Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

The Pneumonia Etiology Research for Child Health(PERCH) Study Group

The Lancet 27th June 2019

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UNITID Journal Club

24th July 2019

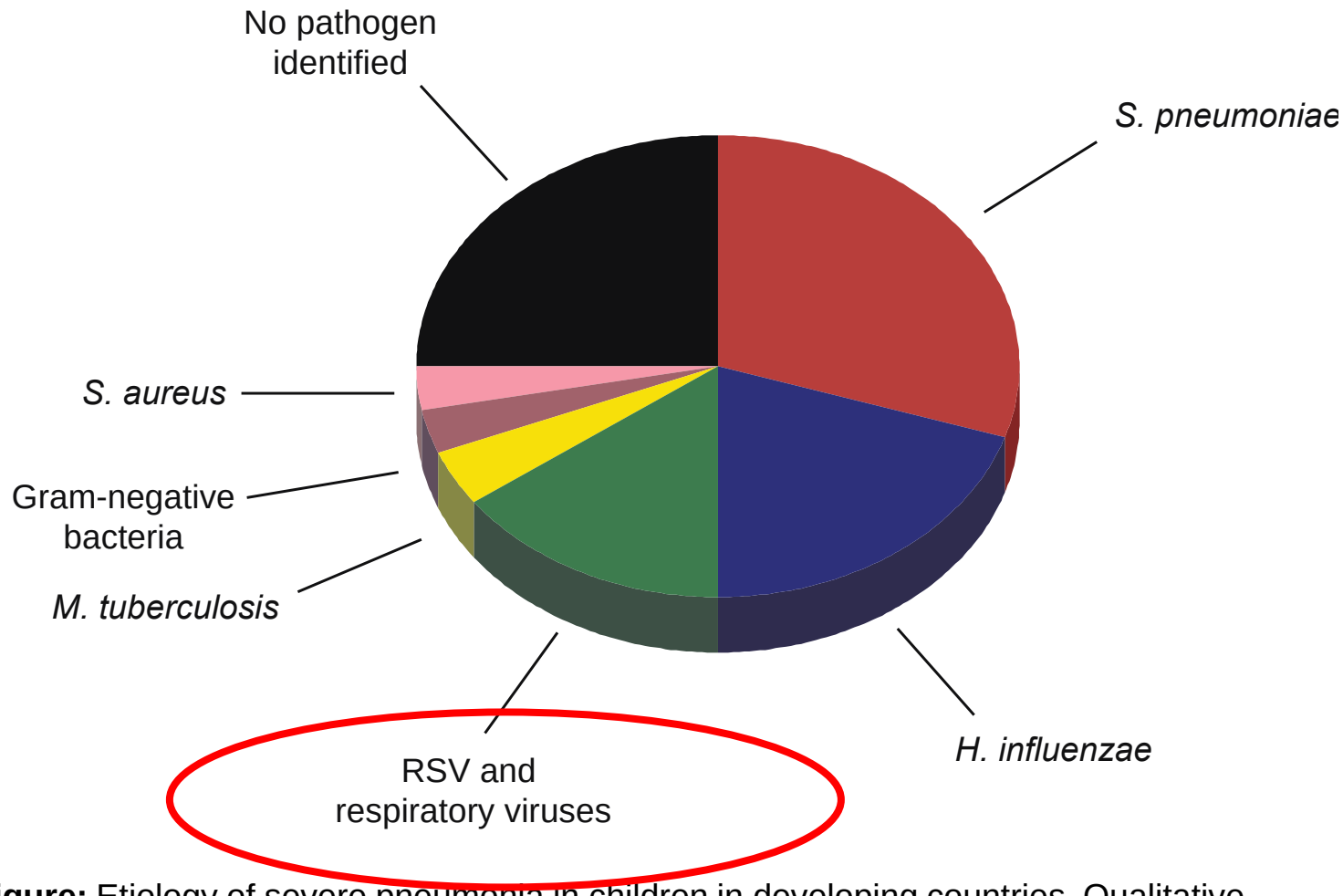
Background

Pneumonia greatest cause of death in under five.

Annually accounts for 12.8% deaths

Significant reduction over years (1.7 million in 1990 to 0.7million in 2015)

Pneumonia aetiology: Kenya before PERCH study



Changes since

1. Introduction of HiB vaccines (2001)
2. Introduction of PCV (2011)

Figure: Etiology of severe pneumonia in children in developing countries. Qualitative representation of the combined results of vaccine probe analyses (12, 113), studies of blood and lung aspirate cultures (14, 111, 153–155), and virus studies (128, 156) in predominantly HIV-uninfected children.

Scott et al. J Clin Invest 2008: 118:1291-300

Study Objectives

- Characterize the causes of severe childhood pneumonia requiring hospital admission (updated evidence).

- Provide rigorous data that would inform future prevention and treatment strategies in LMIC settings.

PERCH study sites (2011-2014)

Case definition (WHO 2005)

Severe pneumonia

Cough or difficulty breathing with lower chest wall indrawing.

Very severe pneumonia

Cough or difficulty breathing and at least one of the following signs: central cyanosis, difficulty breastfeeding or drinking, vomiting everything, convulsions, lethargy, unconsciousness, or head nodding.

