

# Direct & Indirect Effects of PCV13 on carriage & pneumonia, Lao PDR

A/Prof Fiona Russell

Centre for International Child Health,  
WHO Collaborating Centre for Research & Training in Child &  
Neonatal Health, Dept of Paediatrics, The University of Melbourne

Director of Melbourne Children's PhD Excellence Program, Melbourne  
Children's Campus

Team Leader, Clinical/Epidemiology, Pneumococcal Group,  
Murdoch Children's Research Institute, Melbourne



# Collaborators

MCRI



A/Prof Fiona Russell

Prof Kim Mulholland

Jana Lai

Dr Jocelyn Chan

Dr Catherine Satzke

Dr Eileen Dunne

Micro team

Dr Cattram Nguyen

Dr Ruth Lim

Dr Amy Gray

Dr Rupert Weaver



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GATES foundation

Lao PDR Ministry of Health

Dr Anonh Xeuatvongsa

Dr Kongxay Phounphengcak

Dr Chansay Pathammvong



University of Health Science

Dr Vanphanom Sychareun

Dr Molina Choummanivong

& team



LOMWRU

Prof David Dance

Prof Paul Newton

Dr Keo & PneuCAPTIVE team

Dr Audrey Dubot-Pérès



# Overview

- Grand Convergence in Public Health
- Priority vaccines- PCV
- Evidence of PCV impact in Lao PDR

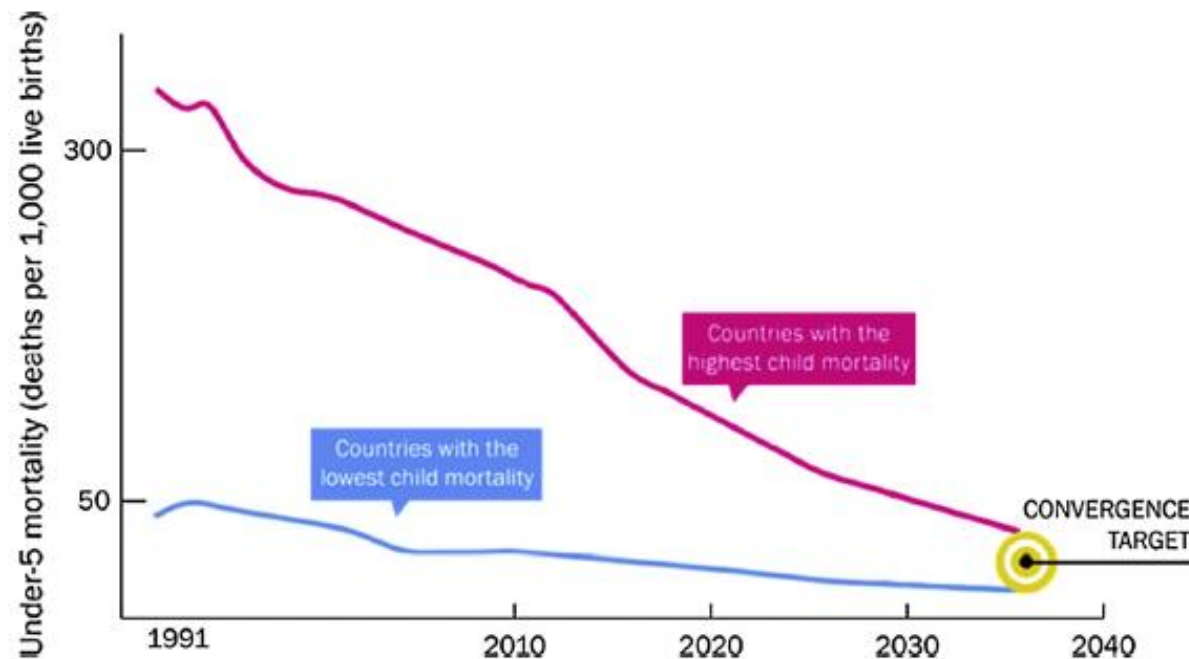
# Grand Convergence in Public Health

## THE LANCET

www.thelancet.com

Global health 2035: a world converging within a generation

*The Lancet* Commission on Investing in Health



"Our report points to the possibility of achieving dramatic gains in global health by 2035 through a grand convergence around infectious, child, and maternal mortality; major reductions in the incidence and consequences of non-communicable diseases and injuries; and the promise of universal health coverage."

GLOBAL  
HEALTH 2035

THE LANCET

**Fig. 1.** Convergence of under-5 mortality rate in countries with the highest child mortality with under-5 mortality rate in countries with the lowest child mortality by enhanced health investments in low- and lower-middle-income countries ([4] ref: <http://globalhealth2035.org/report/key-messages-global-health-2035-report#grand-convergence>).

# Grand Convergence in Public Health- Global goals

- 16-8-4
- U5MR 16 per 1000 livebirths
- Annual AIDS death rate of 8 per 100,000 population
- Annual death rate from TB of 4 per 100,000 population

# Interventions for Grand Convergence

## Reproductive, maternal, newborn, and child health

- Pregnancy-related interventions (antenatal care, treatment of pregnancy complications, delivery interventions, and post-partum care)
- Abortion and complications
- Family planning
- Diarrhoea management
- Pneumonia treatment
- Immunisation
- Nutrition (breastfeeding and supplementation)

## HIV

- Prevention activities: community mobilisation; working with specific groups (intravenous drug users and men who have sex with men)
- Management of opportunistic infections
- Care and treatment
- Collaborative tuberculosis–HIV treatment

## Malaria

- Treatment with appropriate drugs for adults, children, pregnant women, and those with severe malaria
- Indoor residual spraying
- Long-lasting insecticidal bednets
- Intermittent presumptive treatment in pregnancy

