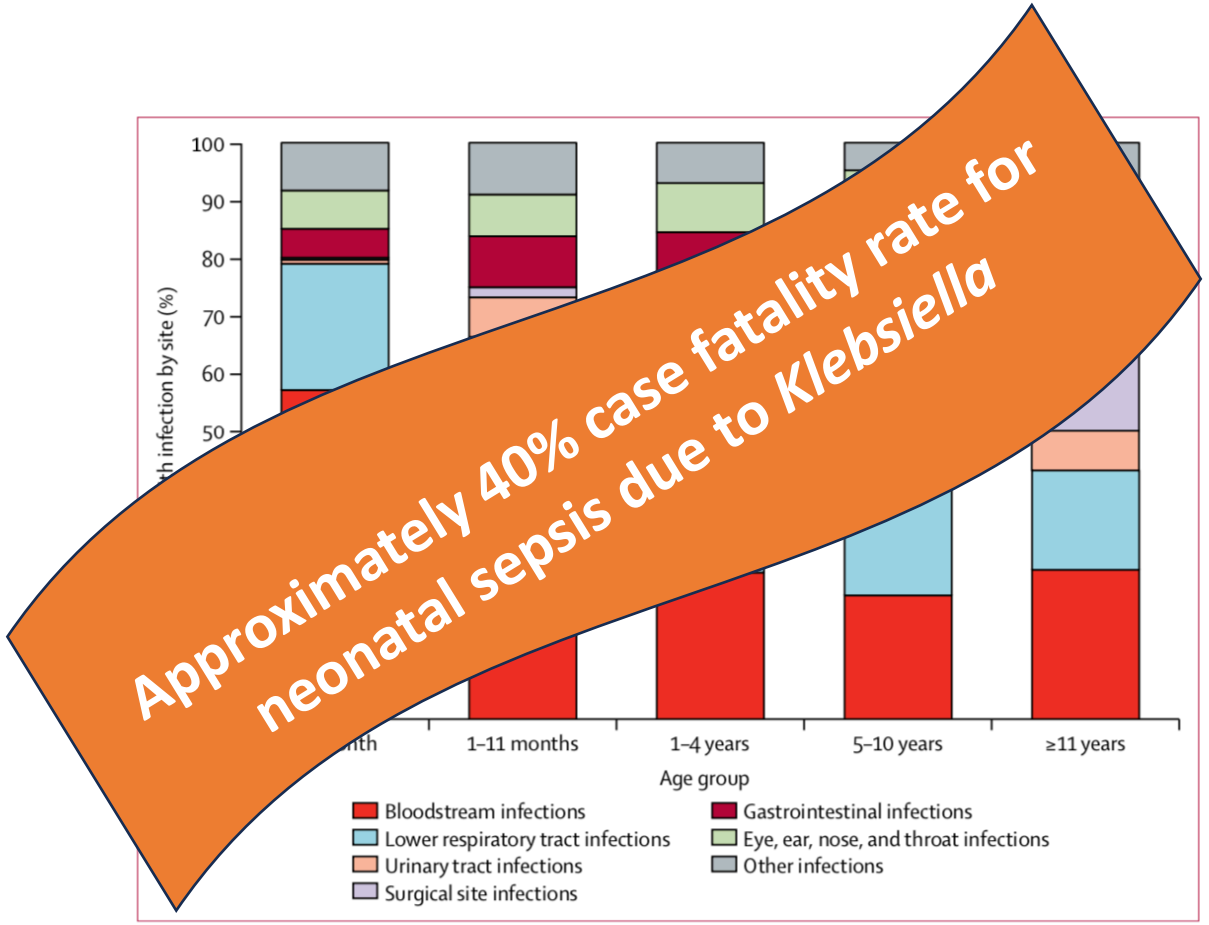
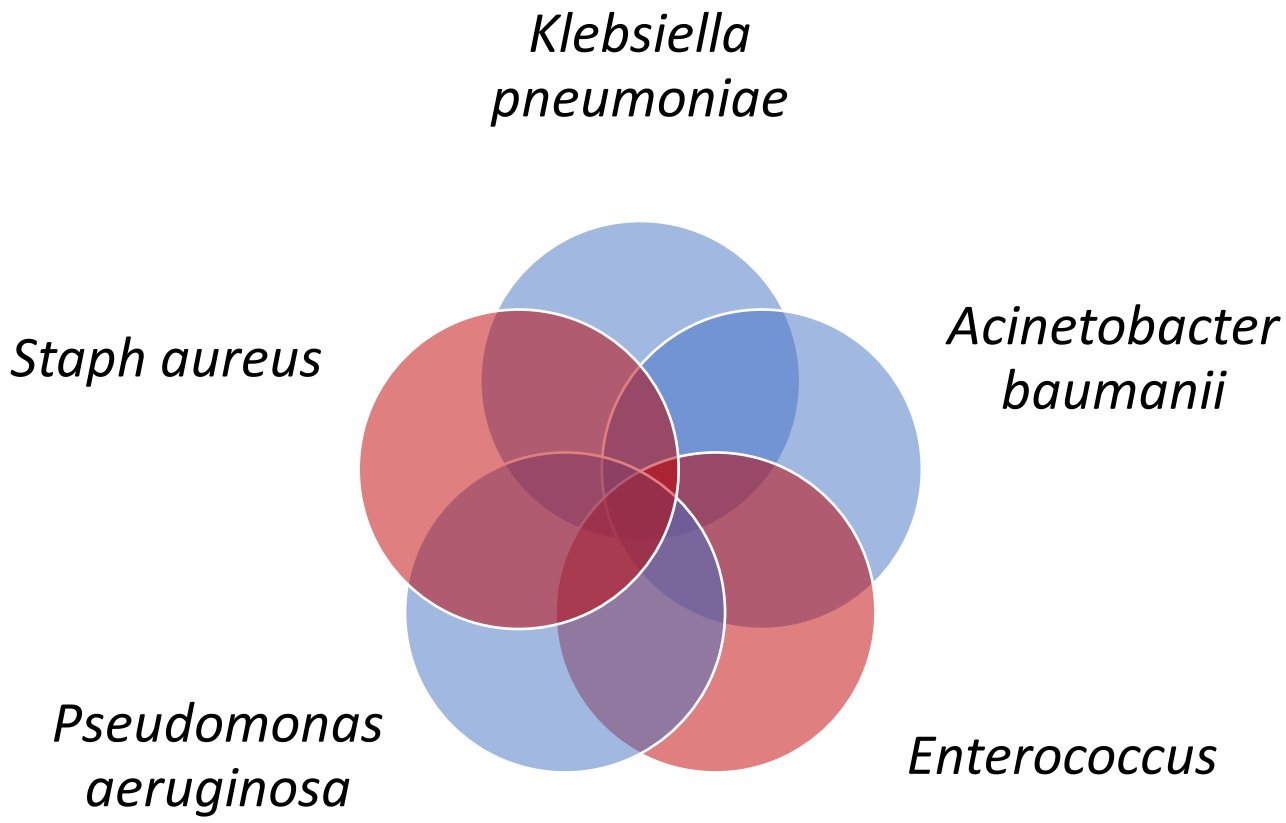
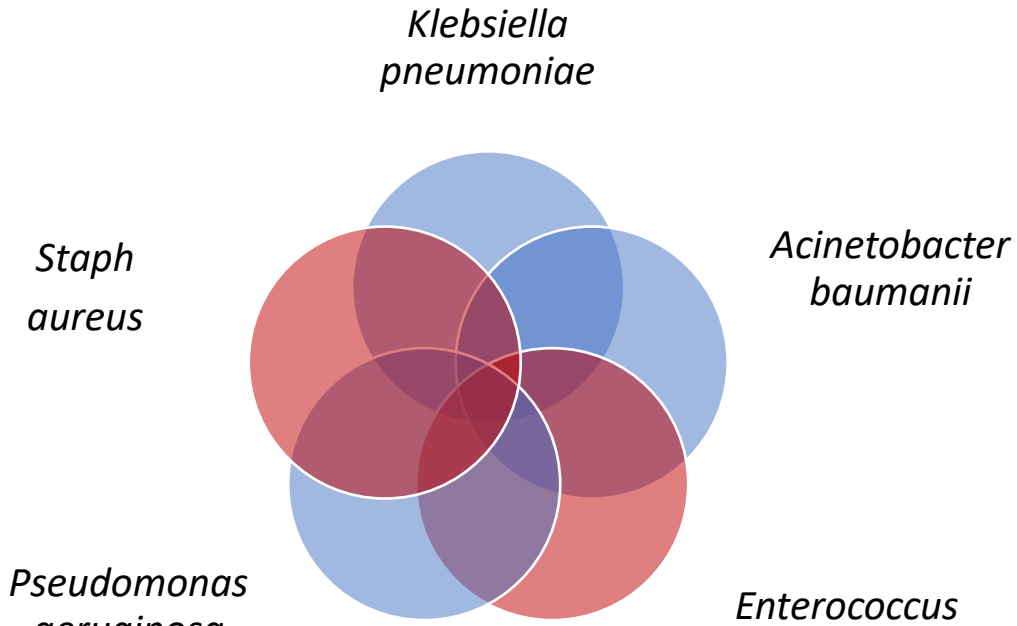


Figure 2: **Distribution of health-care-associated infections in children, by age group**

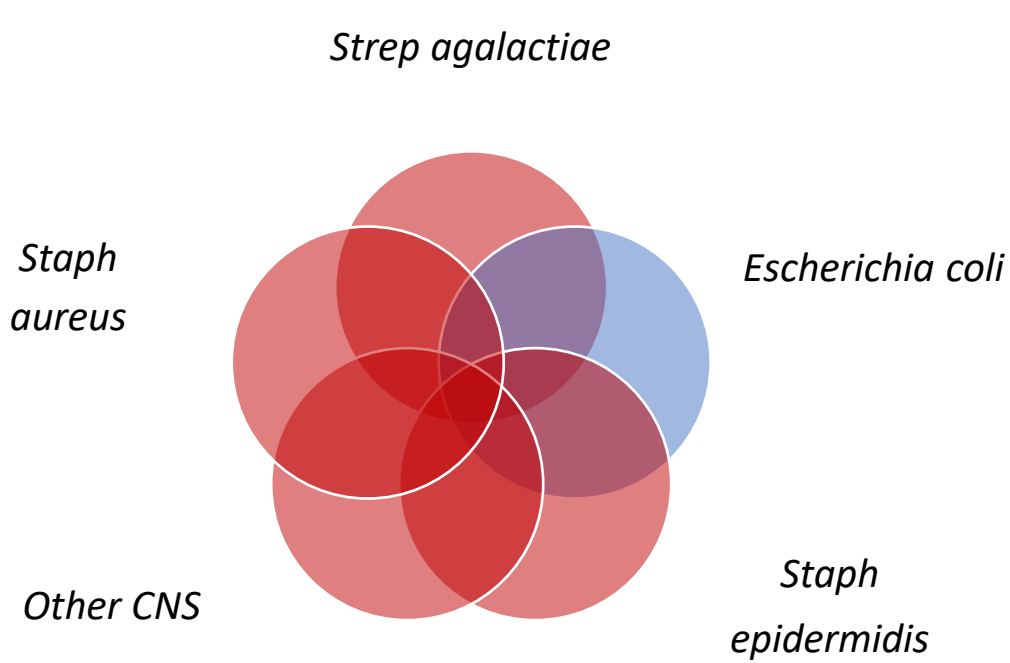
Microbial “Players”