Study Design (15 Aug 2011-30 Jan 2014)

Cases & Controls

Cases:

- hospitalized
- severe OR very severe pneumonia,
- ages 1-59 months

Controls:

- frequency matched on age
- from catchment area
- without severe or very severe pneumonia

Screening and enrolment

Exclusion Criteria:

- ❖Re-admission within 14 days,
- ❖Discharged as PERCH case within 30 days
- ❖Non resident of catchment area

Matching: Target 25 controls per month, minimum 100 cases/year

1-<6 months

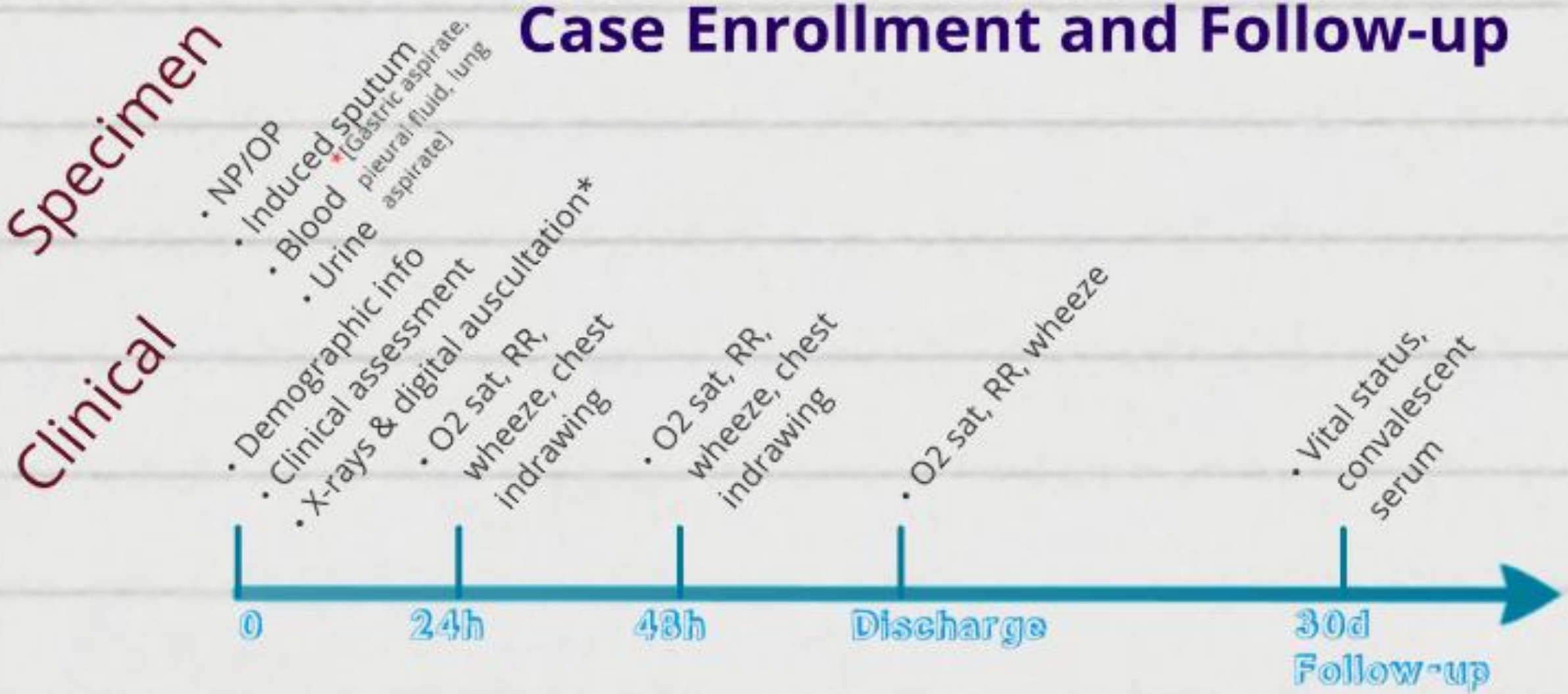
6-<12 months

12-<24 months

24-<59 months

Case assessments within 24 hours of admission

Case Enrollment and Follow-up



Procedures

Samples at enrollment:

Cases and Controls

Oropharyngeal (NP-OP), urine, and blood specimens

Cases only

Blood cultures, induced sputum, lung aspirate, pleural fluid, and gastric aspirates