## Tuberculosis

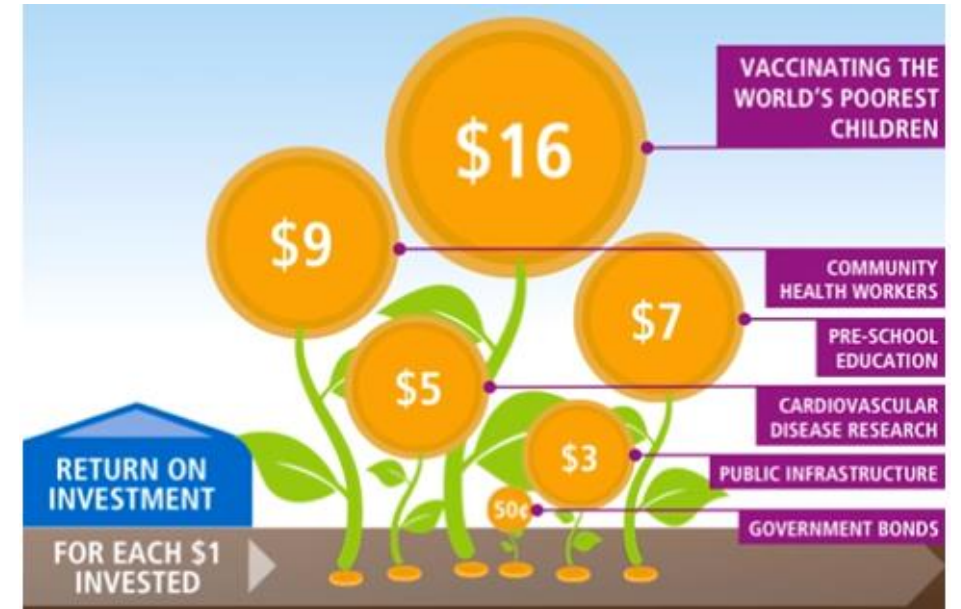
- Diagnosis, care, and treatment of drug-sensitive tuberculosis
- Diagnosis, care, and treatment of multidrug-resistant tuberculosis

## Neglected tropical diseases

### *Community-directed interventions to control:*

- Lymphatic filariasis
- Onchocerciasis
- Schistosomiasis
- Trachoma
- Soil-transmitted helminths

# The Value of Vaccination



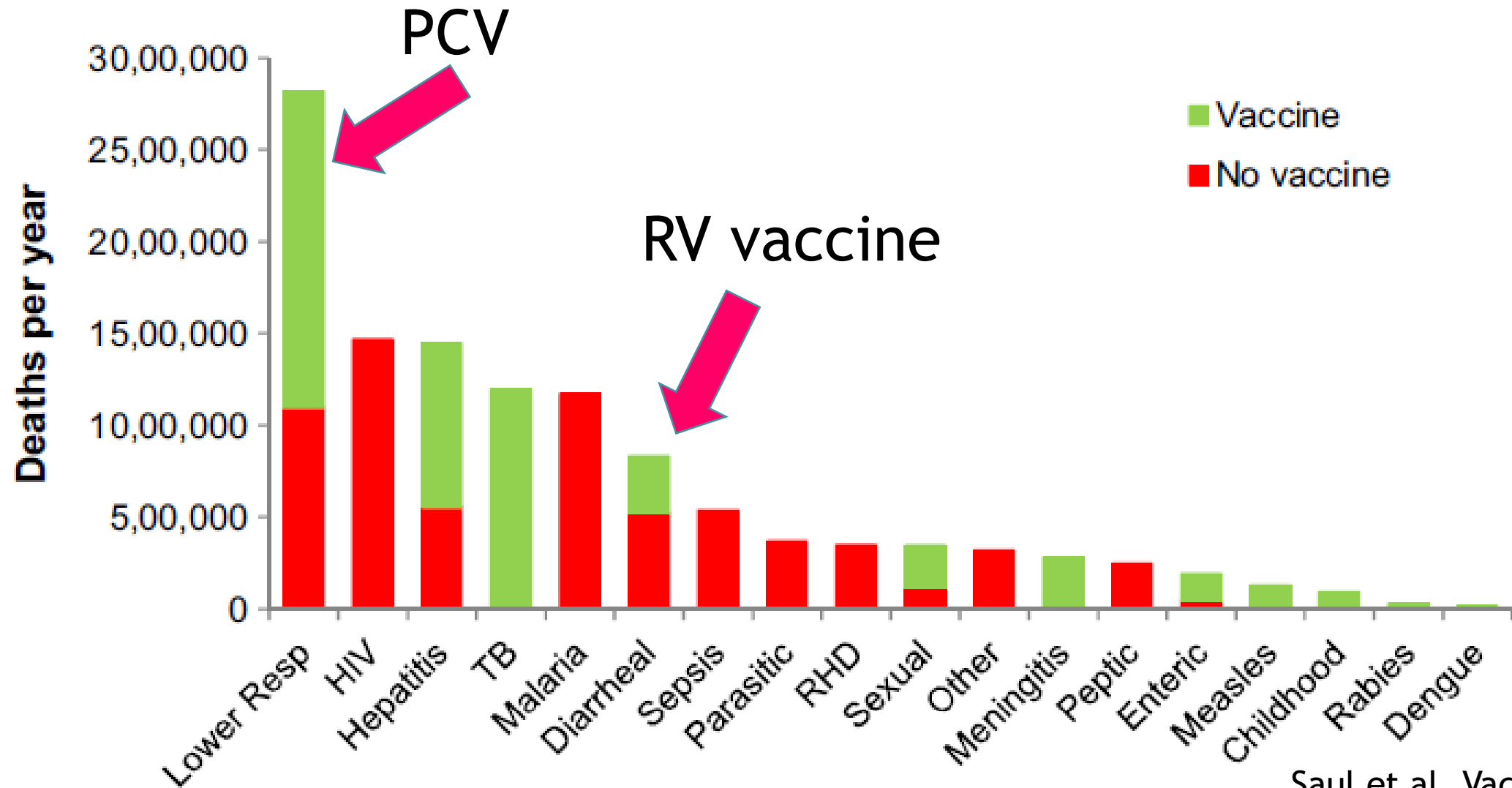
- Study including 94 countries
- Every US\$1 invested in immunisation (2011-2020) results in US\$16 return
- Total economic benefit of US\$586 billion
- Immunisation is one of the best buys in public health
- Taking into account broader economic & social benefits of vaccination (value people place on living longer & healthier lives)= overall economic gain >US\$ 1.5 trillion

