Measuring vaccine impact – principles and examples

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Global public health impact – a daunting prospect

Global Public Health Impact of Vaccines in Children

FREE

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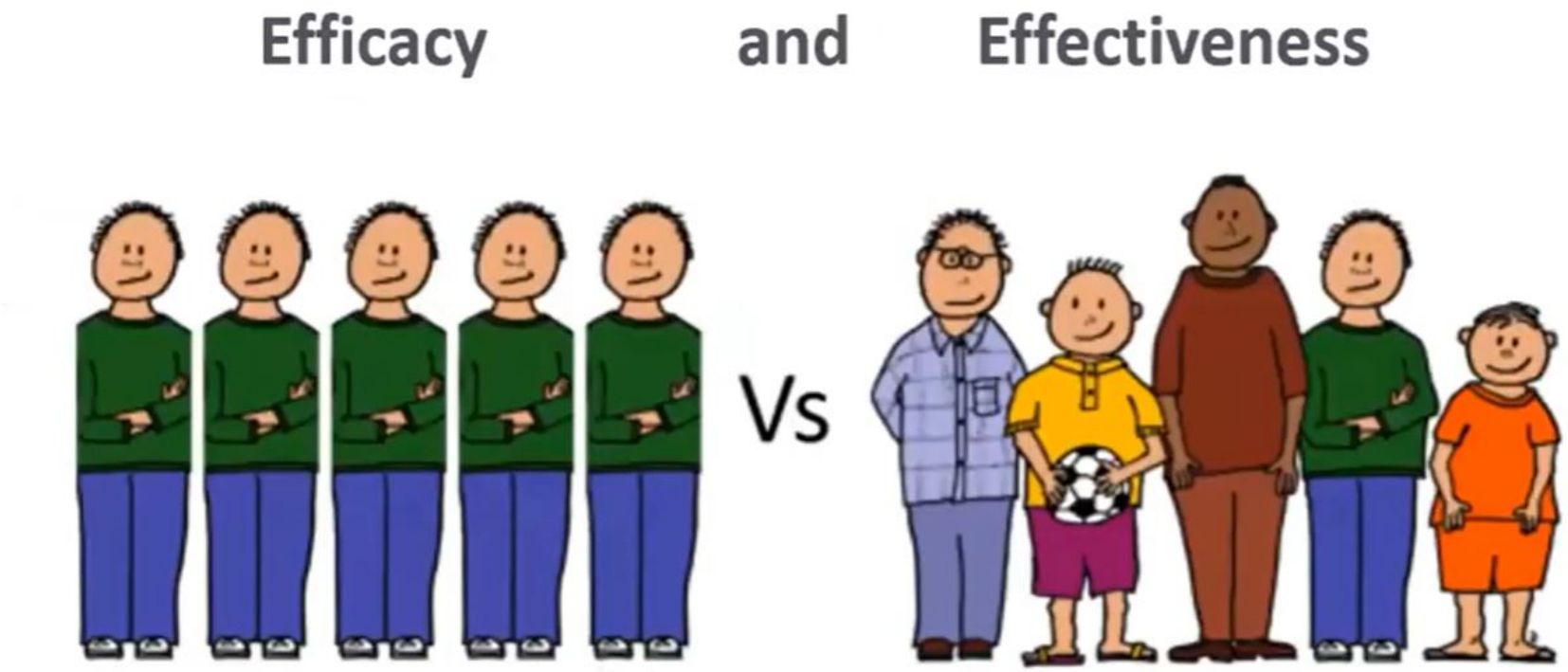
Measuring vaccine impact - Principles

- Efficacy vs Effectiveness
- Direct vs Indirect effects
- Vaccine-Preventable Disease Incidence (VPDI)
  - Syndromic diagnosis versus Laboratory-confirmed
  - “Vaccine Probe”
- Disease severity
- Impacts on health systems and the broader economy
- Negative or “trade-off” effects

Measuring vaccine impact – Examples

- Pertussis – declines in deaths pre-vaccine
- Pneumococcus – invasive disease (IPD) vs pneumonia
- Meningococcal disease – changes background incidence
- Disease severity – COVID vaccines and variants

Principles -1



Dilemma: methodological perfection vs real-world translation

Efficacy vs Effectiveness

Clemens JAMA 1996

Table 1.—Decisions That Determine the Efficacy Perspective of Phase III Trials

Issue	Decisions for Efficacy Trial
Study population	High-risk, highly responsive individuals
Vaccine formulation and regimen	Designed to maximize immunogenicity
Storage and administration of vaccine	Ideal conditions, intensive monitoring, and strict supervision
Comparison agent	Agent with no activity against the target infection
Concomitant therapies and practices	Excluded if they are anticipated to interfere with vaccine immunogenicity
Unit of allocation	Selected to maximize statistical power and to minimize transmission of vaccine organisms to controls and to other vaccinees (usually individuals
Outcomes for assessing the impact of vaccination	Narrowly defined events that are responsive to vaccine-induced immunity
Outcomes for assessing vaccine safety	Adverse effects that are expected and frequent and that have a short latency period
Primary index of vaccine protection	Protective efficacy
Subjects included in the analyses of protection	Completely and correctly dosed
Outcomes included in the analyses of protection	Episodes of target infection beginning after an "immunogenic window"
Duration of the follow-up for evaluating vaccine protection	Sufficiently long to yield statistically precise results
Measurement of the net costs of vaccination	Not essential

Limitations of efficacy trials

Special Communication

Evaluating New Vaccines for Developing Countries

Efficacy or Effectiveness?

John Clemens, MD; Ruth Brenner, MD, MPH; Malla Rao, MEngg; Nebiat Tafari, MD; Charles Lowe, M

Efficacy vs Effectiveness – conflicting RCT results

Clemens JAMA 1996

Table 2.—Examples of Conflicting Sets of Contemporary Randomized Controlled Phase III Trials

Vaccine and Outcome Evaluated, Site (Source)	Age Group (No. of Doses)*	Sample Size†	Post-vaccination Follow-up	Protective Efficacy, % (95% Confidence Interval)
RIT 4237				
Rotavirus diarrhea				
Finland (Vesikari et al[33])	8-11 mo (1)	178	5 mo	47/88‡§ (−10 to 75)/(63 to 96)
Rwanda (De Mol et al[36])	3-8 mo (1)	245	≤4 mo	0/NR‡ (−304 to 67) . . .
The Gambia (Hanlon et al[34])	2.5-4.5 mo (1-3)	253	≥3 mo	33/7‡ (4 to 53)/(−37 to 37)
Peru (Lanata et al[35])	2-18 mo (1)	196	18 mo	15/63‡ (−41 to 48) (−9 to 85)
Ty21a				
Typhoid fever				
Egypt (Wahdan et al[37])	6-7 y (3)	32 388	3 y	96‖ (70 to 99)
Chile (Levine et al[17])	5-14 y (3)	81 621	3 y	77 (60 to 87)
Indonesia (Simanjuntak et al[14])	3-19 y (3)	9460	2.5 y	53 (35 to 66)
PRP-D				
Invasive Hib				
Finland (Eskola et al[38])	2-6 mo (3)	114 000	8-12 mo	90‖ (70 to 96)
Alaska (Ward et al[39])	2-6 mo (3)	2102	2-18 mo	35 (−57 to 73)

Hib vaccine trial in low vs high incidence population

Herd immunity

INVITED ARTICLE VACCINES
Stanley Plotkin, Section Editor

"Herd Immunity": A Rough Guide

Paul Fine, Ken Eames, and David L. Heymann
Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom

The term "herd immunity" is widely used but carries a variety of meanings [1–7]. Some authors use it to describe the proportion immune among individuals in a population. Others use it with reference to a particular threshold proportion of immune individuals that should lead to a decline in incidence of infection. Still others use it to refer to a pattern of immunity that should protect a population from invasion of a new infection. A common implication of the term is that the risk of infection among susceptible individuals in a population is reduced by the presence and proximity of immune individuals (this is sometimes referred to as "indirect protection" or a "herd effect"). We provide brief historical, epidemiologic, theoretical, and pragmatic public health perspectives on this concept.