Chest x-rays

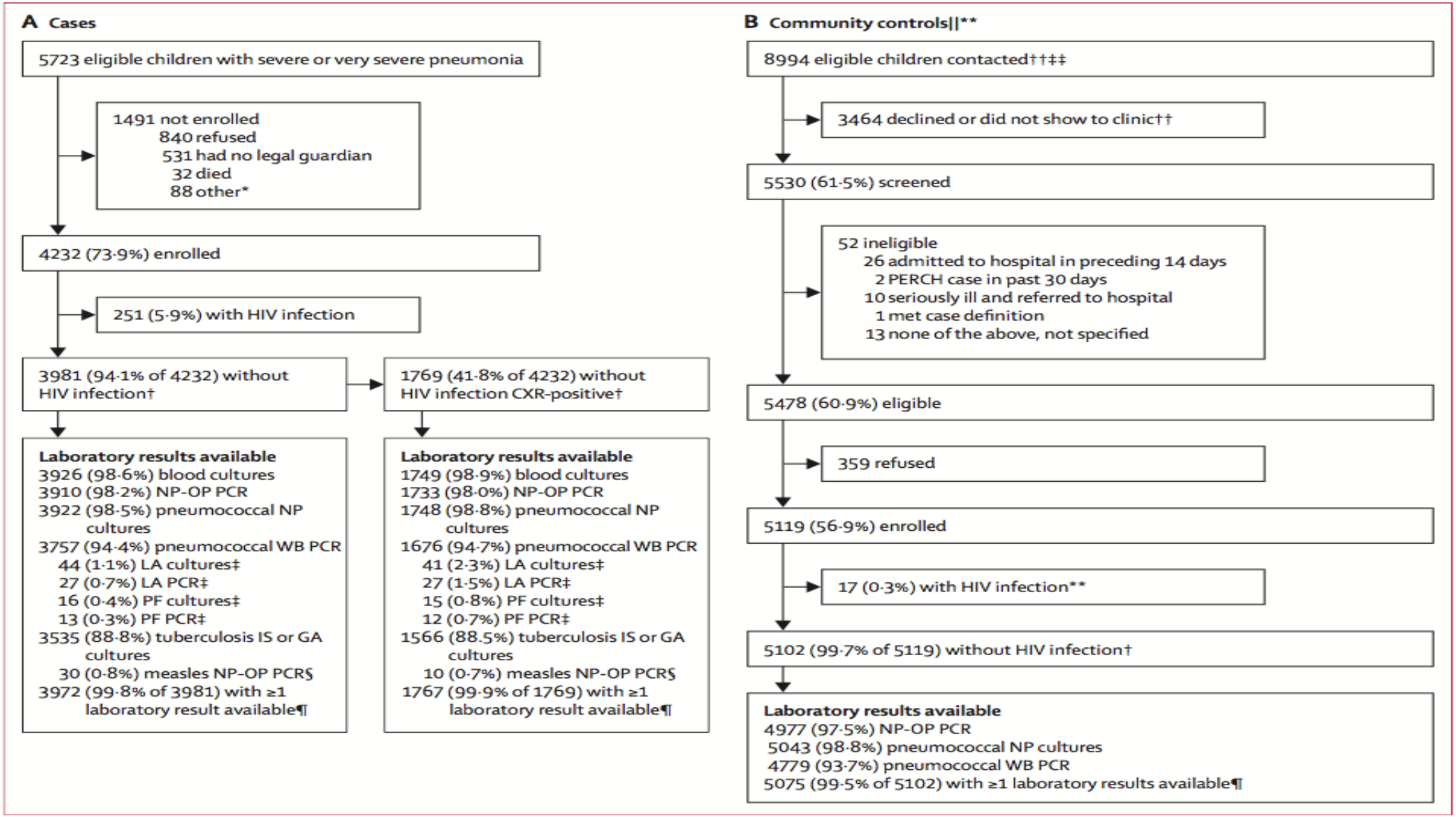
Laboratory

33-pathogen multiplex quantitative PCR for NP swabs, NPS cultures for SPN, Mycobacterium cultures (Pleural fluid, Induced sputum &lung aspirate)