# Criteria to Choose Which Vaccine

- Mortality & severity of disease
- Safety of vaccine
- Full economic benefit



# Mortality from Infectious Diseases



# Pneumococcal carriage & disease

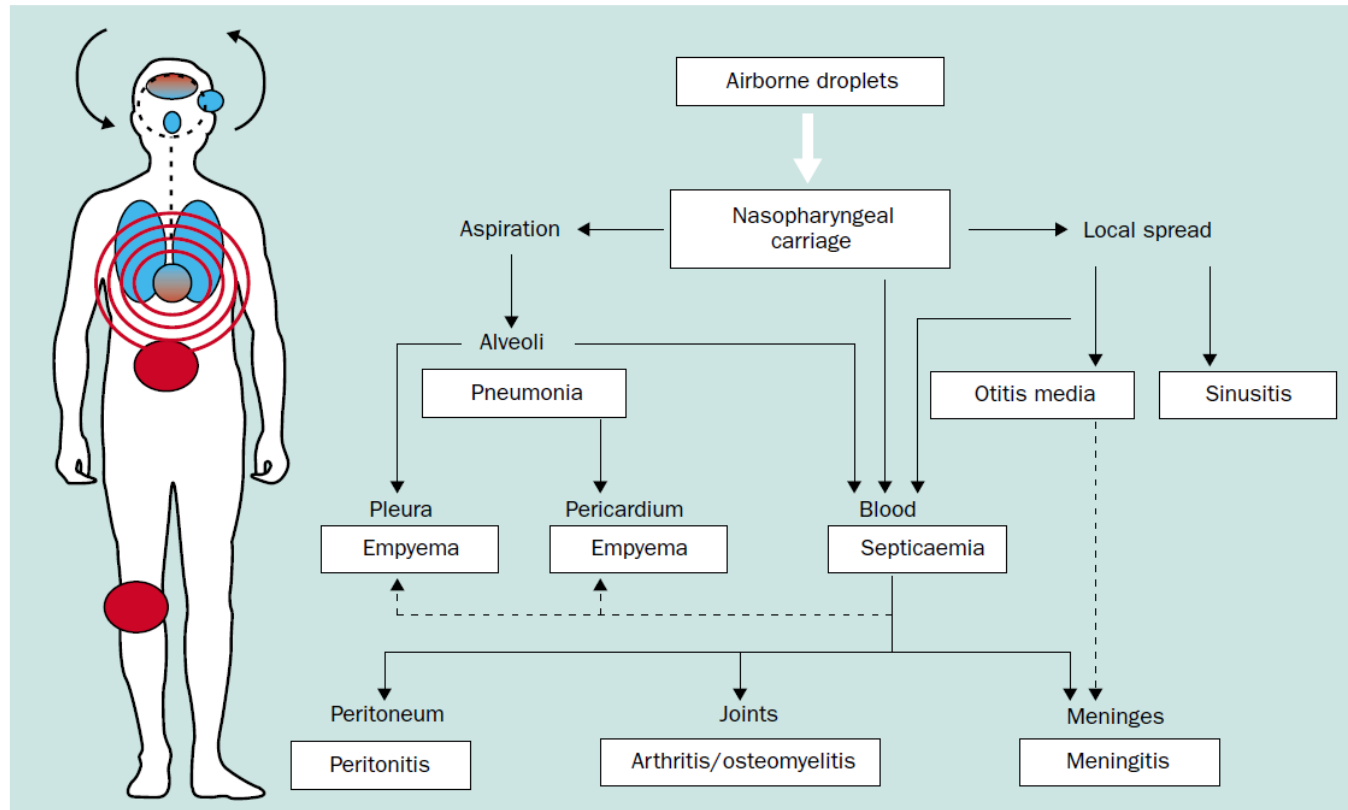


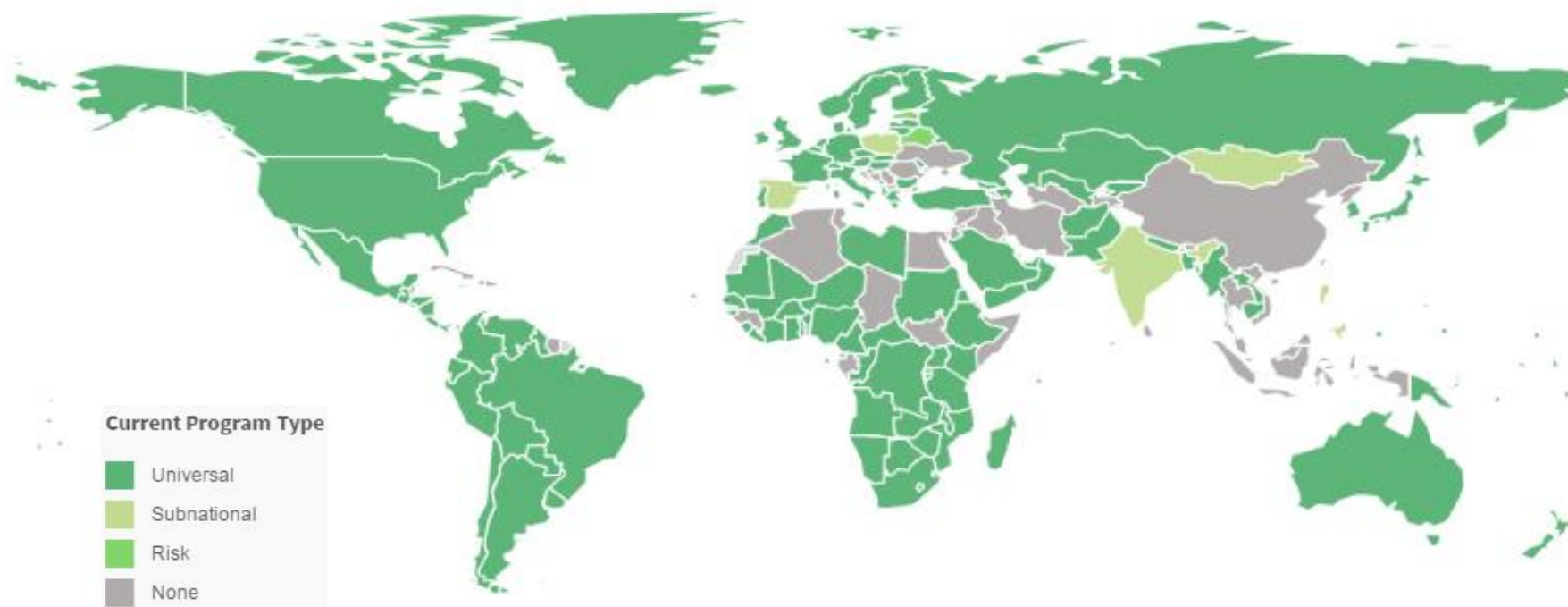
Figure 1. Pathogenic route for *S. pneumoniae* infection. Redrawn from reference 2. Organs infected through the airborne and haematogenic routes are depicted in blue and red, respectively.