Microbial “Players”



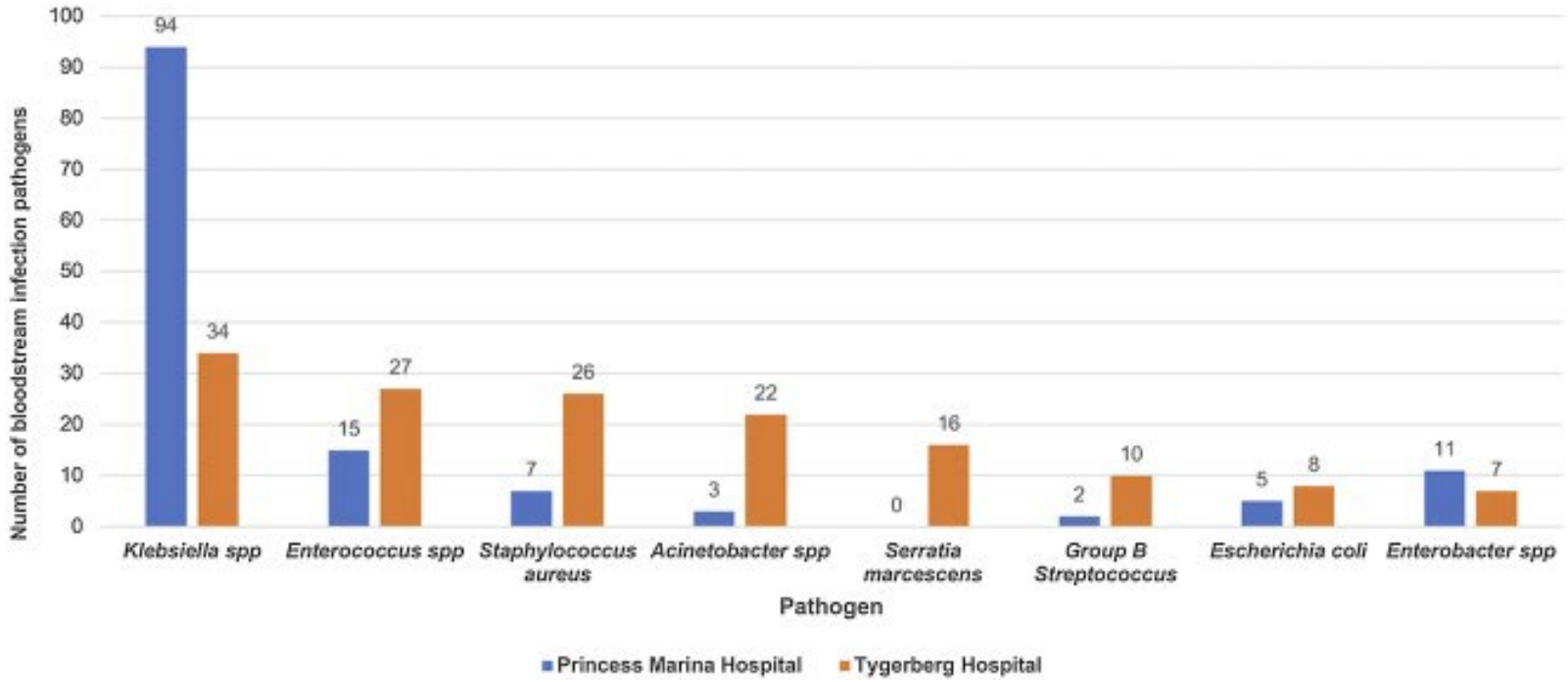
LMIC



HIC

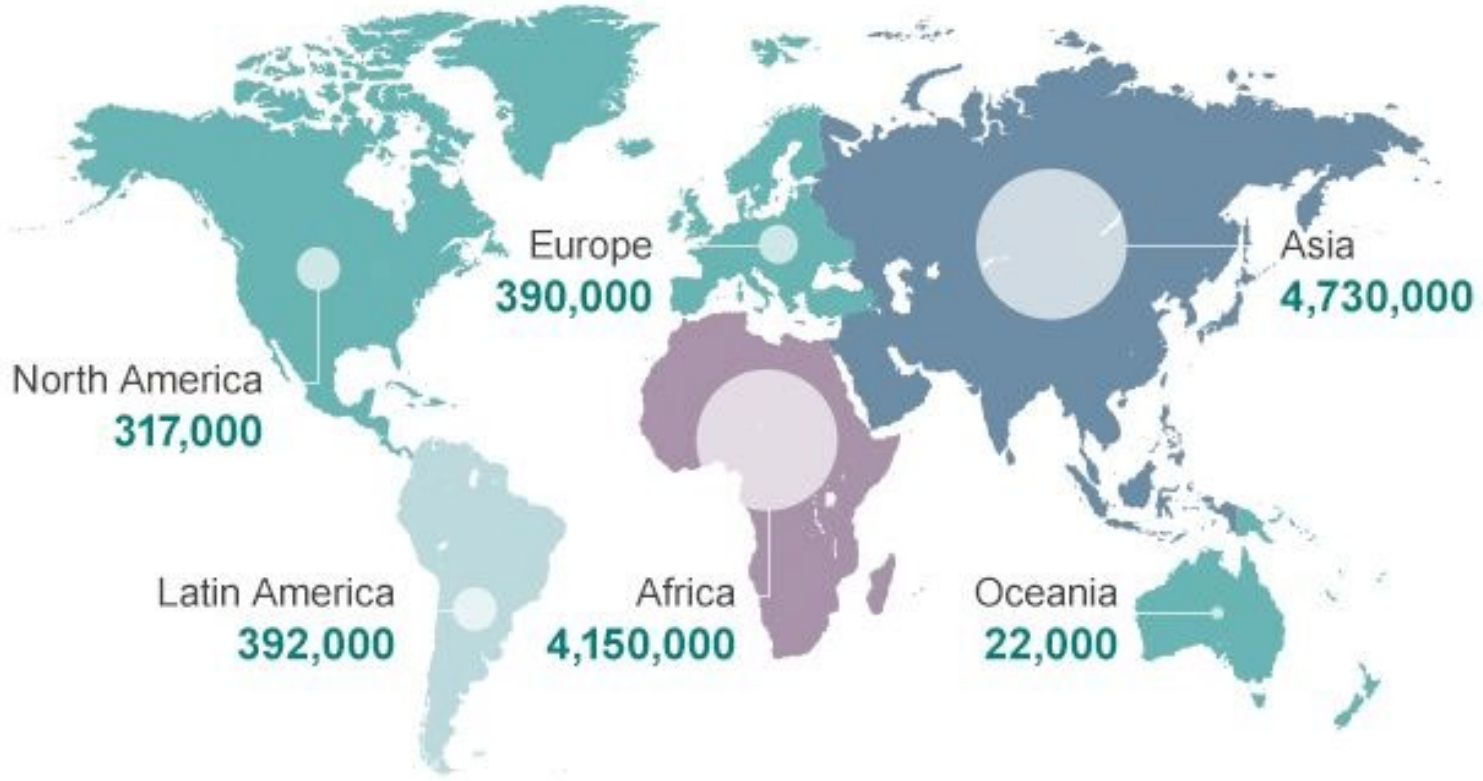
Laboratory-confirmed bloodstream infections in two large neonatal units in sub-Saharan Africa

Alemayehu Mekonnen Gezmu [1], Andre N H Bulabula [2], Angela Dramowski [3], Adrie Bekker [4], Marina Aucamp [5], Sajini Souda [6], Britt Nakstad [7]



Gezmu, Int J Infect Dis, 2021.