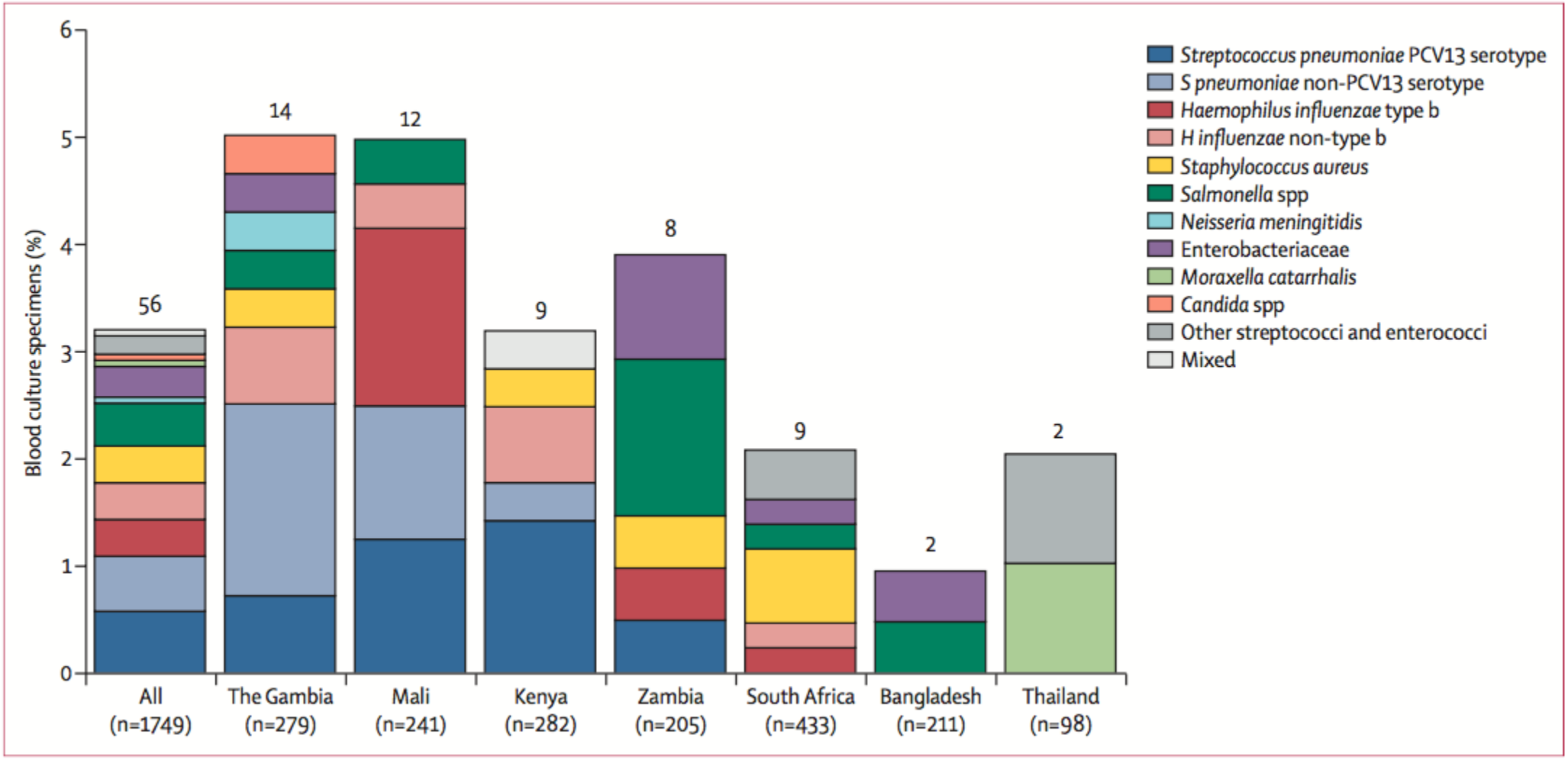
Statistical Analysis

- Single data entry into a centralised electronic data capture system.
- **Primary analysis**: Estimate the aetiological fraction of severe and very severe pneumonia among cases with a positive chest x-ray.
- PERCH Integrated Analysis model assumption: All cases had a lung infection.
- Missing data imputed during model estimation by use of standard Bayesian methods.
- Logistic regression methods to compare cases and controls.
- Focus pathogen if etiology >5% (n=7) or >2% for treatable by antibiotics.