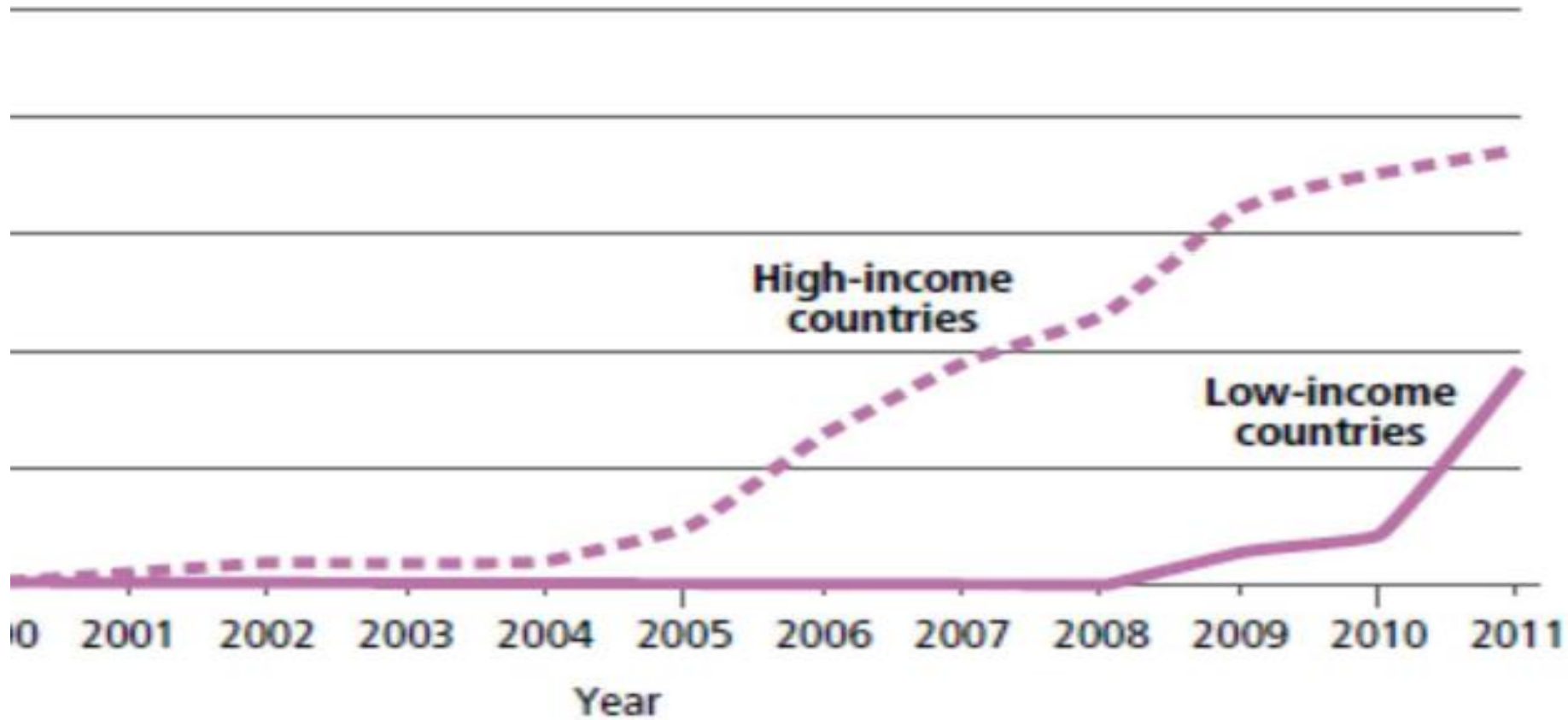
Pneumonia causes ~20% of U5 deaths  
1/3 pneumonia deaths due to pneumococci

NP carriage  
Common  
Most asymptomatic  
Precursor for disease  
Transmission  
Herd immunity

# Pneumococcal Conjugate Vaccines

PCVs used successfully for ~ 17 years





Timeline for PCV introduction in low- & middle-income countries

# Importance of indirect effects

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- Substantial component of overall effects
- 2x IPD cases through indirect effects cf. direct effects in US

- Cost-effectiveness of vaccine

Including indirect effects → Significant increase of results in favour of PCV

- Protect individuals unable to be vaccinated/poor vaccine response

# Direct & Indirect Effects of PCV13 on carriage & pneumonia, Lao PDR



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# Background

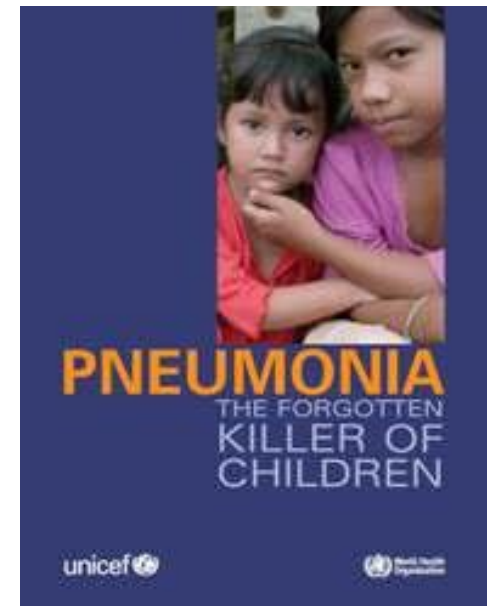
In Lao PDR: ~20% of all-cause childhood hospitalisations due to pneumonia

Treatment: oxygen & antibiotics

Catastrophic health event  
(ICU, oxygen, referral) poor parents  
need to make choices:

- Pay for the treatment
- Discharge the child & hope for the best

PCV13 introduced in late 2013



# Aims

1. Describe epidemiology of childhood pneumonia
2. Determine the PCV13 VE against hypoxic pneumonia & pneumonia cases requiring supplementary oxygen in U5s
3. Determine direct & indirect effect of PCV13 on pneumococcal carriage in community (transmission & herd immunity)
4. Determine PCV13 coverage required to show herd immunity
5. Determine the PCV13 VE against antimicrobial resistance (ongoing)