Deaths attributable to antimicrobial resistance every year by 2050



Source: Review on Antimicrobial Resistance 2014

Contribution of Resistant Pathogens to Neonatal Sepsis Deaths

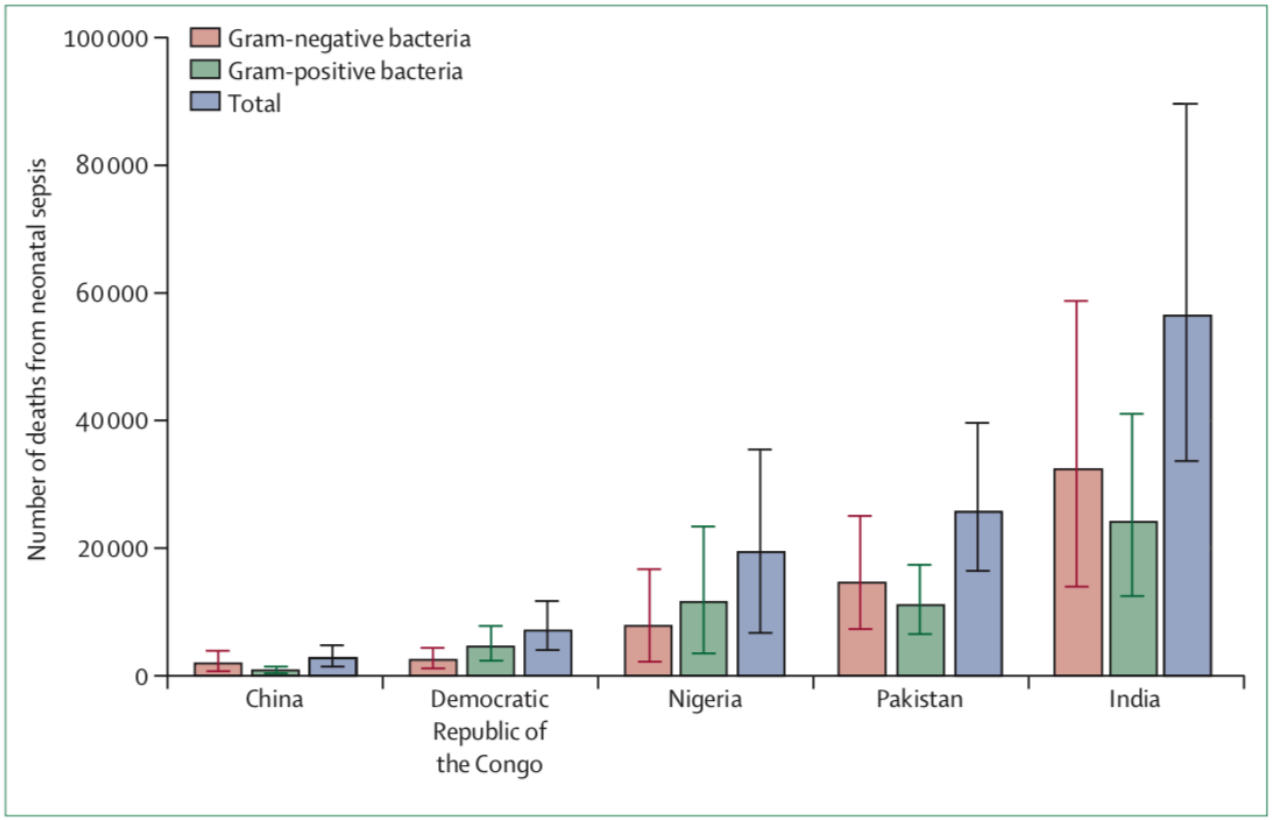
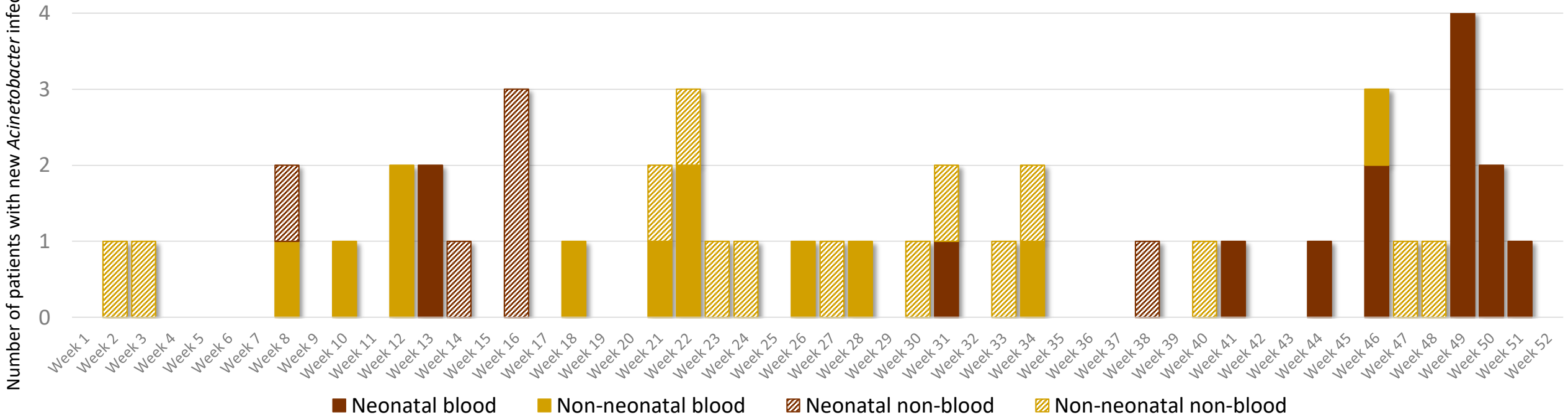


Figure 2: **Estimated neonatal sepsis deaths caused by bacteria resistant to first-line antibiotics in five high-burden countries**

Bars represent maximum and minimum values from Latin Hypercube Sampling model in appendix.

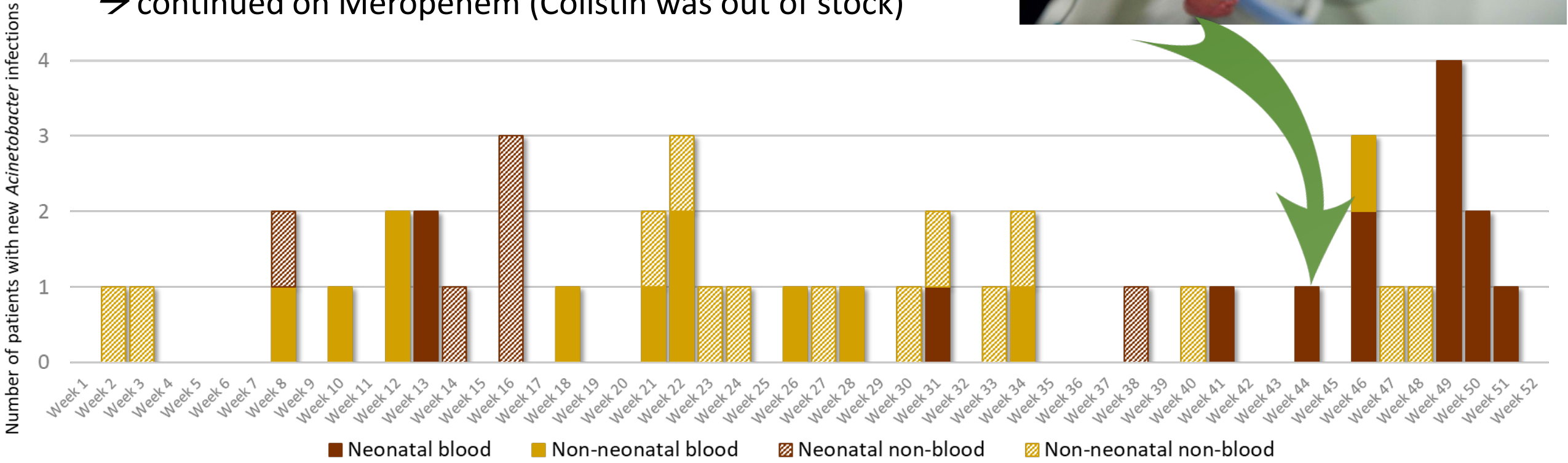
Laxminarayan, Lancet, 2016.

- Incidence of CRAb neonatal bloodstream infections are increasing:
  - 2012: 1%
  - 2017: 2%
  - 2021:16%
    - Median age of symptom onset=4 days; case fatality rate=56%



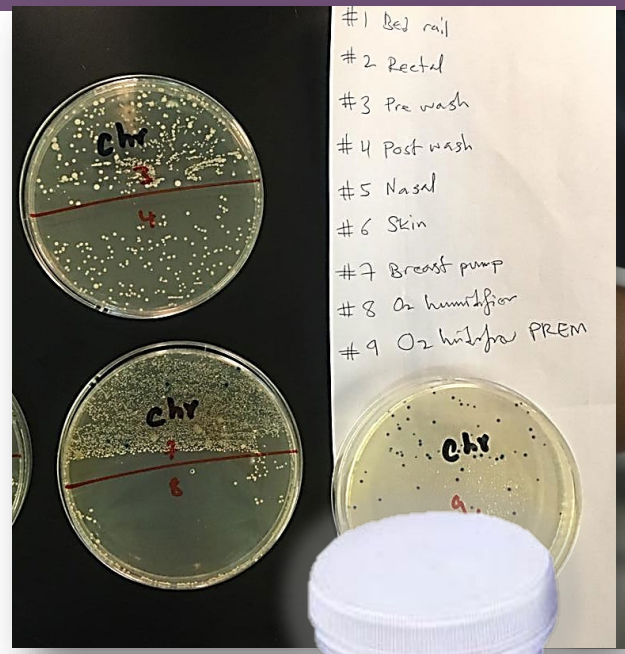
Just one patient's story

- Premature neonate (born at 28 weeks, BW 785 gms)
- DOL 1: Infection suspected as cause of preterm birth → 1st line antibiotics (Amp & Gent) started
- DOL 11: Concern for sepsis → 2nd line antibiotics (Amikacin & Pip-tazo) started
- DOL 12: Blood culture grew CONS → switched to 3rd line antibiotic (Meropenem)
- DOL 15: Blood culture grew pan-resistant *Acinetobacter* →continued on Meropenem (Colistin was out of stock)



Timing is Everything

- Unit in midst of an *Acinetobacter* cluster
  - bed rails
  - feeding equipment (breast pumps)
  - cleaning buckets
- Shortage of disinfectant suspected as cause of cluster
- Mother's breastpump subsequently grew *Acinetobacter*



OUT OF STOCK

Drivers of Neonatal Sepsis Outbreaks

Vurayai *et al.*
Antimicrobial Resistance & Infection Control (2022) 11:14
https://doi.org/10.1186/s13756-021-01042-2

Antimicrobial Resistance and Infection Control

RESEARCH Open Access

Characterizing the bioburden of ESBL-producing organisms in a neonatal unit using chromogenic culture media: a feasible and efficient environmental sampling method

Moses Vurayai[1*†], Jonathan Strysko[2,3,4†], Kgomotso Kgomanyane[5], One Bayani[2], Margaret Mokomane[1], Tichaona Machiya[5], Tonya Arscott-Mills[2,3,4], David M. Goldfarb[6], Andrew P. Steenhoff[2,3,4,7], Carolyn McGann[3,7], Britt Nakstad[2,8], Alemayehu Gezmu[2], Melissa Richard-Greenblatt[7] and Susan Coffin[3,7]

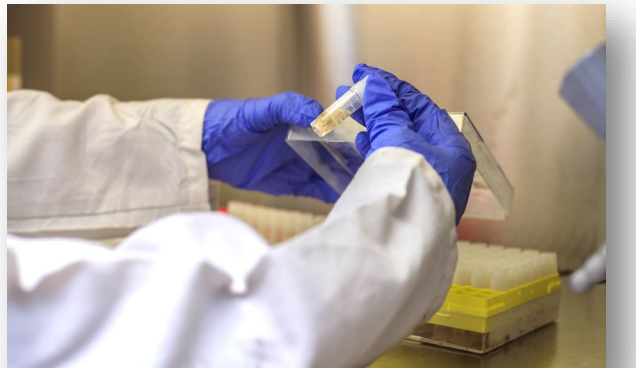
- Infection prevention efforts are often thwarted because of overcrowded wards, equipment re-use, limited laboratory capacity to detect and respond to outbreaks, and a critical shortage of healthcare workers to implement infection prevention and control measures.