Indirect effects = disease incidence in unvaccinated typically can't be assessed in a RCT

- Is disease incidence measured similarly in non-vaccinated?
  - Blood culture practice for pneumonia (IPD)?
  - Stool testing for pathogens (rotavirus)?
  - Clinical syndrome vs laboratory testing (varicella, zoster)?

- May be very influential in cost-effectiveness considerations
  - Pneumococcal conjugate vaccine
  - Meningococcal ACWY

Vaccine-Preventable Disease Incidence

$$\text{Vaccine efficacy} = \frac{\text{Incidence in controls} - \text{Incidence in vaccinated}}{\text{Incidence in controls}}$$

$$\text{VPDI} = \text{VE} \times \text{Incidence in controls}$$

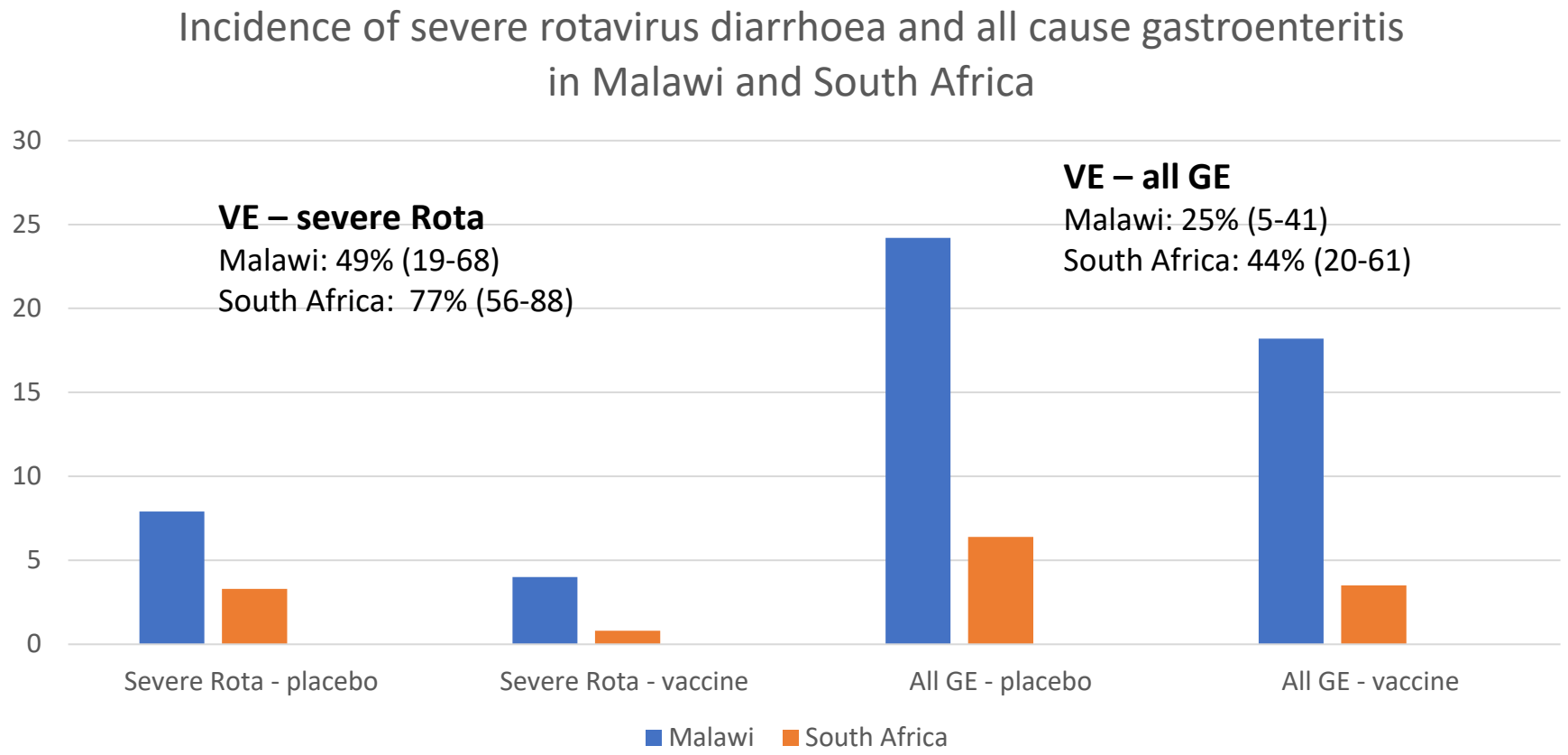
ie takes into account disease incidence in the population

Vaccine trial	Outcome with highest VE				Outcome with lowest, statistically significant VE			
	Outcome	Incidence controls[a]	VE	VPDI[a]	Outcome	Incidence controls[a]	VE	VPDI[a]
Indonesia Hib vaccine (4)	Culture-confirmed Hib meningitis	0.19	86%	0.16	Clinical pneumonia	395	4.0%	15.8
Gambia PCV (5)	Vaccine-serotype IPD[b]	2.5	77%	1.9	Clinical pneumonia	249	7%	17.0
Kenya rotavirus vaccine (7)	Severe rotavirus gastroenteritis attending health facility (1st year)	40	83%	33	Gastroenteritis with severe dehydration reported at home (1st year)	550	34%	190

[a] All incidences and VPDIs are given as per 1000 person-years.
[b] IPD, invasive pneumococcal disease.

Effect of Human Rotavirus Vaccine on Severe Diarrhea in African Infants

Shabir A. Madhi, M.D., Nigel A. Cunliffe, M.B., Ch.B., Ph.D., Duncan Steele, Ph.D., Desirée Witte, M.D., Mari Kirsten, M.D., Cheryl Louw, M.D., Bagrey Ngwira, M.D., John C. Victor, Ph.D., M.P.H., Paul H. Gillard, M.D., Brigitte B. Cheuvart, Ph.D., Htay H. Han, M.B., B.S., and Kathleen M. Neuzil, M.D., M.P.H.