# Study 1: Methods-epidemiology of childhood pneumonia

Design: Retrospective medical record review of pneumonia admissions pre-PCV13 (2011-2013)

Site: Vientiane Capital

Mahosot Hospital

National Child Hospital

Mother and Child Hospital

Settathirath Hospital

April 5th Hospital

103 Hospital

& the 9 district hospitals in VC

# 1. Methods-epidemiology of childhood pneumonia

## Include:

2-59 months old

diagnosed with severe pneumonia (WHO Pocketbook of Hospital Care for Children (2013))

## Exclude:

bronchiolitis or asthma

# 1. Results

3801  
pneumonia  
admissions

20.3% of all  
admissions  
due to  
pneumonia

Hospital		2011	2012	2013
<b>Central Hospitals</b>				
Settathirath Hospital	Number of pneumonia hospitalizations	133	134	157
	Number of all-cause hospitalizations	720	780	837
	% of all-cause hospitalizations due to pneumonia	18.5%	17.2%	18.8%
Mahosot Hospital	Number of pneumonia hospitalizations	325	333	256
	Number of all-cause hospitalizations	1321	1435	1607
	% of all-cause hospitalizations due to pneumonia	24.6%	23.2%	15.9%
National Child Hospital	Number of pneumonia hospitalizations	N/A	603 <sup>2</sup>	603 <sup>1</sup>
	Number of all-cause hospitalizations	N/A	2762 <sup>2</sup>	2762 <sup>1</sup>
	% of all-cause hospitalizations due to pneumonia	N/A	21.8% <sup>2</sup>	21.8% <sup>1</sup>
Mother and Child Hospital	Number of pneumonia hospitalizations	603 <sup>3</sup>	N/A	N/A
	Number of all-cause hospitalizations	2762 <sup>3</sup>	N/A	N/A
	% of all-cause hospitalizations due to pneumonia	21.8% <sup>3</sup>	N/A	N/A
Hospital 103	Number of pneumonia hospitalizations	163 <sup>5</sup>	200 <sup>4</sup>	126
	Number of all-cause hospitalizations	849 <sup>5</sup>	943 <sup>4</sup>	755
	% of all-cause hospitalizations due to pneumonia	19.2% <sup>5</sup>	21.2% <sup>4</sup>	16.7%
<b>9 District Hospitals</b>	Number of pneumonia hospitalizations	47	55	63
	Number of all-cause hospitalizations	293	443	437
	% of all-cause hospitalizations due to pneumonia	16%	12.4%	14.4%
<b>Total</b>	Number of pneumonia hospitalizations	1271	1325	1205
	Number of all-cause hospitalizations	5926	6363	6398
	% of all-cause hospitalizations due to pneumonia	21.4%	20.8%	18.8%

	2-59 mo	2-5 mo	6-11 mo	12-23 mo	24-59 mo
All-cause hospitalizations	n = 9674	n = 1167	n = 2243	n = 2844	n = 3420
Pneumonia hospitalizations, n (% of all hospitalizations, by age group)	1999 [20.7%]	386 [48.5%]	457 [25.0%]	623 [27.7%]	533 [18.2%]
Pneumonia hospitalizations, n (% of all hospitalizations, by age group)	n = 931	n = 141	n = 202	n = 335	n = 253
Severity classification, n (% of all pneumonia hospitalizations, by age group)					
Pneumonia (non-severe)	418 [44.9%]	54 [38.3%]	82 [40.6%]	158 [47.2%]	124 [49.0%]
Severe pneumonia	513 [55.1%]	87 [61.7%]	120 [59.4%]	177 [52.8%]	129 [51.0%]
Clinical features and management, n (% of all pneumonia hospitalizations, by age group)					
Cyanosis or hypoxia	146 [15.7%]	45 [31.9%]	36 [17.8%]	45 [13.4%]	20 [7.9%]
ICU admission	136 [14.6%]	45 [31.9%]	39 [19.3%]	32 [9.6%]	20 [7.9%]
Supplemental oxygen required	159 [17.1%]	54 [38.3%]	39 [19.3%]	39 [11.6%]	27 [10.7%]
Outcomes, n (% of all pneumonia hospitalizations, by age group)					
Alive and well	883 [94.8%]	125 [88.7%]	191 [94.6%]	324 [96.7%]	243 [96.0%]
Unwell at discharge or discharged home to die	45 [4.8%]	15 [10.6%]	10 [5.0%]	10 [3.0%]	10 [4.0%]
Dead	3 [0.3%]	1 [0.7%]	1 [0.5%]	1 [0.3%]	0 [0.0%]

# 1. Results

- 48.5% of all-cause hospitalisations due to pneumonia in 2-5m infants
- 57% of children hospitalised with pneumonia were severe
  - 61.7% of infants aged 2-5 mo with pneumonia were severe
- Median age 15m (IQR 8-24)
- Median length of stay 4d (IQR 3-5)
- 14.6% needed ICU
- 3 died during admission: 4.8% of cases were discharged against medical advice, and still unwell or discharged home to die- CFR may be 5.2%

## Study 2: Methods- PCV13 effectiveness against hypoxic pneumonia

- Prospective cohort study at the Mahosot Hospital between Dec 2013 to Jul 2017 (ongoing)
- U5s admitted with acute respiratory infection & pneumonia
- For this analysis, only pneumonia cases were included
- At enrolment demographic, clinical information & PCV13 vaccination status from written record were recorded
- NP swab- RSV by PCR

# Methods- hypoxic pneumonia

- PCV13 vaccinated:  
≥2 doses of PCV13 for those <12m  
≥ 1 dose if ≥ 12m
- Hypoxic pneumonia: pneumonia (WHO definition) + O2 saturation <90% (in room air) or O2 during admission

# Methods- hypoxic pneumonia

Vaccine effectiveness (VE) against hypoxic pneumonia calculated using ORs adjusted by inverse probability weighting using propensity scores using logistic regression of covariates: age, RSV status, maternal education, income, comorbidities, time since PCV13 introduction, access to piped water, residing in a rural or urban setting, number of children in the household, number of adults in the household, and day care attendance