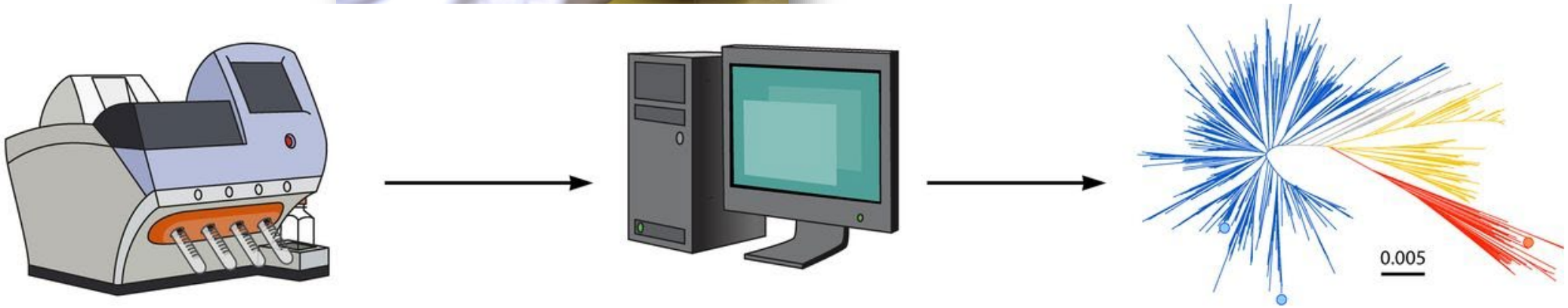

Whole genome sequencing (WGS), once considered cost-prohibitive, is proving to be a promising tool for outbreak detection in LMICs where traditional epidemiologic approaches fall short

Methods

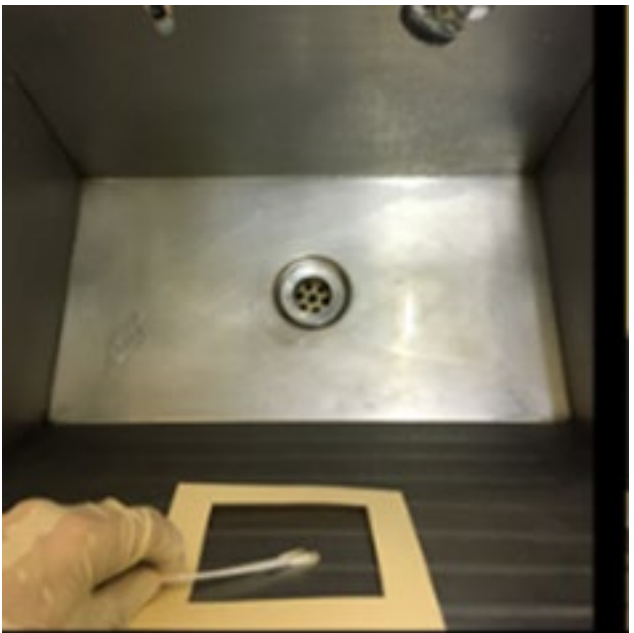
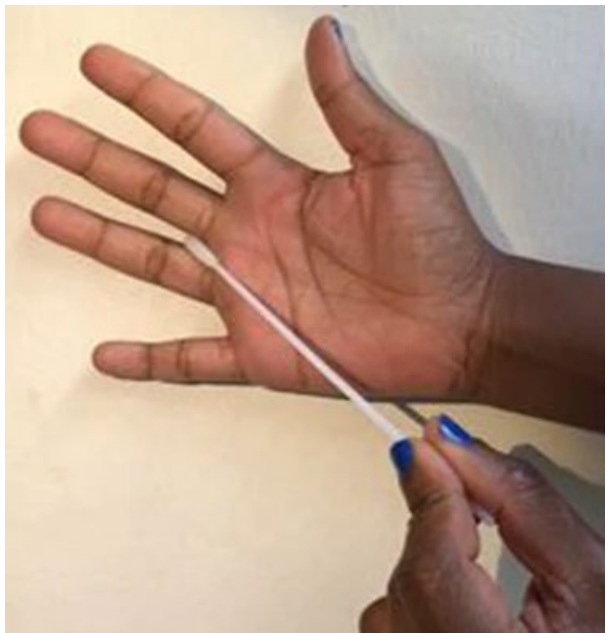
- We performed whole genome sequencing on 43 preserved clinical and environmental isolates collected in 2021-2022