Severity and sequelae: comparing 5 VPDs – US data (Black Vaccine 2013)

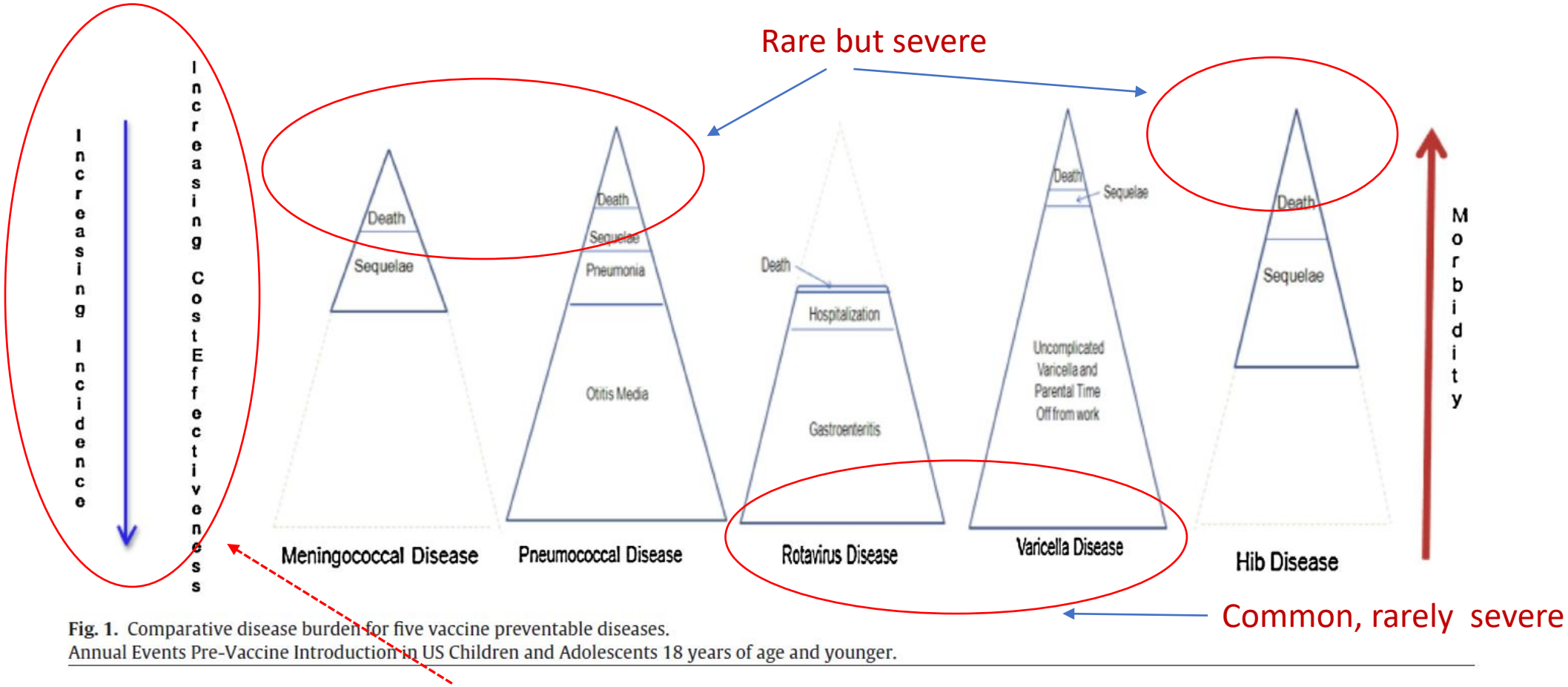


Fig. 1. Comparative disease burden for five vaccine preventable diseases.
Annual Events Pre-Vaccine Introduction in US Children and Adolescents 18 years of age and younger.

Cost-effectiveness driven by overall incidence, not by rare severe outcomes

“Full” value of vaccination

Table 1. Framework of vaccination benefits

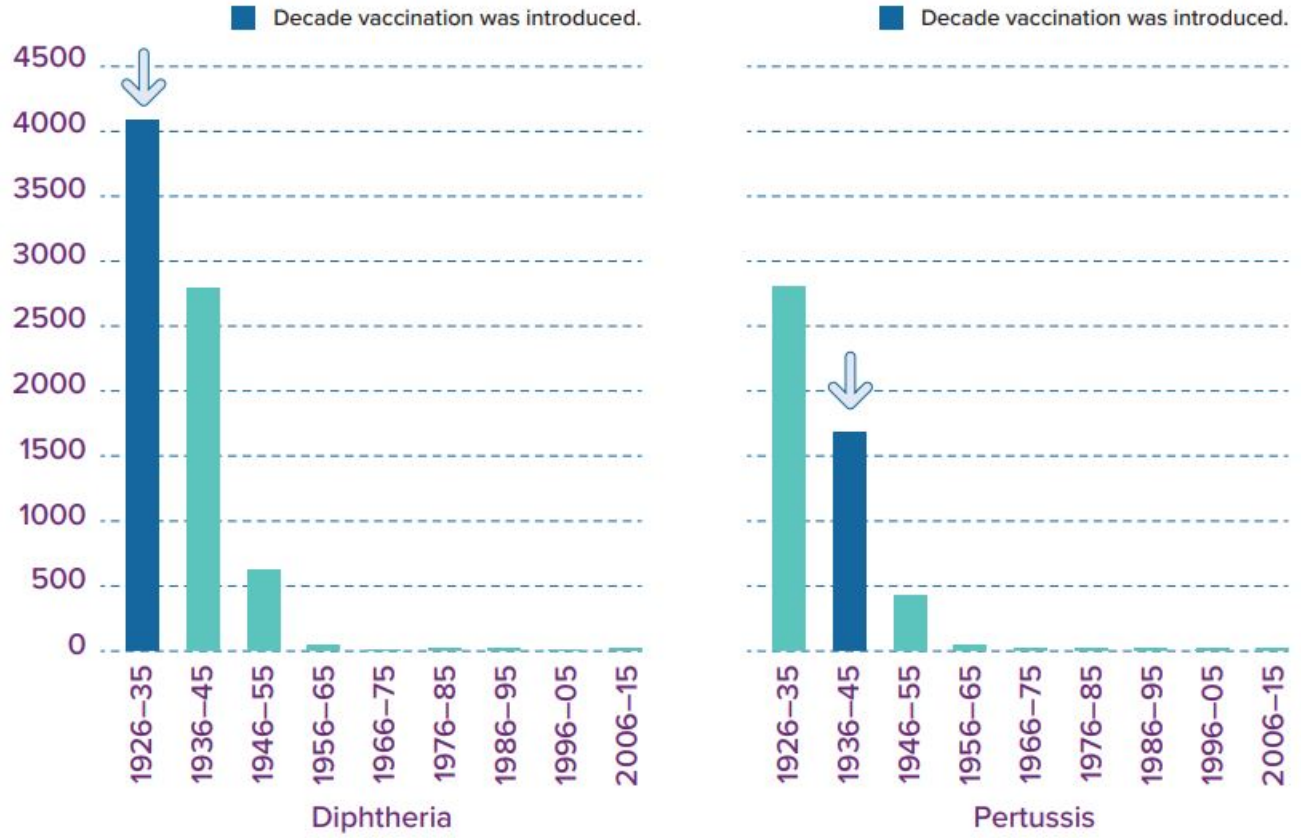
Perspective		Benefit categories
Broad	Narrow	Health care cost savings
		Care-related productivity gains
		Outcome-related productivity gains
		Behavior-related productivity gains
		Community health externalities
		Community economic externalities
		Risk reduction gains
		Health gains