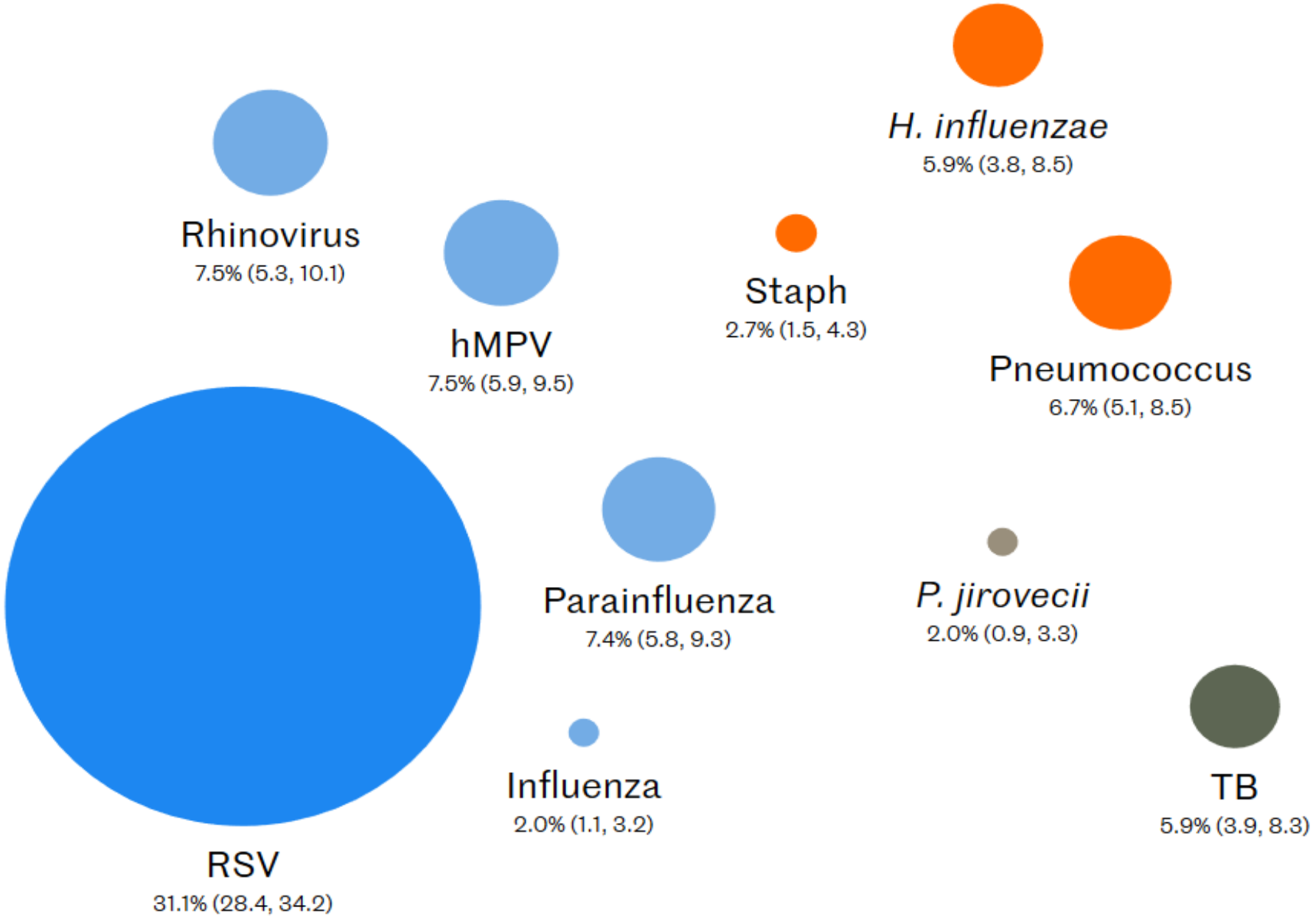
Results: Enrolment and specimen profile



Results: Blood culture results by site

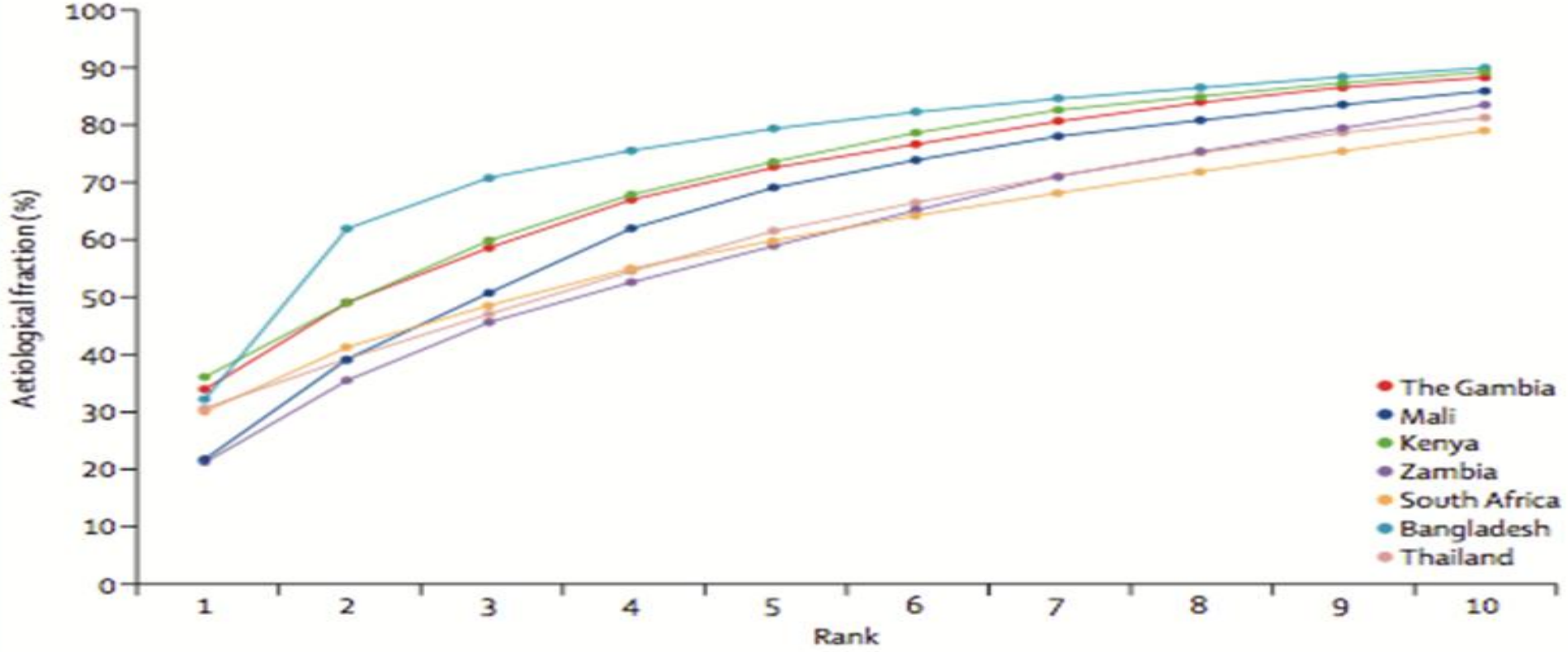


Top 10 causes of Severe Pneumonia (All ages)