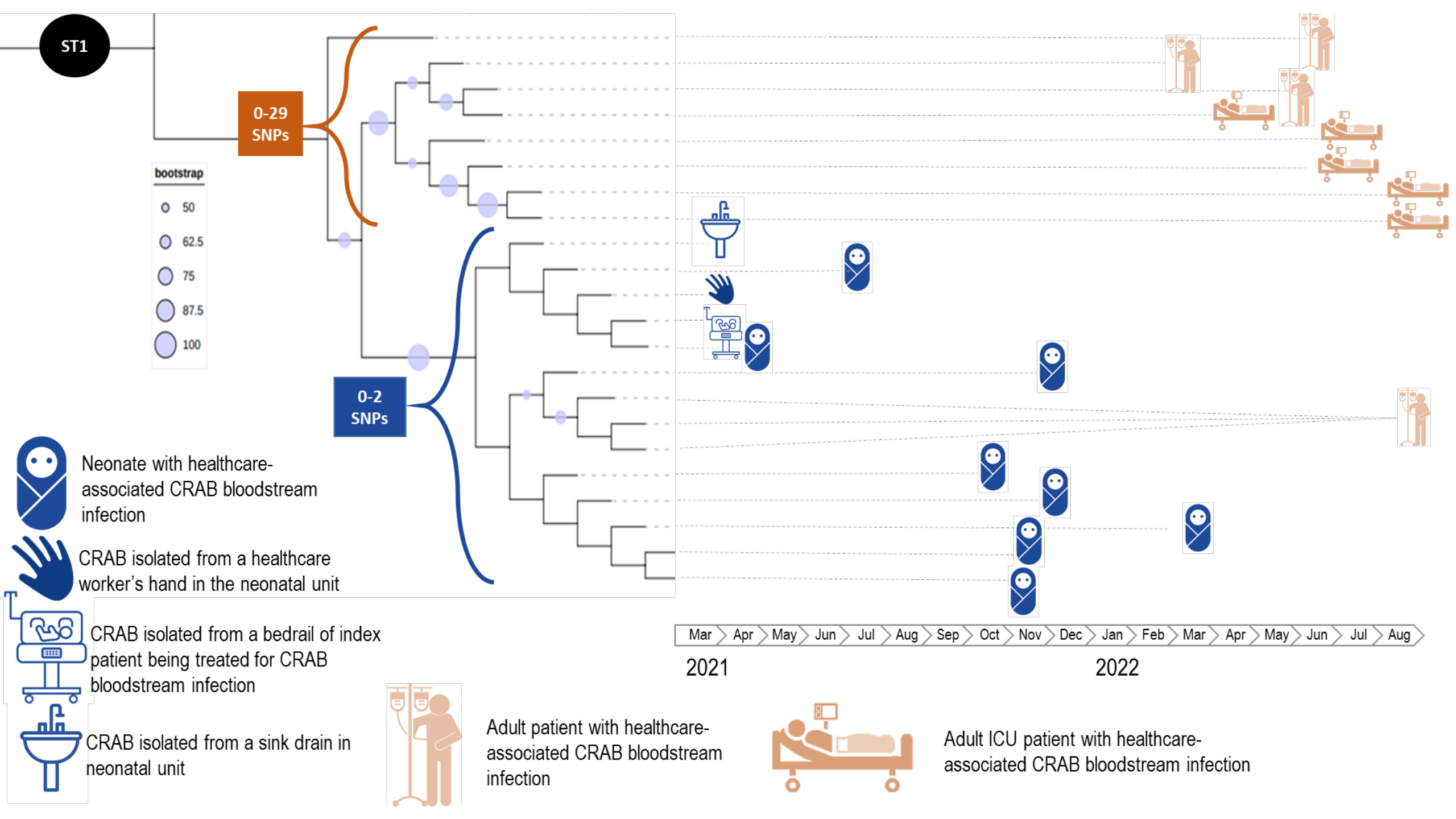
SEQAFRICA

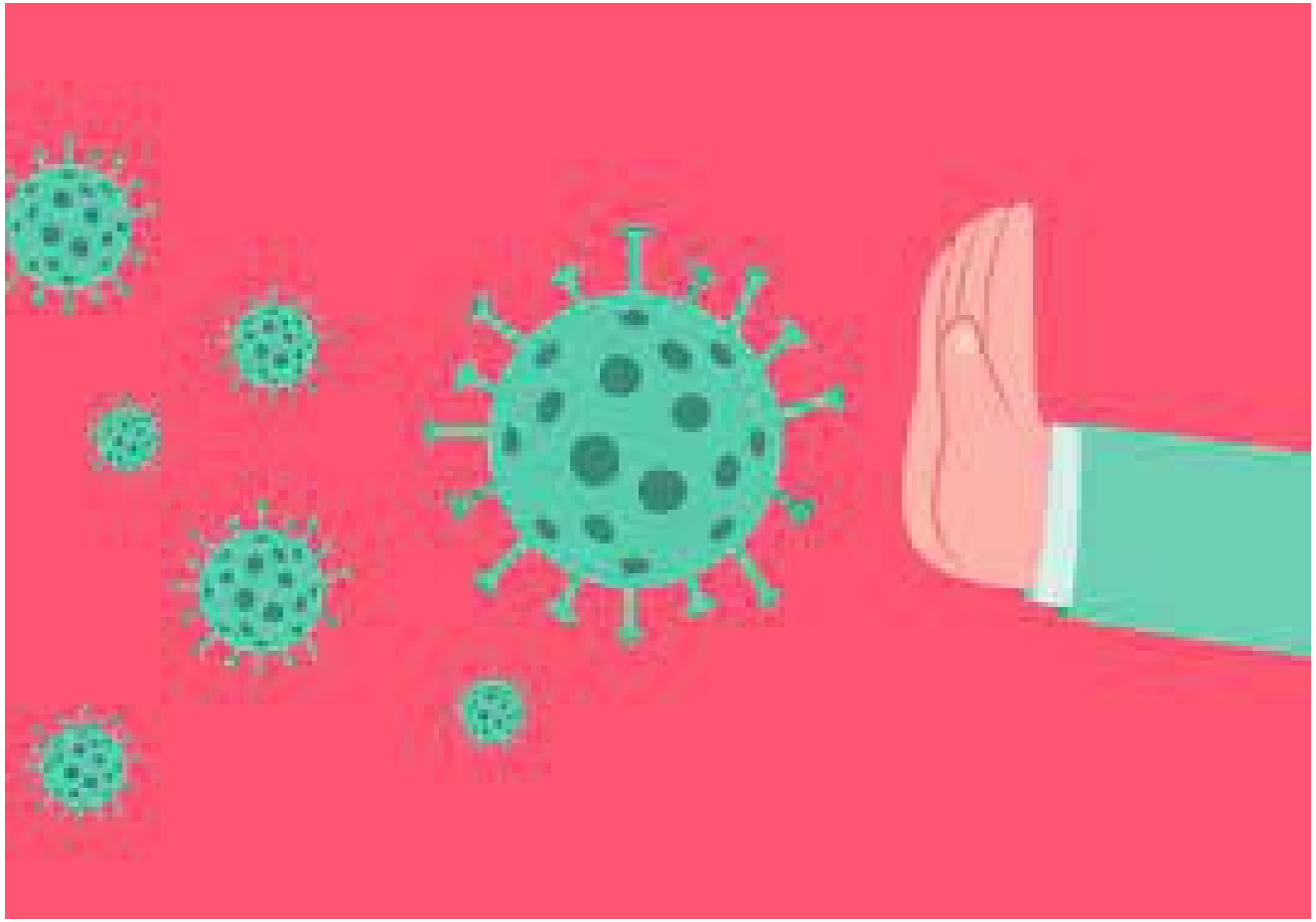




- Phylogenetic analysis of the ST1 clone demonstrated spatial clustering by hospital unit
- Related isolates spanned wide ranges in time (>1 year), suggesting ongoing transmission from environmental sources
- A neonatal clade (0-2 SNPs) containing all 8 neonatal blood isolates was closely associated with 3 environmental isolates from the neonatal unit: a sink drain, bed rail, and a healthcare worker's hand


ST1
0-29 SNPs
0-2 SNPs
bootstrap
50
62.5
75
87.5
100
Neonate with healthcare-associated CRAB bloodstream infection
CRAB isolated from a healthcare worker's hand in the neonatal unit
CRAB isolated from a bedrail of index patient being treated for CRAB bloodstream infection
CRAB isolated from a sink drain in neonatal unit
Adult patient with healthcare-associated CRAB bloodstream infection
Adult ICU patient with healthcare-associated CRAB bloodstream infection
Mar Apr May Jun Jul Aug Sep Oct Nov Dec Jan Feb Mar Apr May Jun Jul Aug
2021
2022



Prevention Matters

Preventing HAI = Preventing Antimicrobial Resistance

- Proportion of HAI caused by resistant organism can exceed 80% in some settings
- 3x greater risk of death if infection is due to a resistant organism

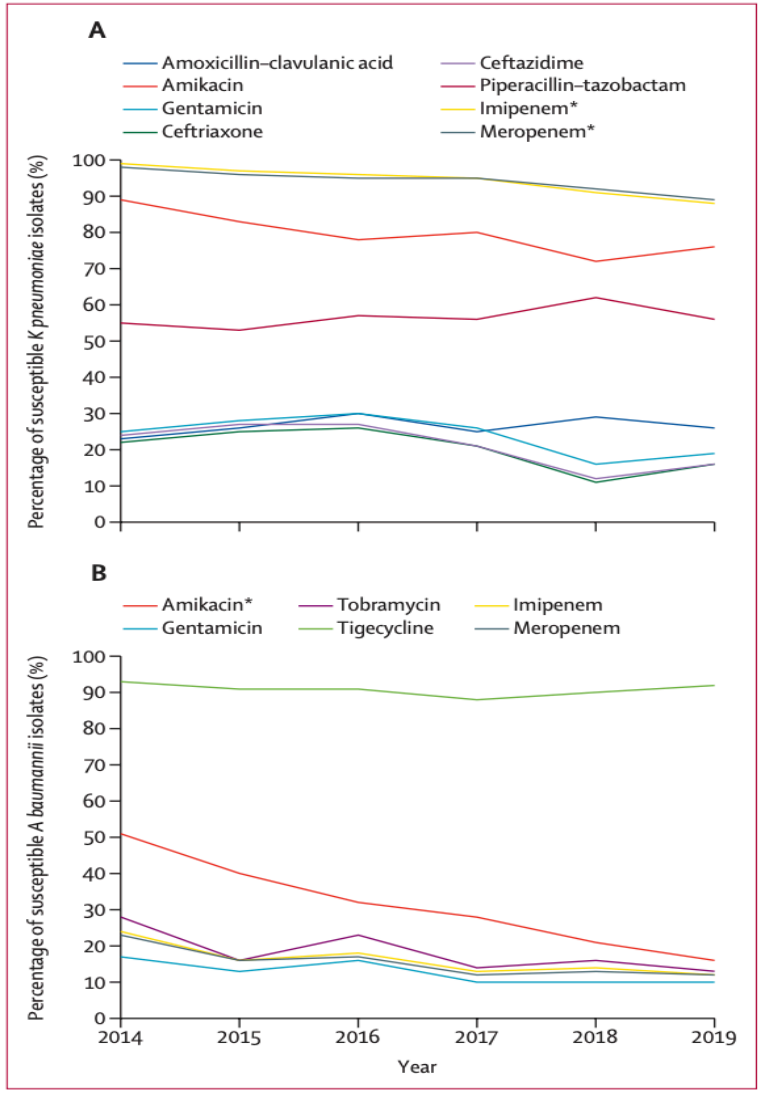
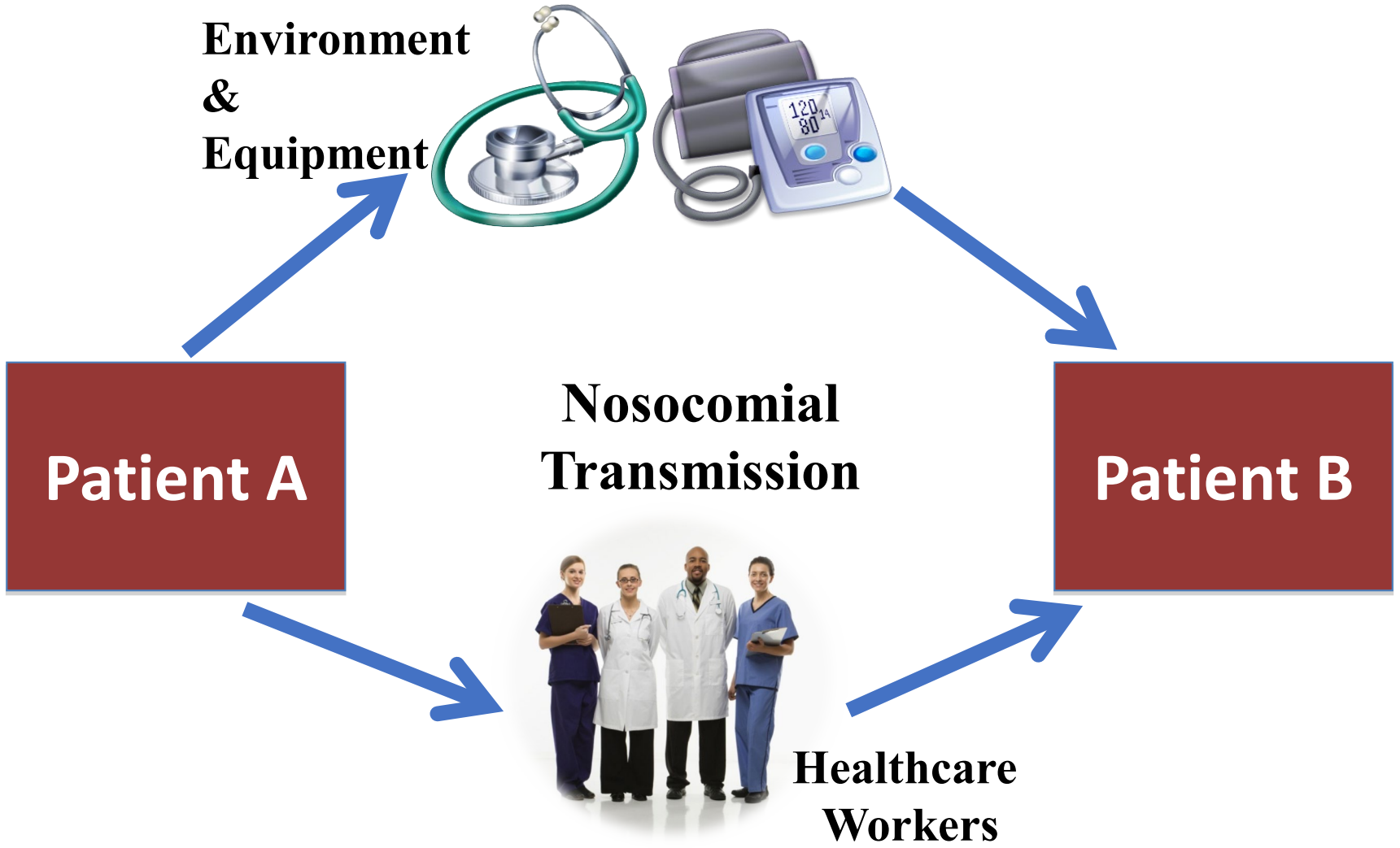


***Figure 3*: Antimicrobial susceptibility of *Klebsiella pneumoniae* and *Acinetobacter baumannii* isolates among neonates with culture-confirmed bloodstream infection or meningitis**
(A) *Klebsiella pneumoniae*. (B) *Acinetobacter baumannii*. *p<0·05.

Masau, Lancet, 2022

Preventing Transmission



Preventing Spread of Resistant Organisms*

- Hand hygiene
- Environmental cleaning
- Contact precautions
- Isolation (if available)
- Surveillance (clinical +/- surveillance cultures)
- Monitoring, auditing, and feedback

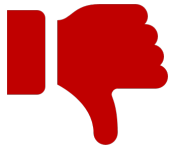
*adapted from WHO CRE Guideline, 2017.

Preventing Spread of Resistant Organisms*

- Hand hygiene 
- Environmental cleaning
- Contact precautions
- Isolation (if available) 
- Surveillance (clinical +/- surveillance cultures)
- Monitoring, auditing, and feedback

*adapted from WHO CRE Guideline, 2017.

Preventing Spread of Resistant Organisms*

- Hand hygiene 
- Environmental cleaning 
- Contact precautions 
- Isolation (if available) 
- Surveillance (clinical +/- surveillance cultures) 
- Monitoring, auditing, and feedback 

*adapted from WHO CRE Guideline, 2017.