Pertussis

“It’s all due to improved living standards, vaccines have had no impact”

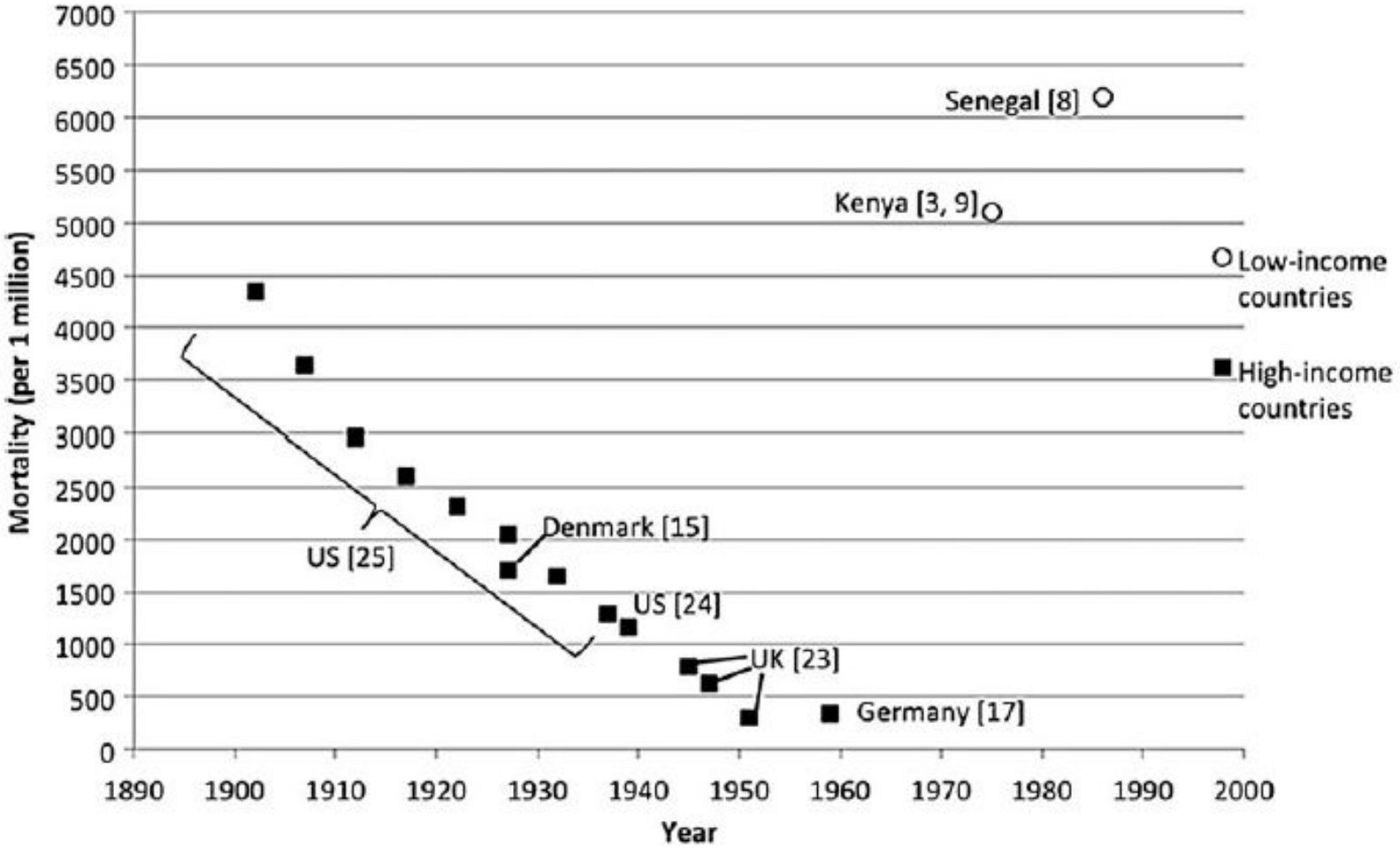
Deaths from diphtheria and pertussis - Australia

Figure 1: Number of deaths from diseases now vaccinated against in Australia, by decade, 1926–2015



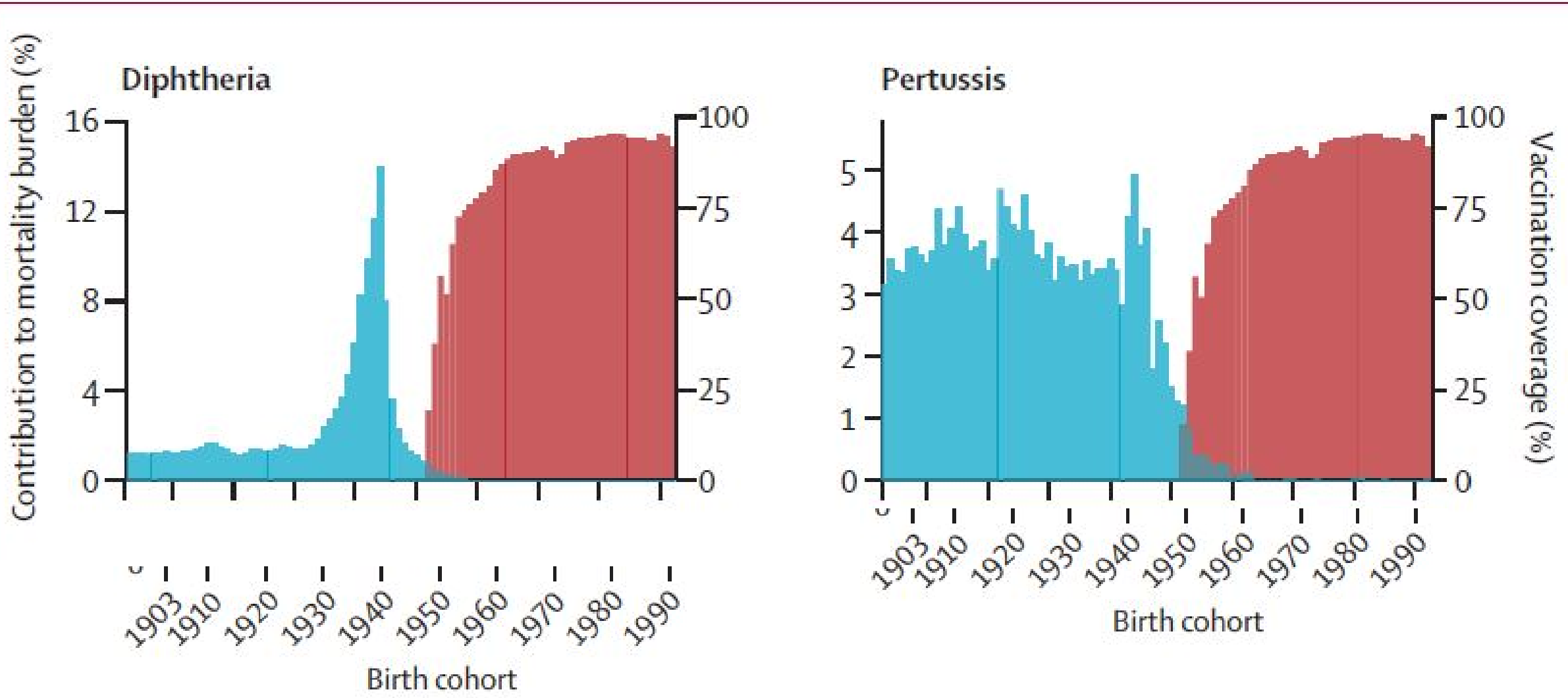
Pertussis: reductions in deaths pre-immunisation