ORs were converted to VE using:  $VE = (1 - OR) * 100$

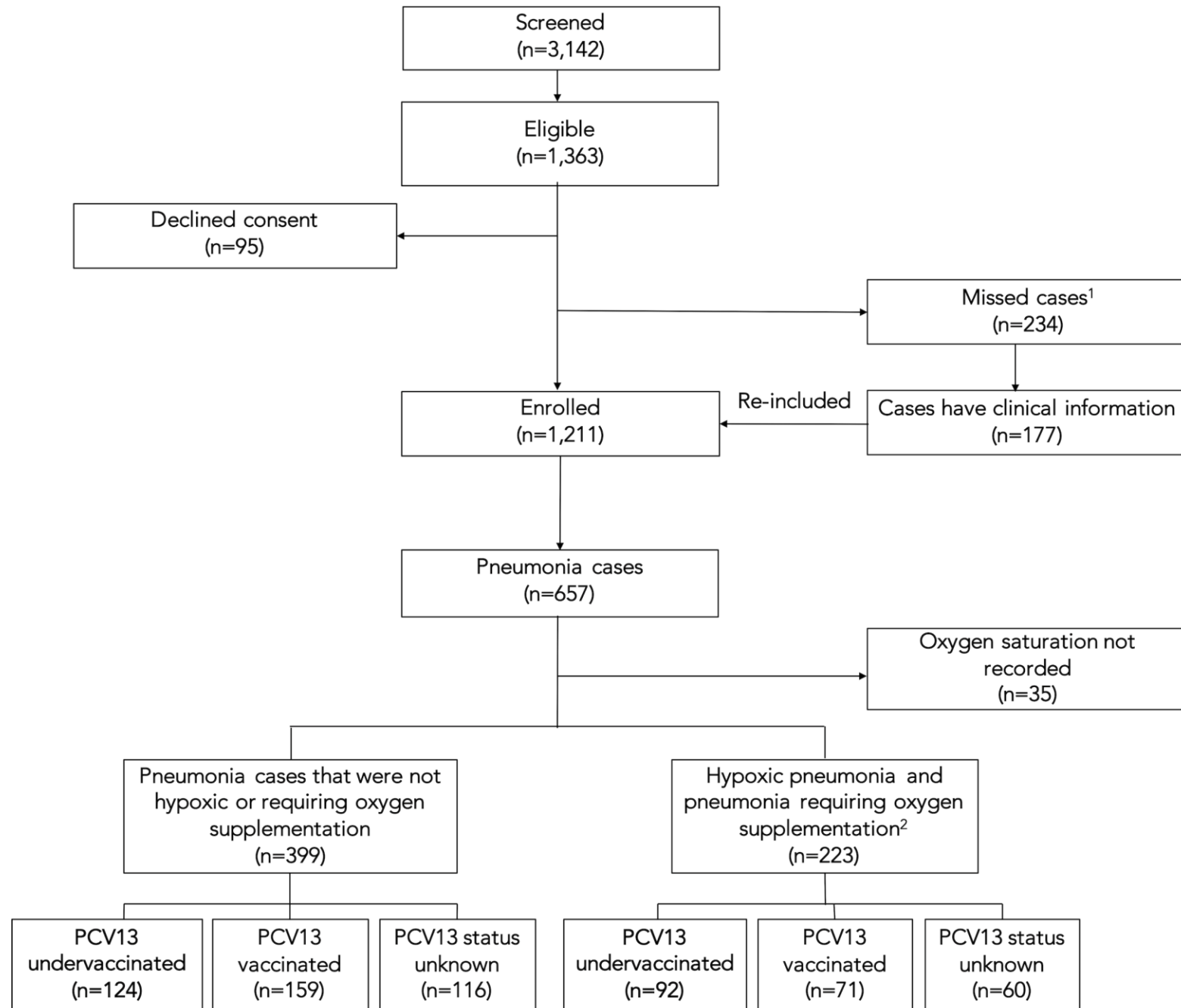


# Results- hypoxic pneumonia

657 pneumonia cases

33.9% hypoxic pneumonia or required O2

36.8% PCV13 vaccinated



## Results- hypoxic pneumonia

	<b>Unadjusted PCV13 VE (95%CI)</b>	<b>p-value</b>	<b>Adjusted PCV13 VE (95%CI)</b>	<b>p-value</b>
Hypoxic pneumonia	39.8% (11.2-59.2)	p=0.01	55.1% (27.3-72.3)	p=0.001