Sepsis Prevention in Neonates in Zambia

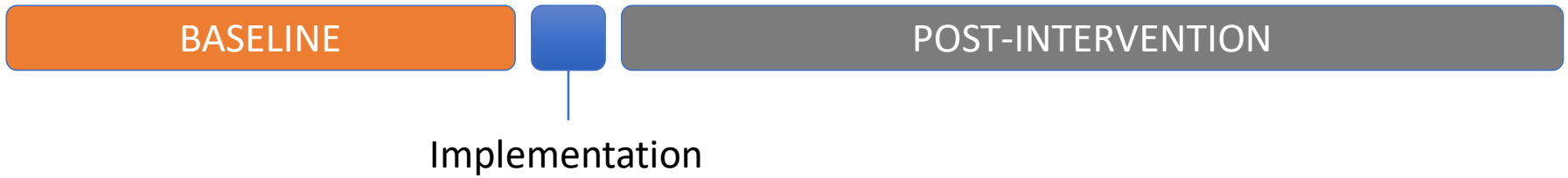
SPINZ

Low-cost infection control strategies:

- IPC training NICU and L&D staff
- Alcohol-based hand rub
- 2% chlorhexidine bathing
- Targeted cleaning
- Text message-based reminders

Study Outline

- Recruit neonates admitted to NICU
- Maternal interview and chart review
- Blood culture if clinical sepsis suspected
  - Temp instability
  - Tachycardia
  - Respiratory distress/apnea

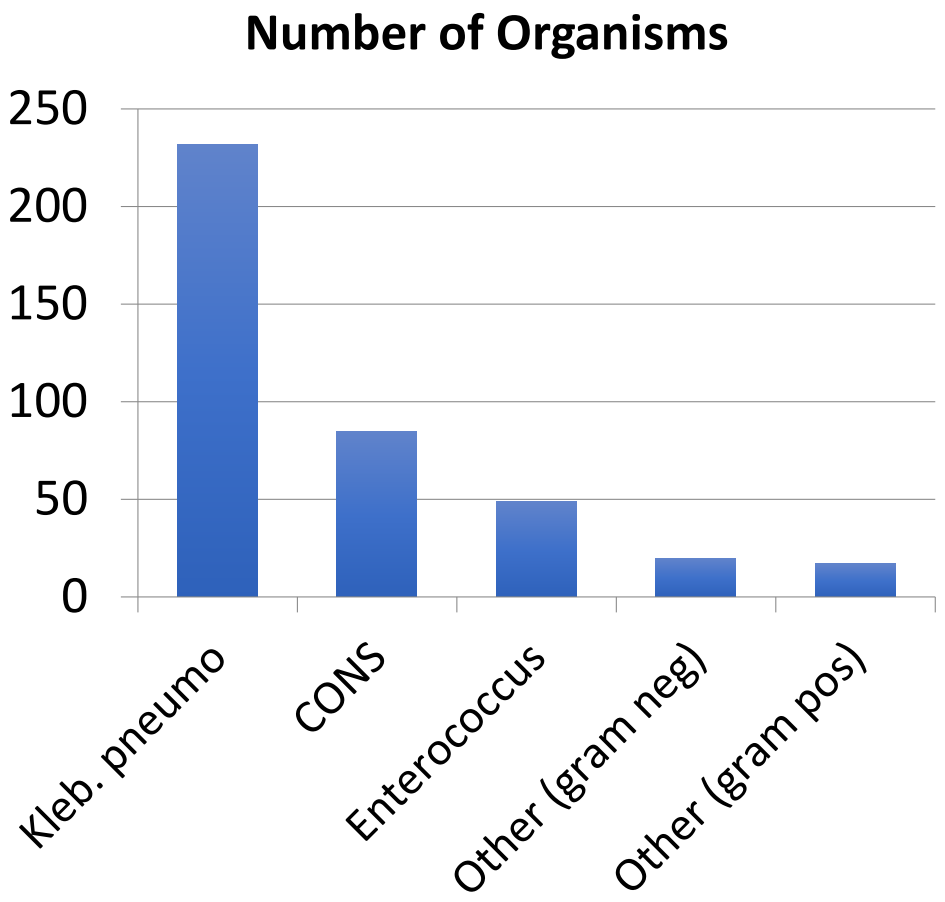


Overall Neonatal Sepsis

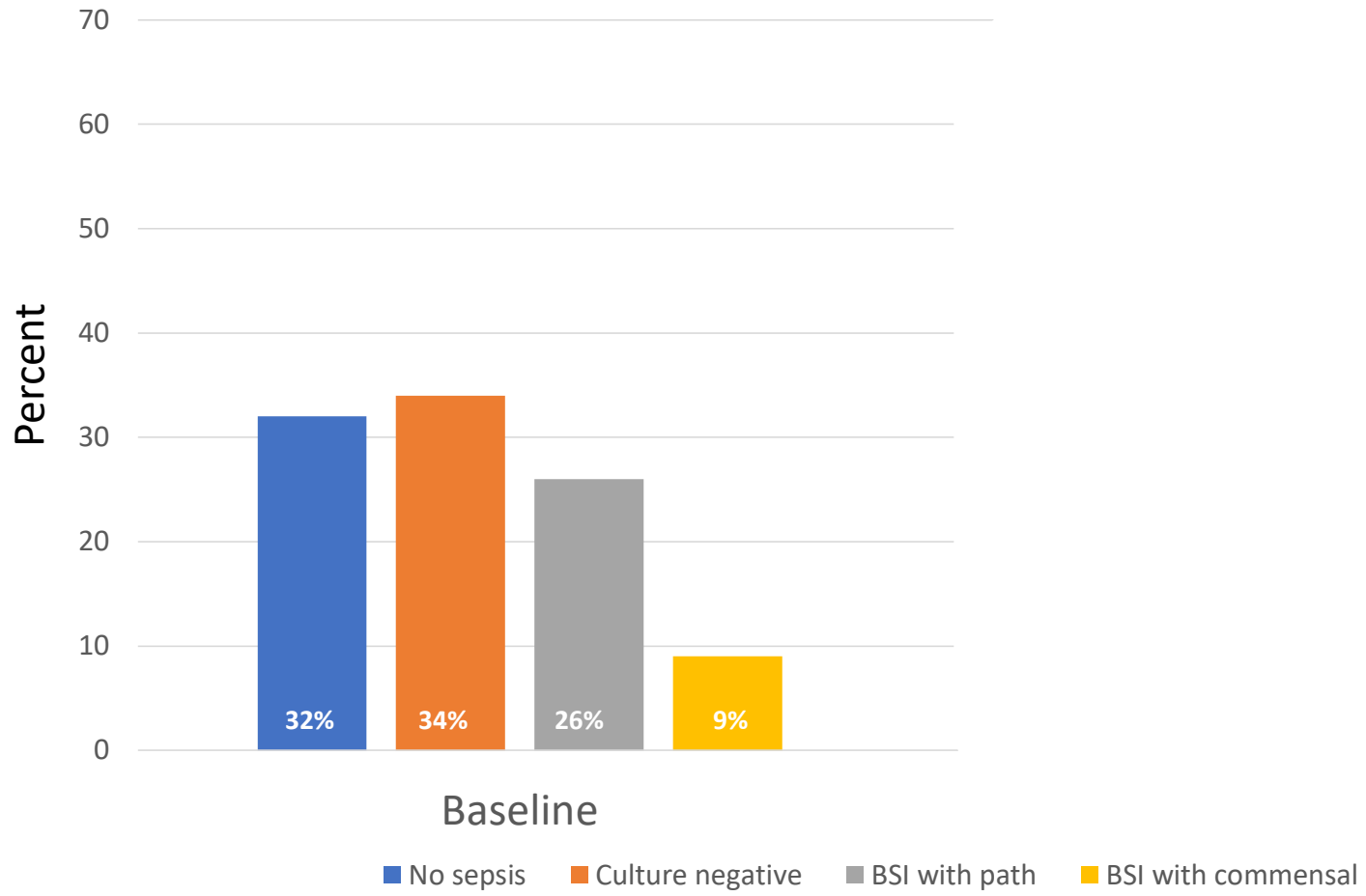
58%
- Sepsis

40%
- Positive culture (23.2%)

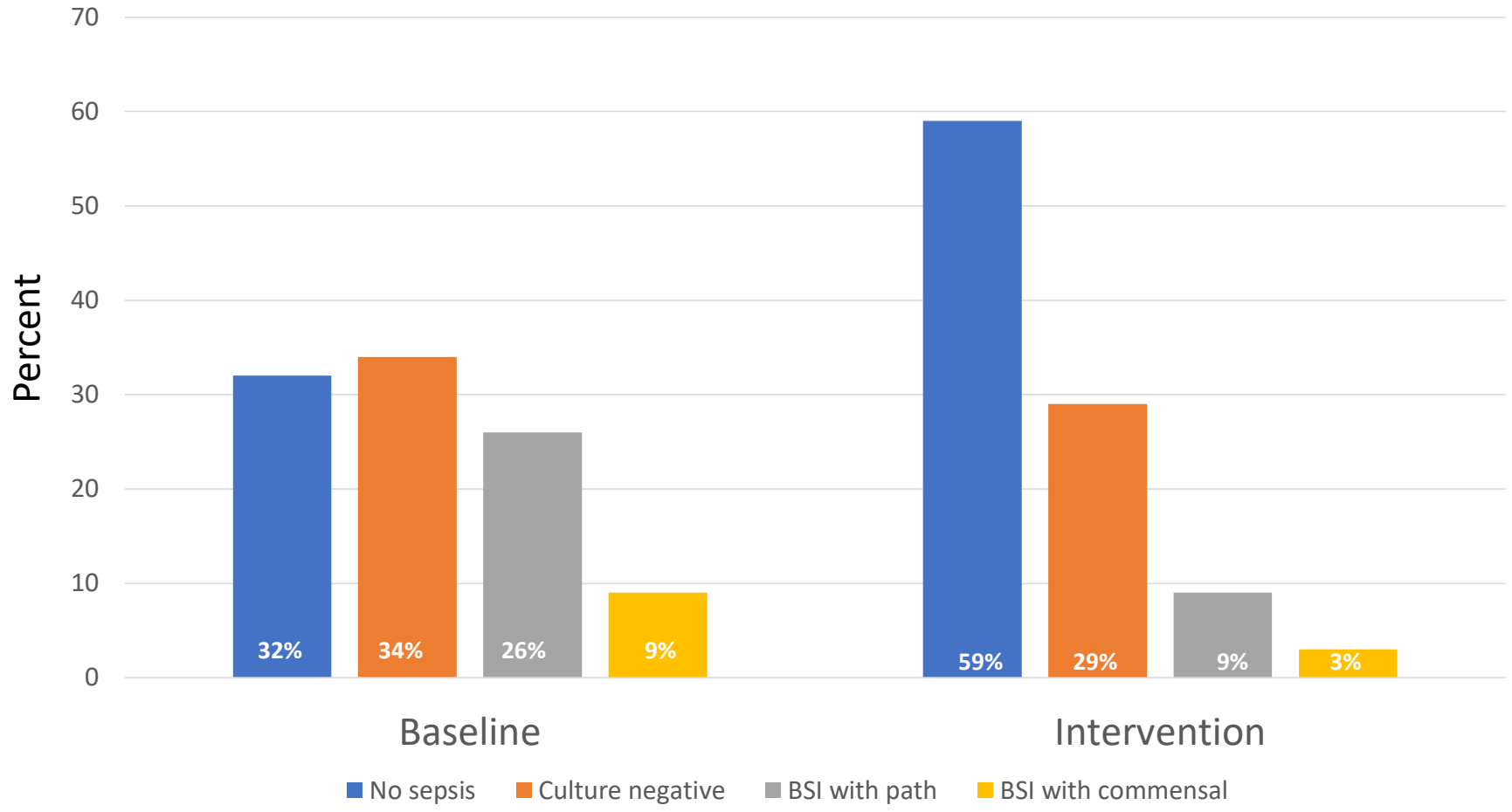
78%
- ”Pathogen” isolated (18.1%)