Chow et al Clin ID 2014



Deaths and vaccine coverage 1903-1992

Netherlands (van Wijhe Lancet ID 2016)



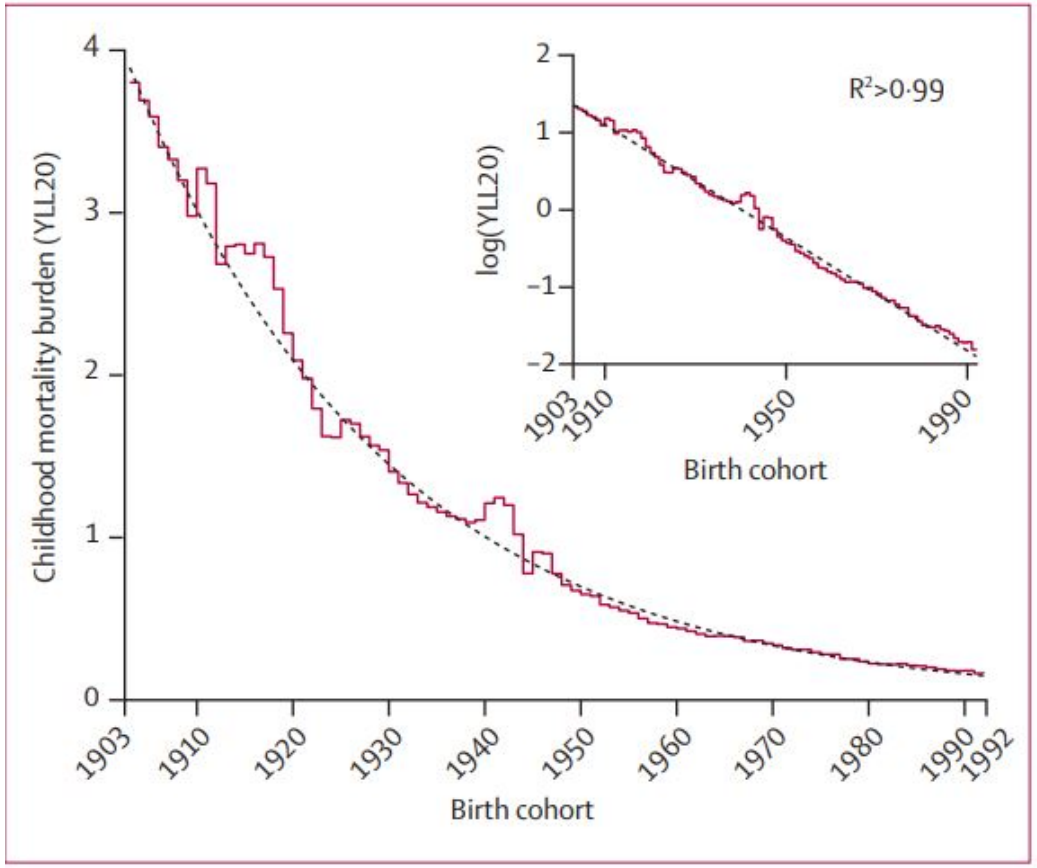


***Figure 2*: All-cause mortality burden in years of life lost up to age 20 years per livebirth in the Netherlands**

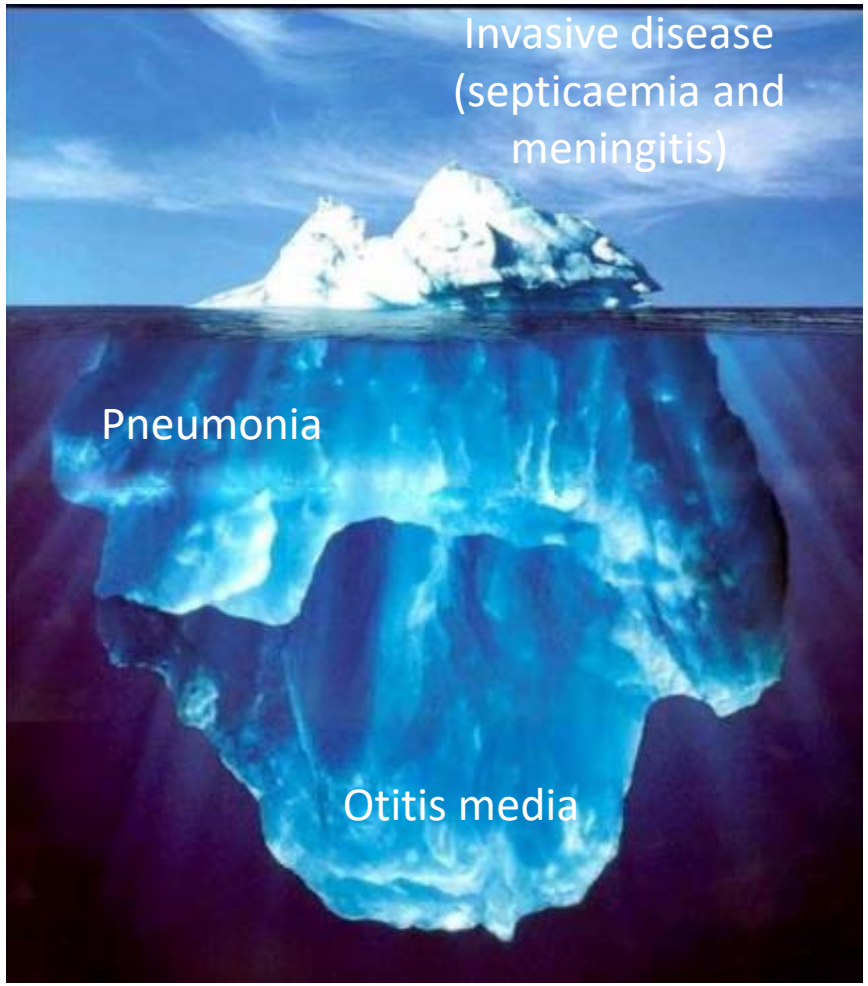
	Year of introduction of vaccination	Average contribution to all-cause mortality burden		Reduction in mortality burden due to mass vaccinations (95% prediction interval)	
		Before introduction	After introduction	YLL20 in thousands	Deaths in thousands
Diphtheria	1953	1·36%	0·004%	38 (28–52)	3 (2–4)
Pertussis	1954	3·75%	0·024%	103 (79–134)	6 (4–7)

Pneumococcal disease

Disease burden measurement

Changes in serotypes – IPD and pneumonia

How much pneumococcal disease?