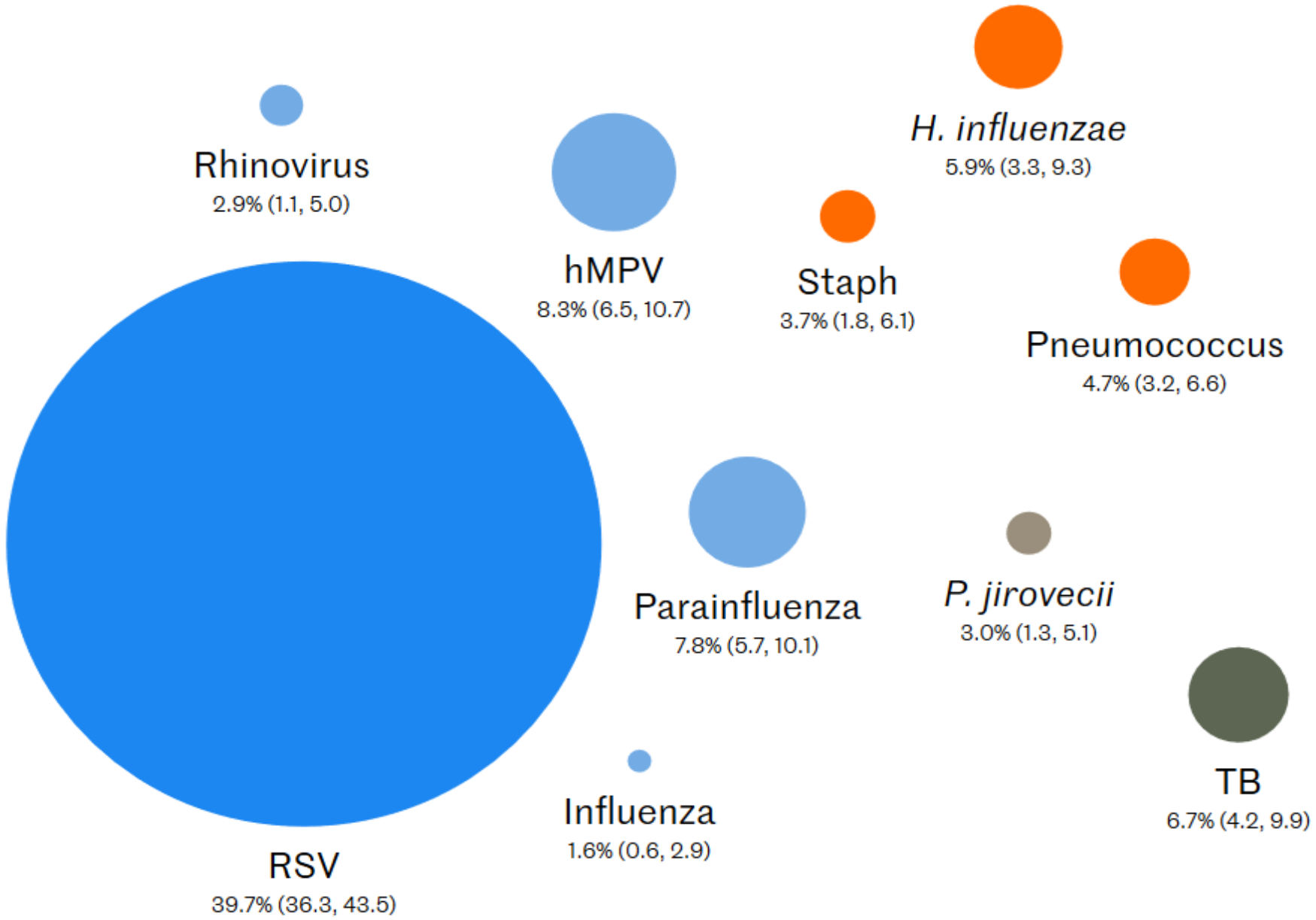
10 pathogens caused the vast majority (about 8 in 10 cases) accounting 79% of etiological fraction:

Site-specific cumulative contribution of 10 most common pathogens



Rank	The Gambia	Mali	Kenya	Zambia	South Africa	Bangladesh	Thailand
1	RSV	RSV	RSV	RSV	RSV	RSV	RSV
2	S pneu	S pneu	Rhino	HMPV	H inf	Rhino	M cat
3	Para	HMPV	HMPV	Mtb	Para	HMPV	Other strep
4	Mtb	Para	Para	Salm sp	Mtb	Para	NOS
5	H inf	H inf	H inf	Entrb	S pneu	PV–EV	Mtb
6	Cand sp	S aur	S pneu	Flu	Adeno	Entrb	H inf
7	HMPV	Boca	PV–EV	H inf	Other strep	Mtb	Rhino
8	M cat	Mtb	Flu	S pneu	S aur	Boca	NFGNR
9	Entrb	Salm sp	P jirov	S aur	Rhino	NOS	Cand sp
10	S aur	P jirov	Mtb	P jirov	HMPV	CMV	HMPV

Top 10 causes of Severe Pneumonia(Under 1 yr)