# Study 3: Methods- PCV13 effect on community carriage

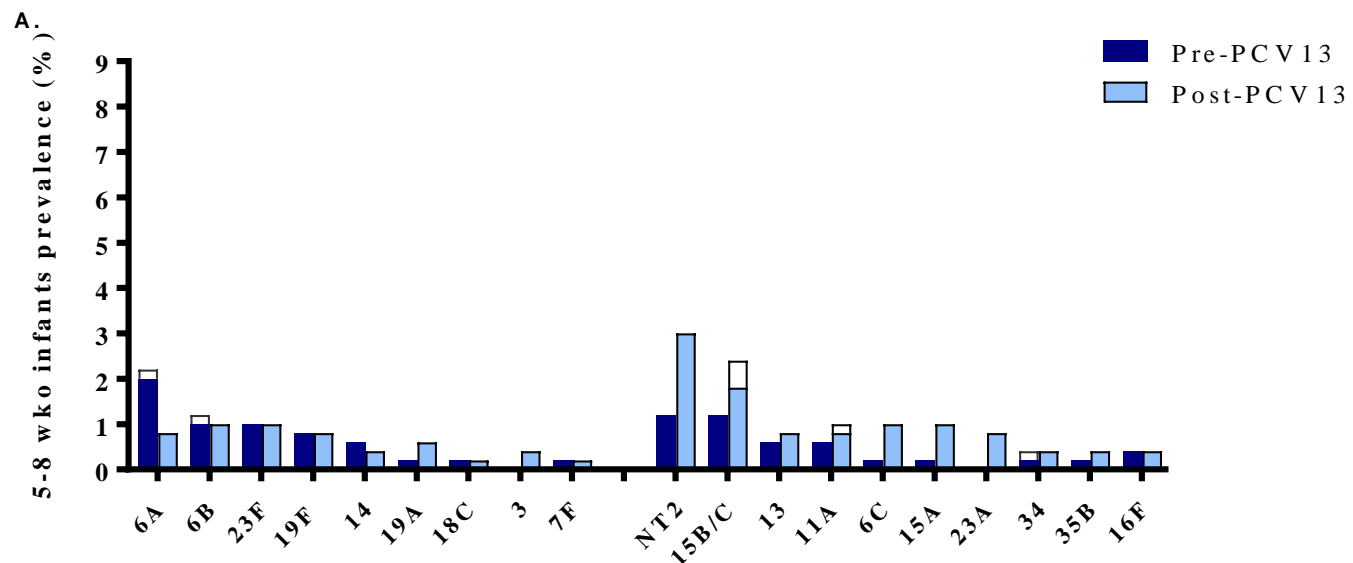
## Pneumococcal carriage

- Community carriage surveys in toddlers (12-23m) & infants too young to be vaccinated (5-8W) pre (2013) & 2y post-PCV13 (2015)
- Urban MCH clinics and rural sites
- Pneumococcal carriage: *lytA* qPCR & microarray

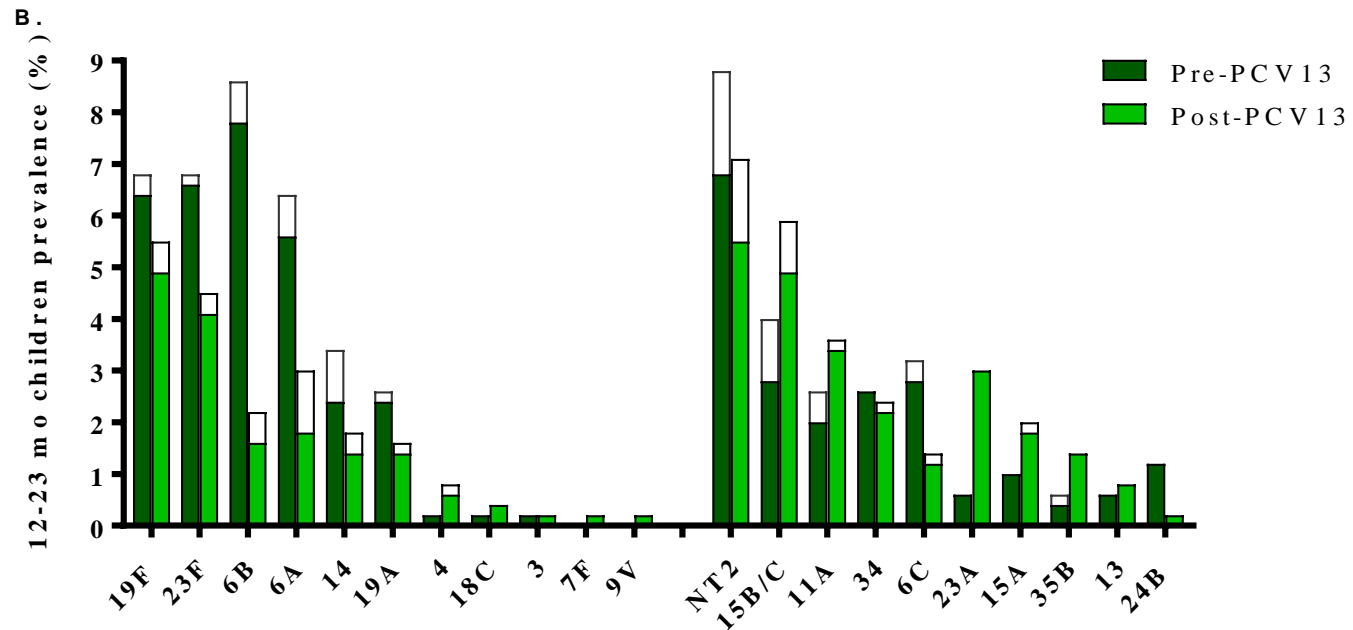
# Results- community carriage (n=1000)

	pre-PCV13		post-PCV13	
	Prevalence (%) (95% CI)	Prevalence (%) (95% CI)	Unadjusted Prevalence ratio (95% CI)	Adjusted prevalence ratio <sup>1</sup> (95% CI)
All pneumococci				
5-8 wko	14.3 (11.3 - 17.6)	17.1 (13.9 - 20.7)	1.20 (0.90 - 1.60)	1.13 (0.85 - 1.51)
12-23 mo	55.8 (51.3 - 60.2)	45.6 (41.2 - 50.0)	0.82 (0.72 - 0.92)	0.87 (0.78 - 0.97)
PCV13 serotypes				
5-8 wko	6.5 (4.5 - 9.0)	5.2 (3.4 - 7.5)	0.80 (0.49 - 1.33)	0.76 (0.46 - 1.26)
12-23 mo	32.9 (28.8 - 37.2)	19.8 (16.4 - 23.6)	0.60 (0.49 - 0.75)	0.69 (0.56 - 0.85)
Non-PCV13 serotypes				
5-8 wko	7.7 (5.5 - 10.4)	12.2 (9.4 - 15.4)	1.59 (1.08 - 2.33)	1.49 (1.01 - 2.19)
12-23 mo	26.9 (23.1 - 31.1)	30.0 (26.0 - 34.2)	1.11 (0.91 - 1.35)	1.18 (0.97 - 1.43)

Decline in PCV13 carriage for toddlers and non-significant decline in young infants



45% of pneumococci belonged to PCV13 serotypes in 2013 compared to 30% in 2015 ( $p = 0.049$ )



54.5% of pneumococci belonged to PCV13 serotypes in 2013 compared to 38.5% in 2015 ( $p < 0.001$ )