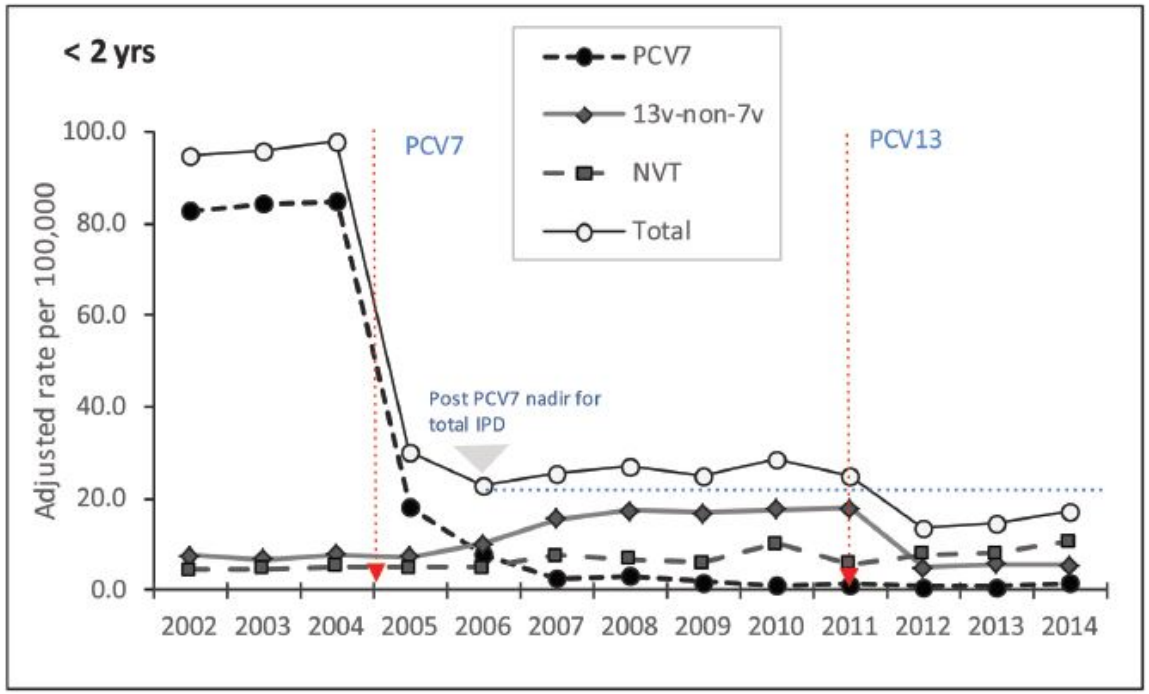
The 3+0 schedule

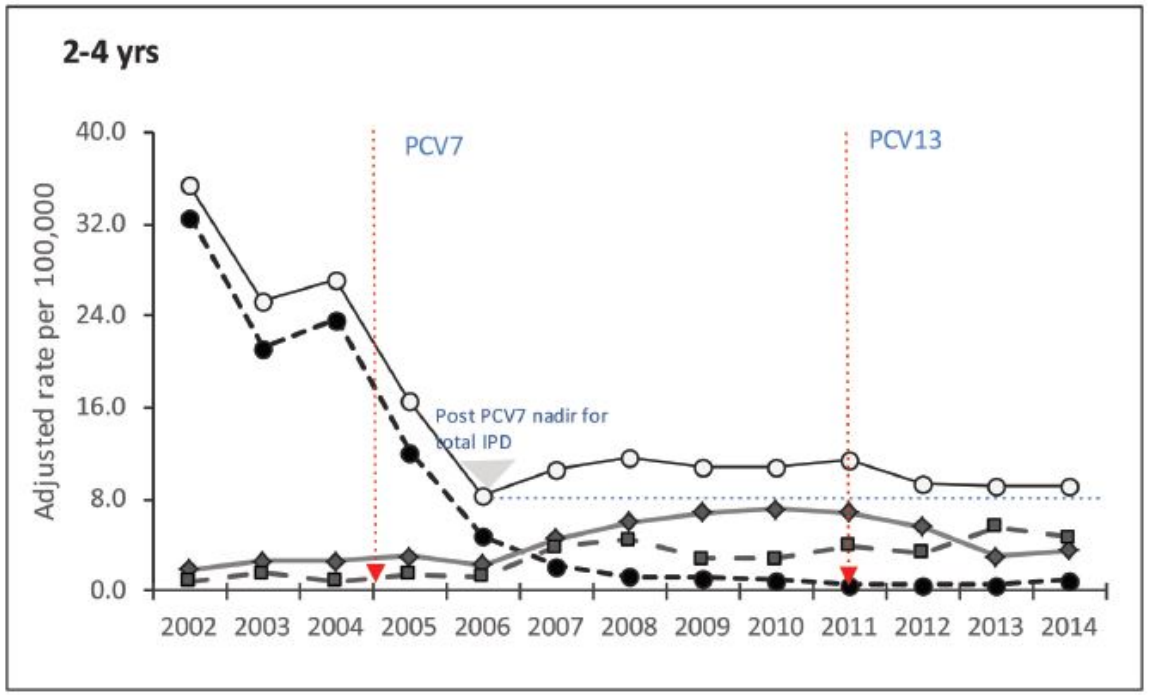
Clinical Infectious Diseases

MAJOR ARTICLE

Effectiveness of 7- and 13-Valent Pneumococcal Conjugate Vaccines in a Schedule Without a Booster Dose: A 10-Year Observational Study

Sanjay Jayasinghe,[1] Clayton Chiu,[1] Helen Quinn,[1] Rob Menzies,[2] Robin Gilmour,[3] and Peter McIntyre[1]





The Incidence rate ratio

Table 2. Incidence Rates (per 100 000) and Incidence Rate Ratios Before and After Vaccine Introduction for 7-Valent and 13-Valent Pneumococcal Conjugate Vaccine, by Serotype Categories and Age Group

		PCV7				PCV13					
Age Group	Serotype Category	Pre–Vaccine Introduction (2002–2004)	Post–Vaccine Introduction (2007–2008)	IRR	(95% CI)	Pre–Vaccine Introduction (2008–2009 to 2010–2011)	Post–Vaccine Introduction (2014)	IRR	(95% CI)	IRR Post-PCV13 vs Pre-PCV7	(95% CI)
<2 y	VT[a]	84 (402.6)	3.0 (15.7)	0.04	(.02–.06)	19.9 (107.0)	6.9 (40.2)	0.35	(.24–.48)	0.02	(.01–.04)
	NVT[b]	12.1 (57.8)	22.2 (116.3)	1.84	(1.44–2.34)	7.9 (42.7)	10.5 (60.8)	1.32	(.96–1.82)	1.32	(1.02–1.71)
	Total	96 (460.3)	25.2 (132)	0.26	(.22–.31)	27.8 (149.7)	17.5 (101.0)	0.63	(.50–.78)	0.18	(.15–.22)
2–4 y	VT[a]	25.8 (185.6)	1.8 (14.2)	0.07	(.04–.12)	7.9 (63.7)	4.4 (38.4)	0.56	(.38–.79)	0.04	(.02–.07)
	NVT[b]	3.5 (25.0)	8.8 (68.8)	2.52	(1.80–3.55)	3.7 (30.0)	4.7 (40.6)	1.26	(.86–1.86)	2.35	(1.67–3.30)
	Total	29.3 (210.7)	10.6 (83.0)	0.36	(.28–.45)	11.6 (93.7)	9.1 (79.0)	0.78	(.60–1.01)	0.31	(.24–.40)