Infectious Outcomes By Phase of Intervention

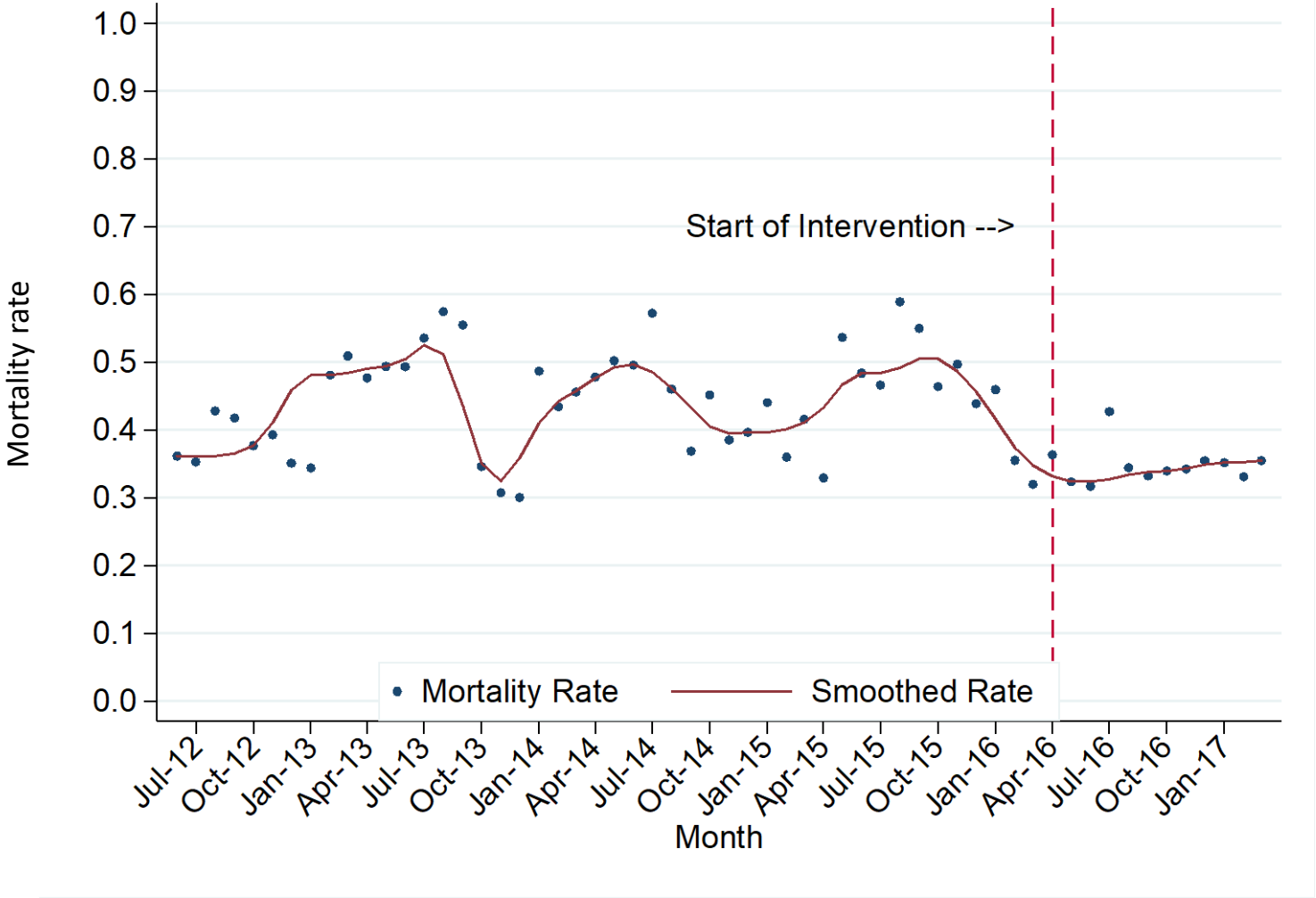


Infectious Outcomes By Phase of Intervention



Similar trends seen when stratified by birthweight category, except for infants <1 kg

All-Cause Mortality



Factors Associated with Death Among Septic, Culture-positive Patients*

	aOR (95% CI)
Klebsiella infection	2.43 (1.52- 3.87)
Neonatal weight (kg)	0.54 (0.41-0.70)
C-section delivery	0.72 (0.37-1.39)
Born at study hospital	0.90 (0.55-1.48)
Maternal HIV-positive	0.80 (0.46-1.38)

*preliminary analysis

Conclusions

- Neonatal sepsis driven by unintended consequences of “advancing perinatal care”
- Neonatal mortality due to sepsis strongly associated with pathogen mix and prevalence of AMR organisms
- Prevention is possible…but requires resources!

Acknowledgements

SPINZ

- David H. Hamer, MD
- Lawrence Mwananyanda, MD
- Cassandra Pierre, MD
- James Mwansa, PhD
- Angela Lyondo and Mox
- Monica Kapasa, MBChB
- Sylvia Machona, MBChB
- Moses Chilufya Malama, MSc
- Surabhi Bhatt
- Chileshe Lukwesa-Musyani, MBChB, MPH, MSc
- Gertrude Munanjala
- Nellisiwe Chizuni
- Matthew Bates, PhD
- Aja Griffin, MPH
- Caitryn McCallum, MPH
- Russell Localio, JD, PhD
- Carter Cowden, MPH

NIMBI

- Jonathan Strysko
- Carolyn McGann
- Morgan Hammerschaimb
- Britt Nakstad
- Alemayhu Gemzu
- Andrew Steenhoff
- Paul Planet
- Kyle Bittinger
- Ahmed Moustafa
- Jameson Dowling
- Janet Moorad
- One Bayani

Children's Hospital of Philadelphia

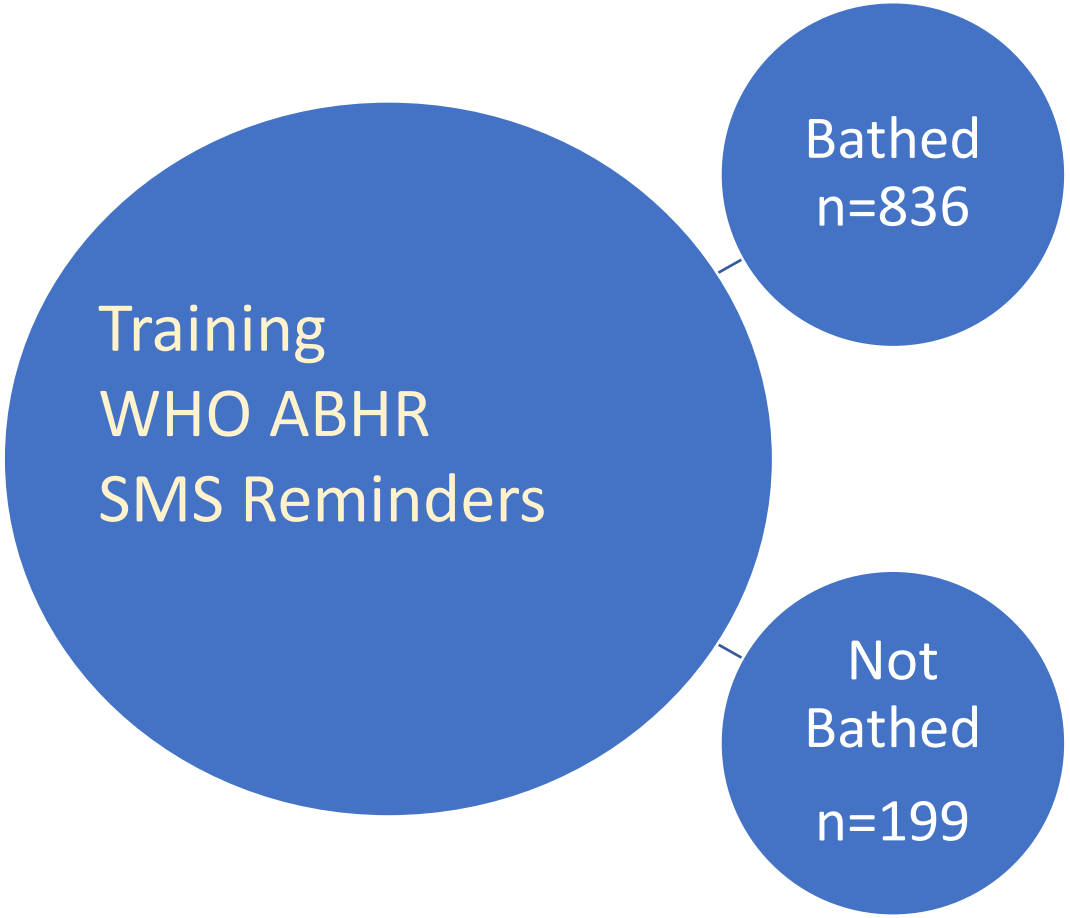
ZCAHRD
Zambia Center for Applied Health Research & Development
in partnership with Boston University Center for Global Health & Development