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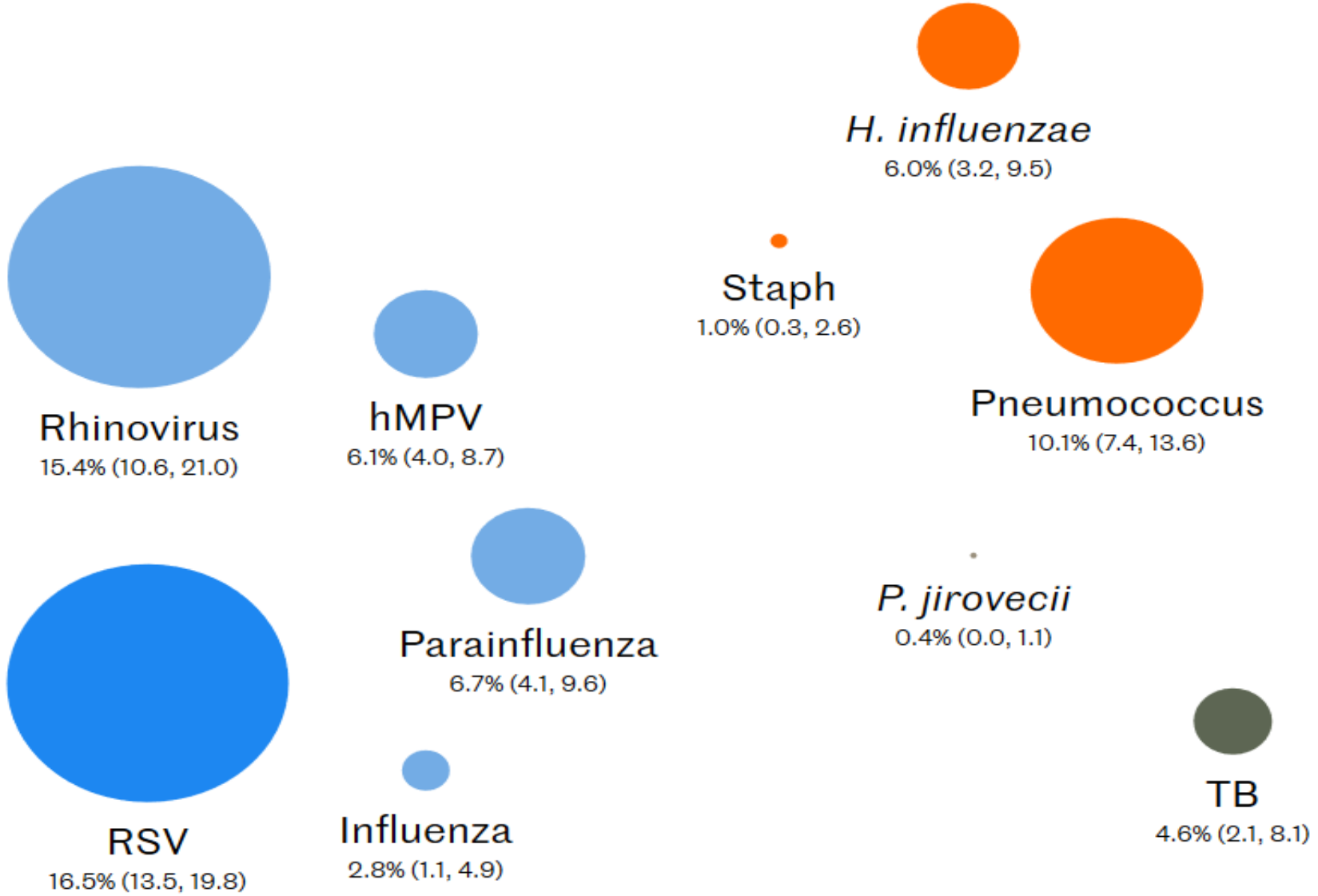
Top 10 causes of Severe Pneumonia(Over 1 yr)



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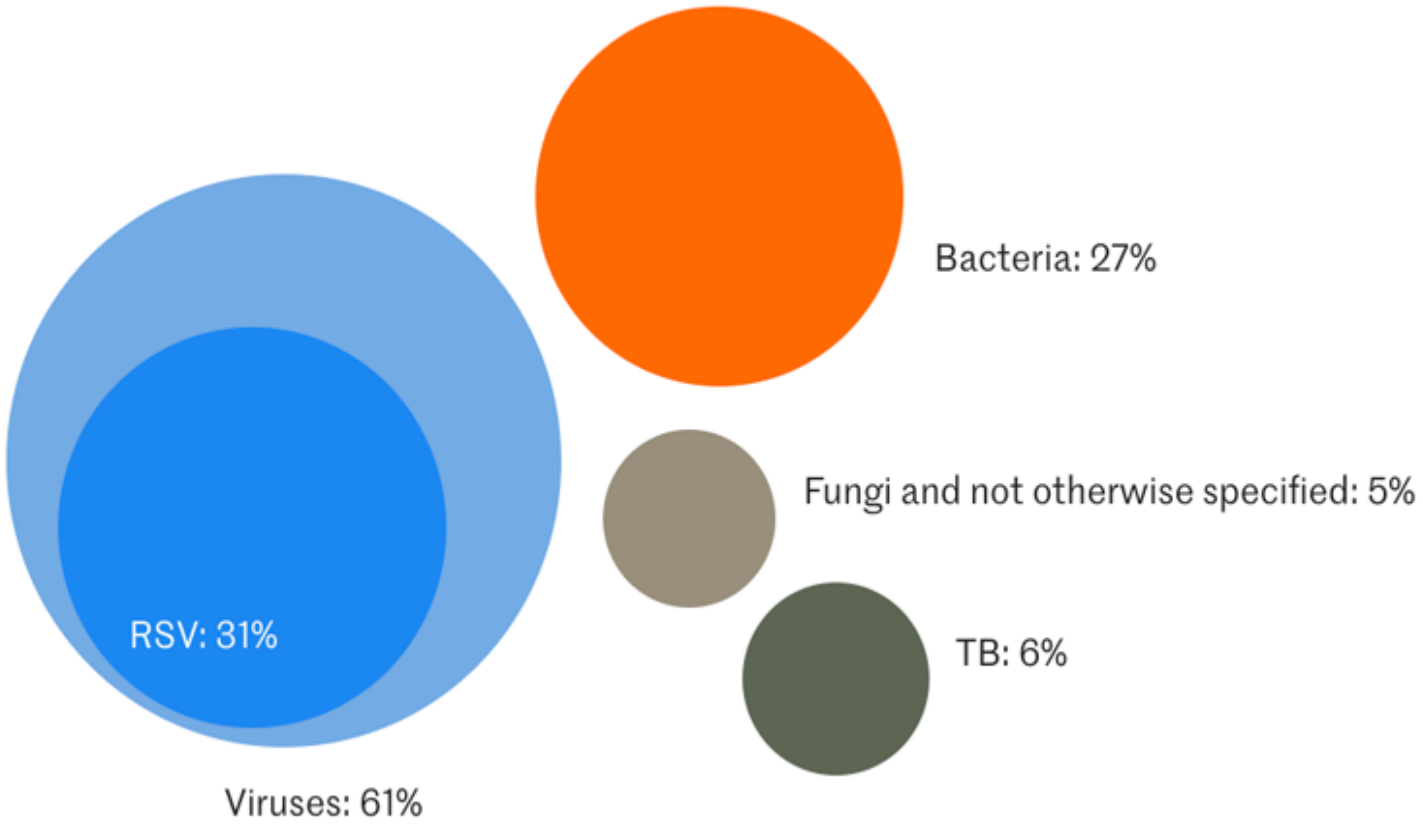
PERCH study Discussion on pneumonia etiology