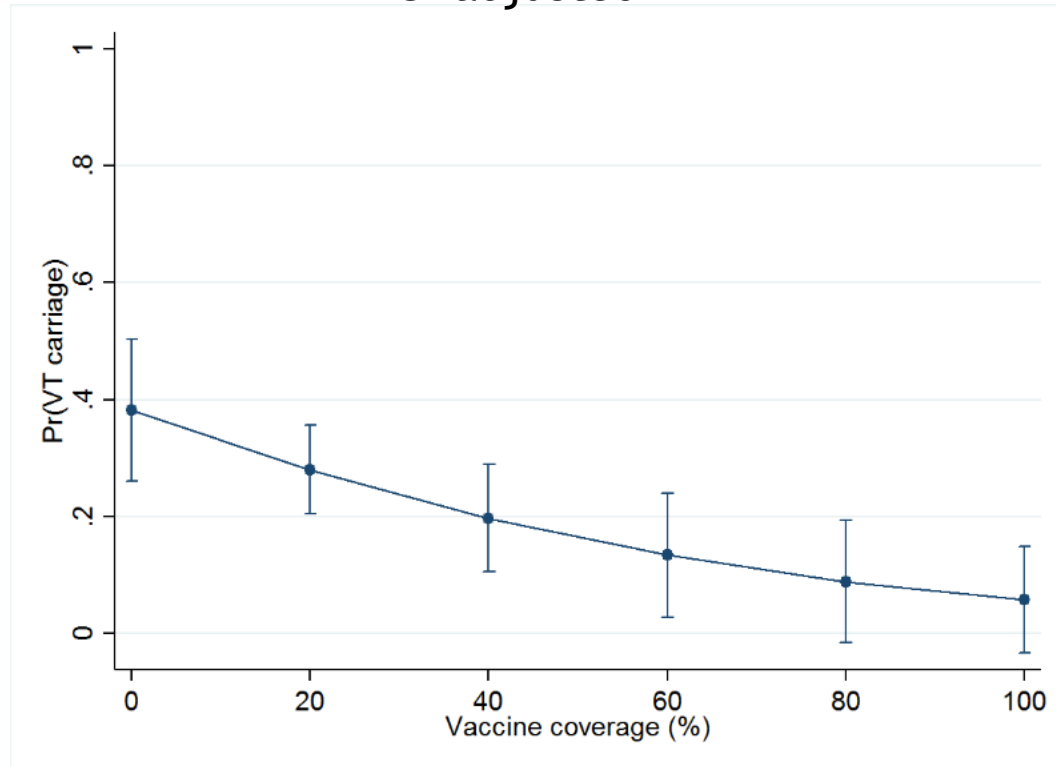
# Study 4: Methods-PCV coverage to show herd protection

- Same prospective cohort study at the Mahosot Hospital, Vientiane, between Dec 2013 to Jul 2017 (ongoing)
- U5s admitted with acute respiratory infection & pneumonia
- At enrolment PCV13 vaccination status from written record were recorded
- NP carriage surveillance- *lytA* qPCR & microarray, for pneumococci and serotype
- PCV13 health centre coverage surveys

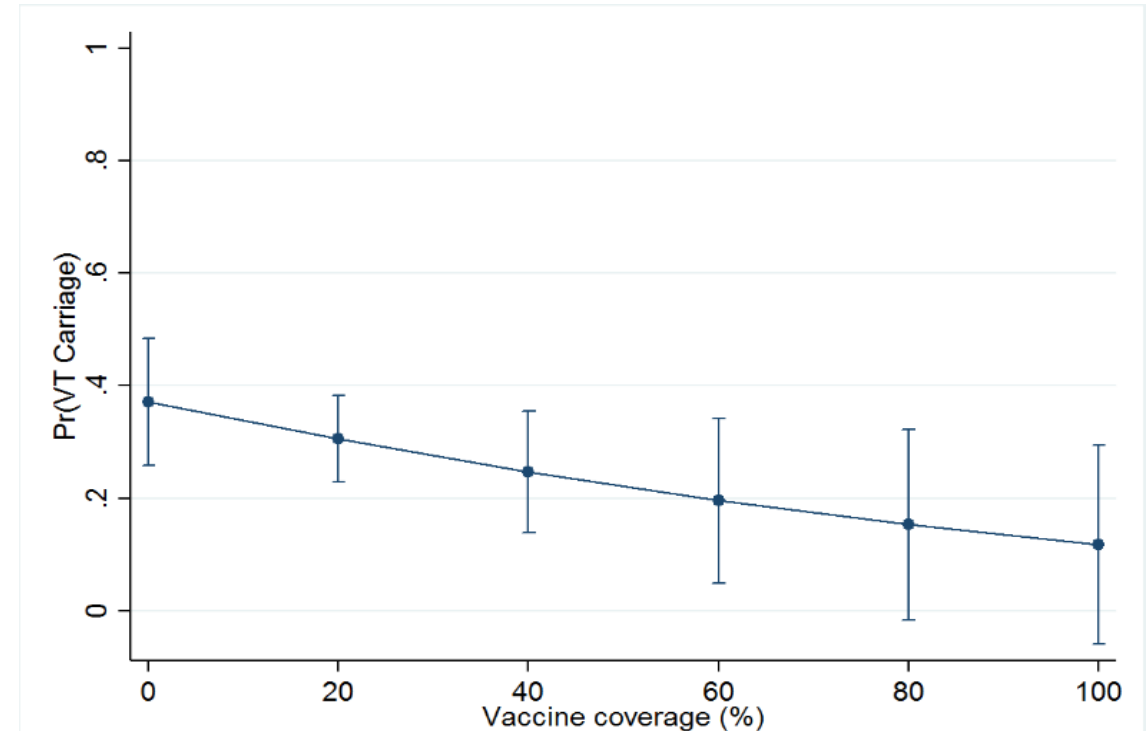
# Preliminary Results- hospital based surveillance

Predicted prevalence of PCV13 carriage among under-vaccinated children U5 at each decile of PCV13 coverage, 2014-2016

Unadjusted



\*Adjusted



\*Adjusted by age, calendar time, residence, maternal education, family income, no. people per room

# Study 5: PCV13 effectiveness against AMR

No data on PCV effect on AMR from Asia or any LIC or MIC

5y of pneumococcal carriage surveillance in Lao PDR  
VE against AMR

Ongoing



# Conclusions

- Preliminary results show PCV13 is effective against hypoxic pneumonia
- Consistent with 2 studies from Africa
- PCV13 is likely to contribute to reducing child mortality
- PCV13 reduces PCV13 carriage which is likely to result in less PCV13 disease
- PCV13 coverage required to show herd immunity to be defined
- Final results will provide a compelling evidence for PCV13 for introduction in the region

# Conclusion

PCV will contribute to Grand Convergence

PCV is effective & should be a priority

Consider broader impacts eg AMR

Further work: equity of access to vaccination and health economic benefits



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