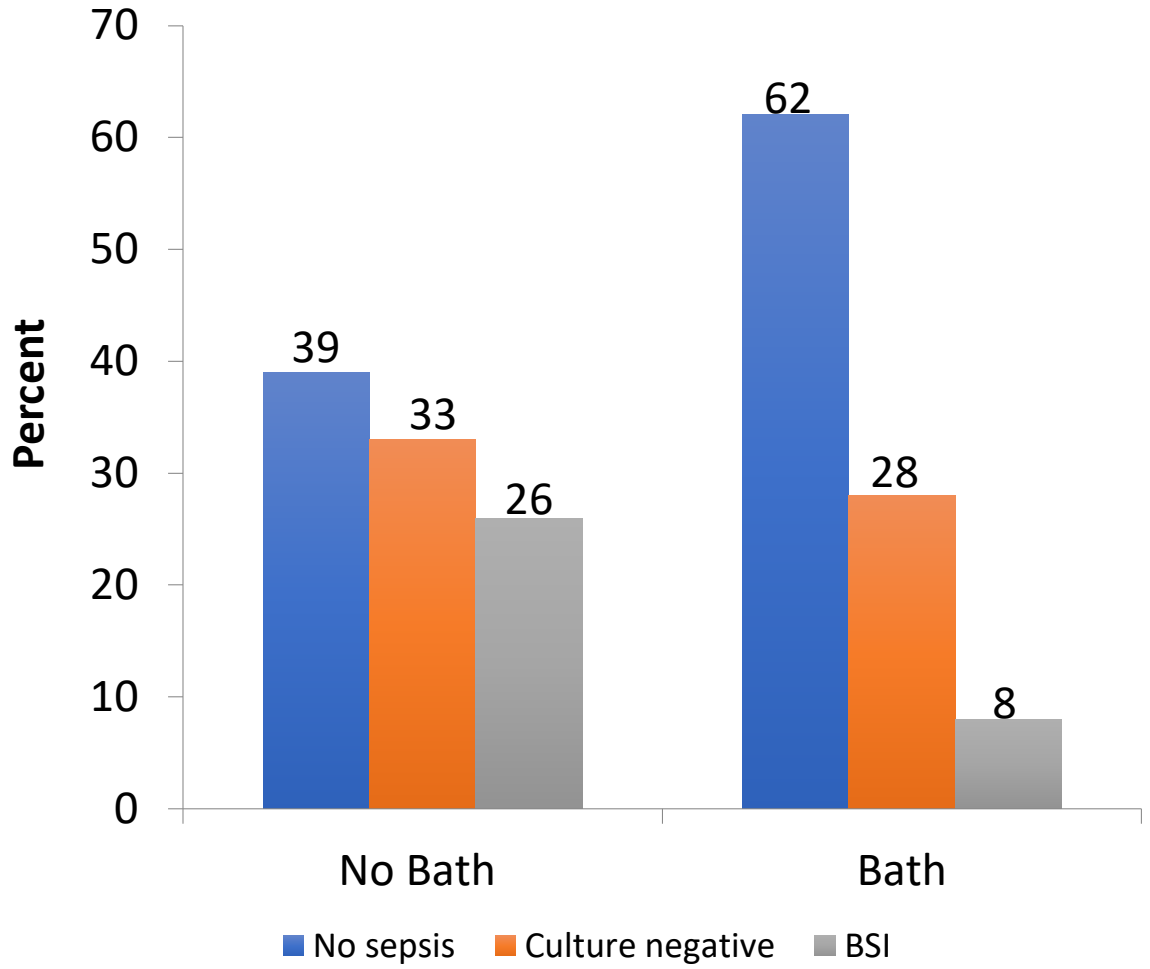
CFAR
Center for AIDS Research
University of Pennsylvania
Children's Hospital of Philadelphia
The Wistar Institute

Thrasher Research Fund
Medical research grants to improve the lives of children


thank you
рахмат
danke
謝謝
ngiyabonga
teşekkür ederim
Баярлалаа
спасибо
mersi
barka
welalin
tack
spas
kia ora
faafetai lava
yinaka
blagodaram
dank je
misaotra
paldies
grazzi
mahalo
tapadh leat
спасибі
matondo
gracias
kiitos
dankie
nanni
nandri
dhanyavad
mauruuru
хвала
asante
manana
obrigada
tenki
bedankt
bayarlalaa
gracie
hvala
koszonom
aciu
dankon
akun
mochchakkeram
murakoze
djiere dieuf
tau
enkosi
dziękuję
дякую
mamnun
chnorakaloutioun
gratias ago
gracies
sulpay
go raibh maith agat
chokrane
sobodi
dėkuji
sagolun
sukriya
kop khun krap
taiku
obrigado
mèsi
ありがとう
arigatô
takk
dakujem
trugarez
didi madloba
najis tuke
tanemirt
grazie
rahmet
мерси
kam sah hamnida
rahmat
terima kasih
ευχαριστώ
diolch
dhanyavadagalu
shukriya
merce
감사합니다
xièxie
merci

Infection Control Bundle and Unadjusted Outcomes, babies with birthweight ≥ 1.5 kg





Causal Inference Methods

- To adjust for potential confounding

- Constructed subcohort
  - Inborn babies ≥ 1.5 kg
  - Implementation and intervention phases

- Compared two models to adjust for potential confounding
  - Cox proportional hazards model
  - Longitudinal Targeted Maximum Likelihood Estimate (LTMLE)

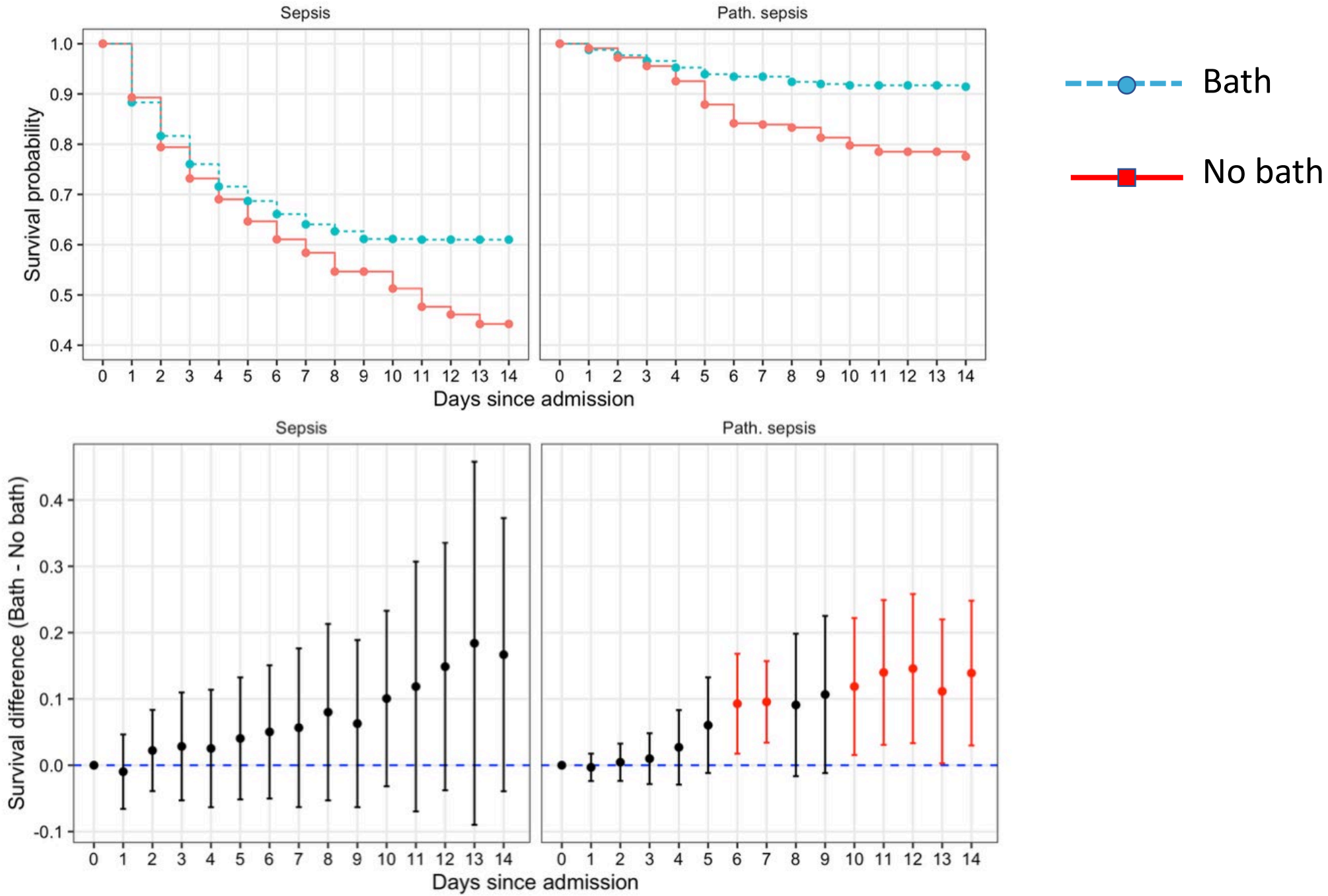
≠

Multivariable Cox Models

Outcome	Hazard ratio* (95% CI)	p-value	# events
Sepsis	1.05 (0.76, 1.45)	0.75	249
Path. sepsis	0.48 (0.24, 0.95)	0.035	48
Culture-neg. sepsis	1.17 (0.81, 1.69)	0.39	199
Sepsis w/contam.	1.45 (0.19, 11.12)	0.72	9
Death	0.83 (0.56, 1.23)	0.35	163
Sepsis or death	0.89 (0.69, 1.16)	0.40	350
Path. sepsis or death^	0.73 (0.51, 1.03)	0.07	198

*adjusted for FIXED VARIABLES: sex, BW, HIV, education, # prenatal visits, prenatal infxn and abx, delivery method
adjusted for TIME VARYING VARIABLES: device use, receipt of O2, CPAP, abx

^to account for competing hazard of death


Sepsis
Path. sepsis
Survival probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Days since admission
Bath
No bath
Sepsis
Path. sepsis
Survival difference (Bath - No bath)
0.4
0.3
0.2
0.1
0.0
-0.1
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Days since admission

Summary

- Admission bathing of babies ≥ 1.5 kg with 2% CHG was associated with reduced risk of sepsis due to a pathogenic organism when applied in presence of other IPC interventions

- Finding is robust when adjusting for maternal, neonatal, and post-natal time-varying exposures using two different analytic techniques.