- RSV an important prevention and therapeutic target among infants.
- NP-OP specimens remain of substantial importance for pneumonia aetiology studies.
- Novel analytical method overcame limitations of traditional approach.
- Need to adjust pneumonia treatment algorithms.
- Role of co-infection.

What is known as cause of severe pneumonia in Kenya?

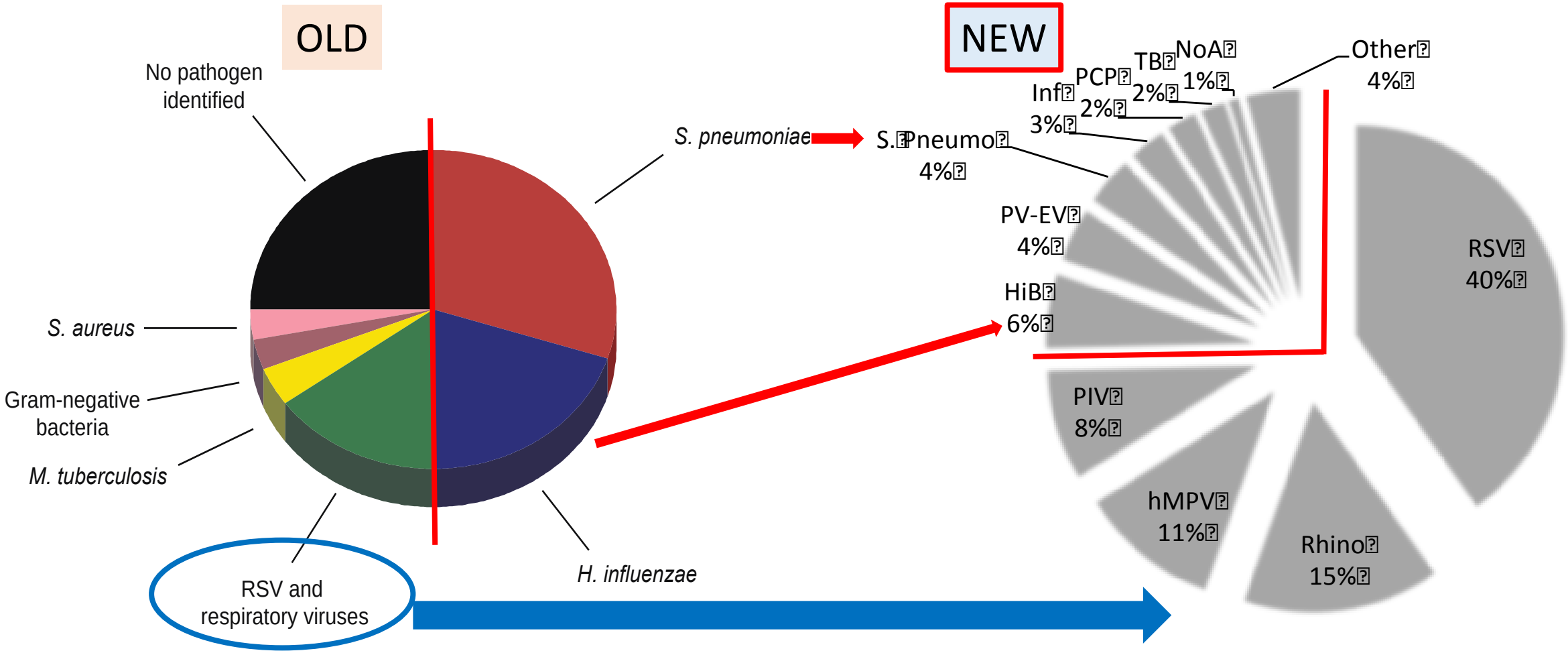


Figure 2. Etiology of severe pneumonia in children in developing countries. Qualitative representation of the combined results of vaccine probe analyses (12, 113), studies of blood and lung aspirate cultures (14, 111, 153–155), and virus studies (128, 156) in predominantly HIV- uninfected children.

Otieno J & Scott A et al Unpublished data, Kilifi

Scott et al. J Clin Invest 2008: 118:1291-300

Relevance of paper to my PhD project

- Enough evidence that RSV is a leading cause of severe pneumonia among children <5yrs.
- No licensed childhood RSV vaccines to date
- Maternal RSV vaccine as an alternative strategy for prevention in focus
- Results of a phase 3 clinical trial announced
- Need to understand the programmatic factors that would influence it's success in Kenya

RESVAX(F-post fusion), Leading

Maternal Characteristics
1. Gest age at ANC attendance
2. Clinical/obstetric events
3.Demographic factors
4.Immunological

Trans-placental transfer of antibodies

1. Birth outcome
2. Duration of protection

Vaccine effectiveness

Questions and Critique