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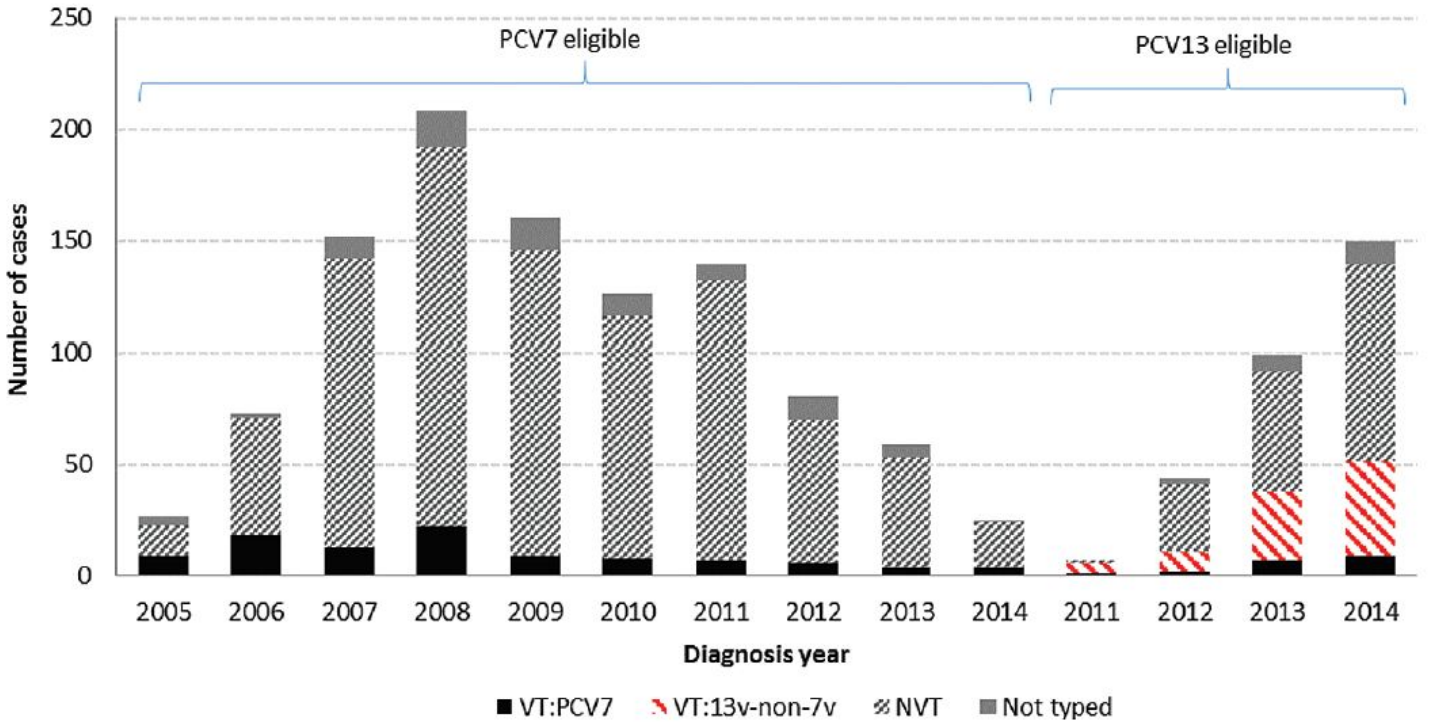


Measuring waning immunity – relative odds of vaccine serotype IPD

Table 4. Effectiveness of Pneumococcal Conjugate Vaccine 7 (PCV7) and PCV13 Against Invasive Pneumococcal Disease (IPD) Due to Vaccine Serotypes (VT) and Relative Odds of VT IPD by Time Since Receipt of the Third Vaccine Dose

Vaccine	Time Interval	Cases N (% Vaccinated)	Controls N (%Vaccinated)	Vaccine Effectiveness, % (95% CI, *P*)	Relative Odds of Vaccine Serotype Invasive Pneumococcal Disease[a] (95% CI, *P*)
PCV7	Up to 12 Months post-last dose	36 (47.2)	393 (78.6)	89.4 (75.8 to 95.3, <.001)	Reference
	12–<24 months post-last dose	33 (42.4)	238 (64.7)	74.0 (23.9 to 91.1, .014)	2.404 (0.782–7.392, .126)
	24–<36 months post-last dose	30 (36.7)	193 (56.5)	40.7 (<–100.0 to 84.7, .450)	5.620 (1.240–25.421, .025)
	≥36 months post-last dose	38 (50.0)	262 (67.9)	16.7 (<–100.0 to 77.8, .787)	4.891(1.751–35.602, .007)
PCV13	Up to 12 months post-last dose	48 (54.2)	460 (78.5)	87.1 (70.6 to 94.3, <.001)	Reference
	12–<24 months post-last dose	50 (56.0)	401 (75.3)	69.6 (23.1 to 88.0, .012)	2.356 (0.811–6.848, .115)
	24–<36 months post-last dose	30 (36.4)	169 (41.4)	23.3 (<–100.0 to 86.1, .760)	5.944 (1.002–35.220, .050)

Abbreviations: CI, confidence interval; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine

Meningococcal disease

Changes in diagnostics

Changes in serotypes

Vaccine impact on bacterial meningitis – US

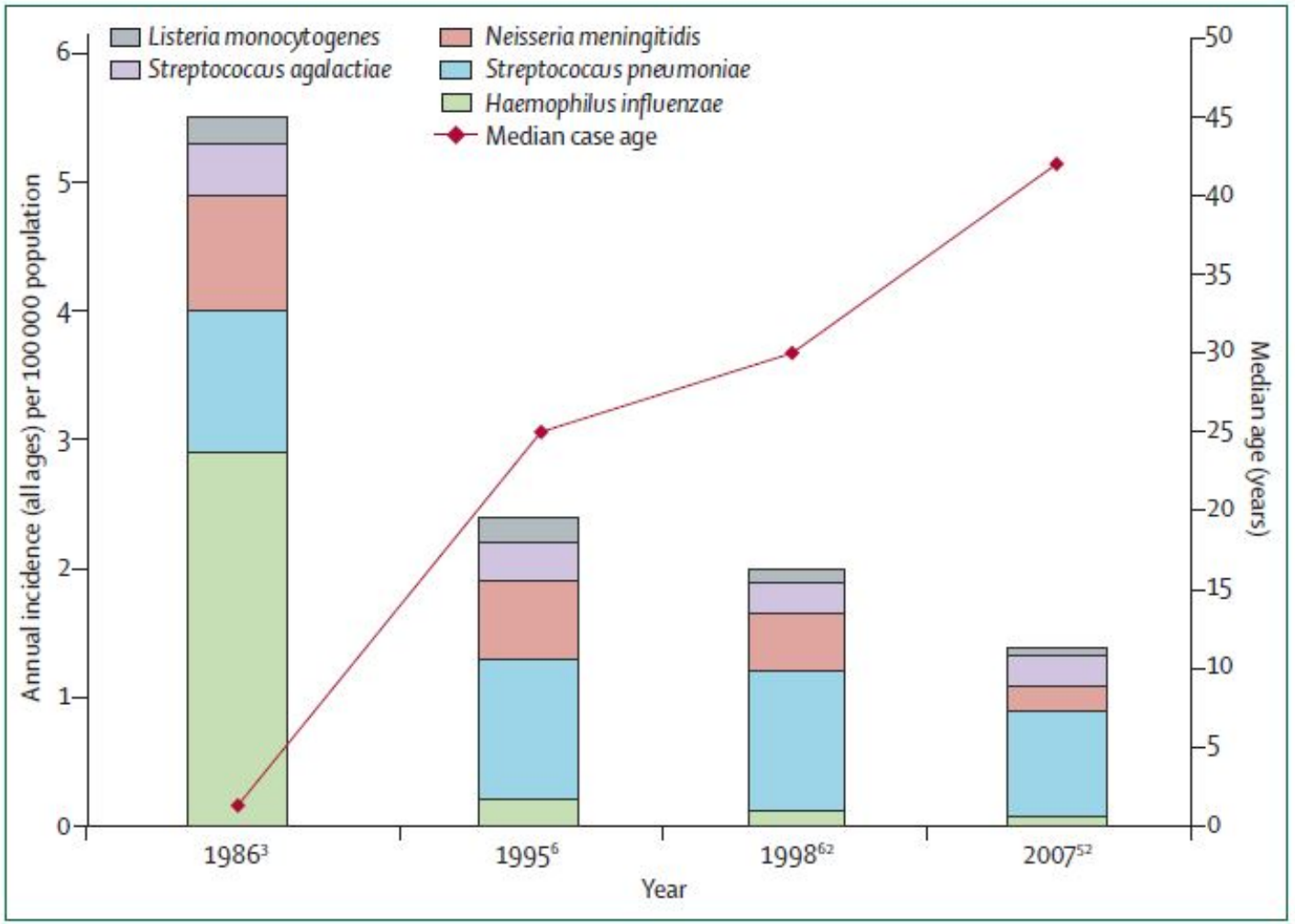
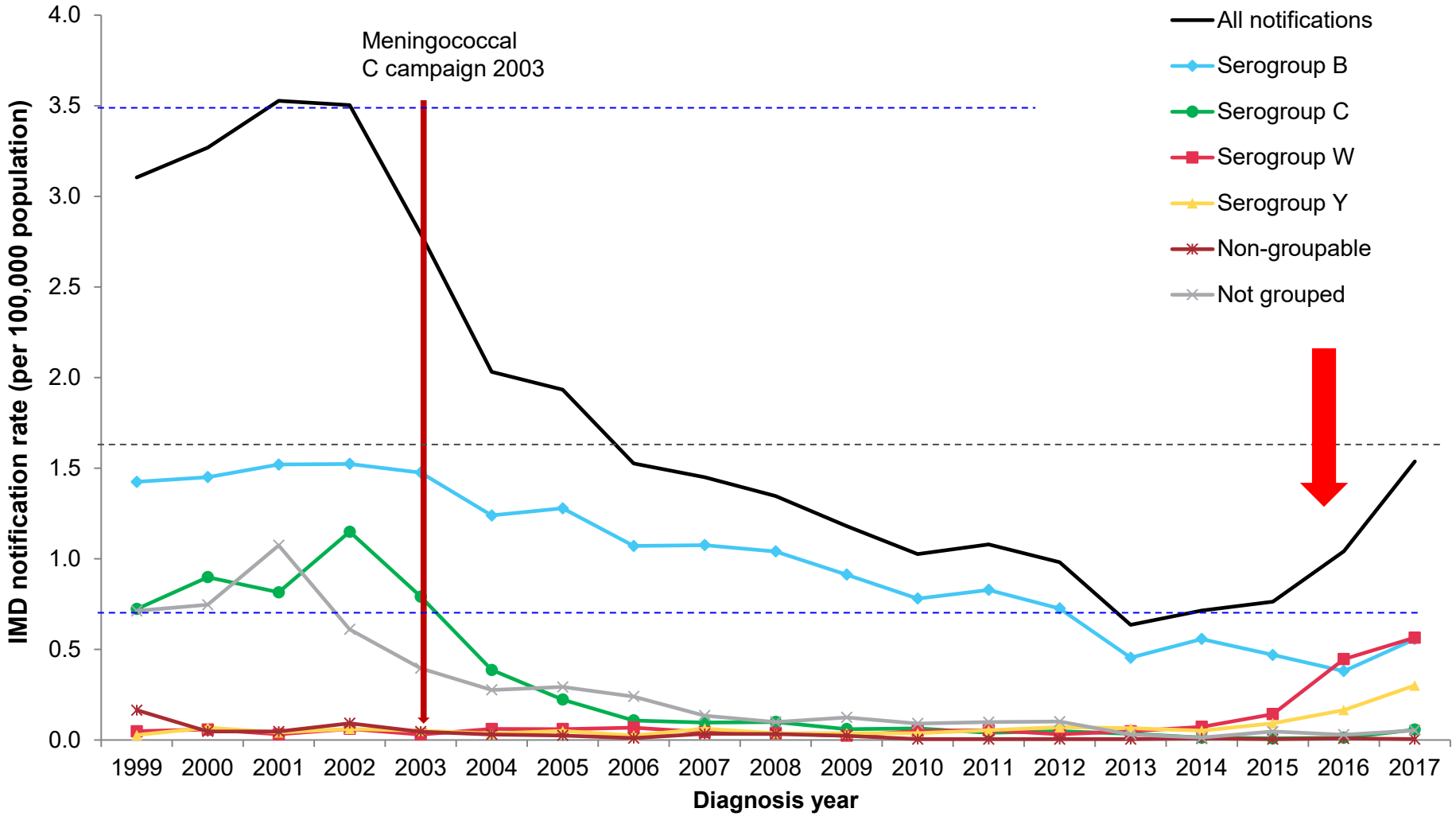


Figure 2: Prevalence of bacterial meningitis in the USA attributable to *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Streptococcus agalactiae*, and *Listeria monocytogenes*, 1986–2007[3,6,52]

Meningococcal disease - Australia by serogroup and year, 1999–2017



Trends are not shown for serogroups A (n=6) and X (n=2)

Epidemiol. Infect. (2016), **144**, 2382–2391.
doi:10.1017/S0950268816000704

Meningococcal disease epidemiology in Australia 10 years after implementation of a national conjugate meningococcal C immunization programme

Table 2. *Meningoccocal disease in Australia by age group, serogroup and year, adjusted for untyped cases*

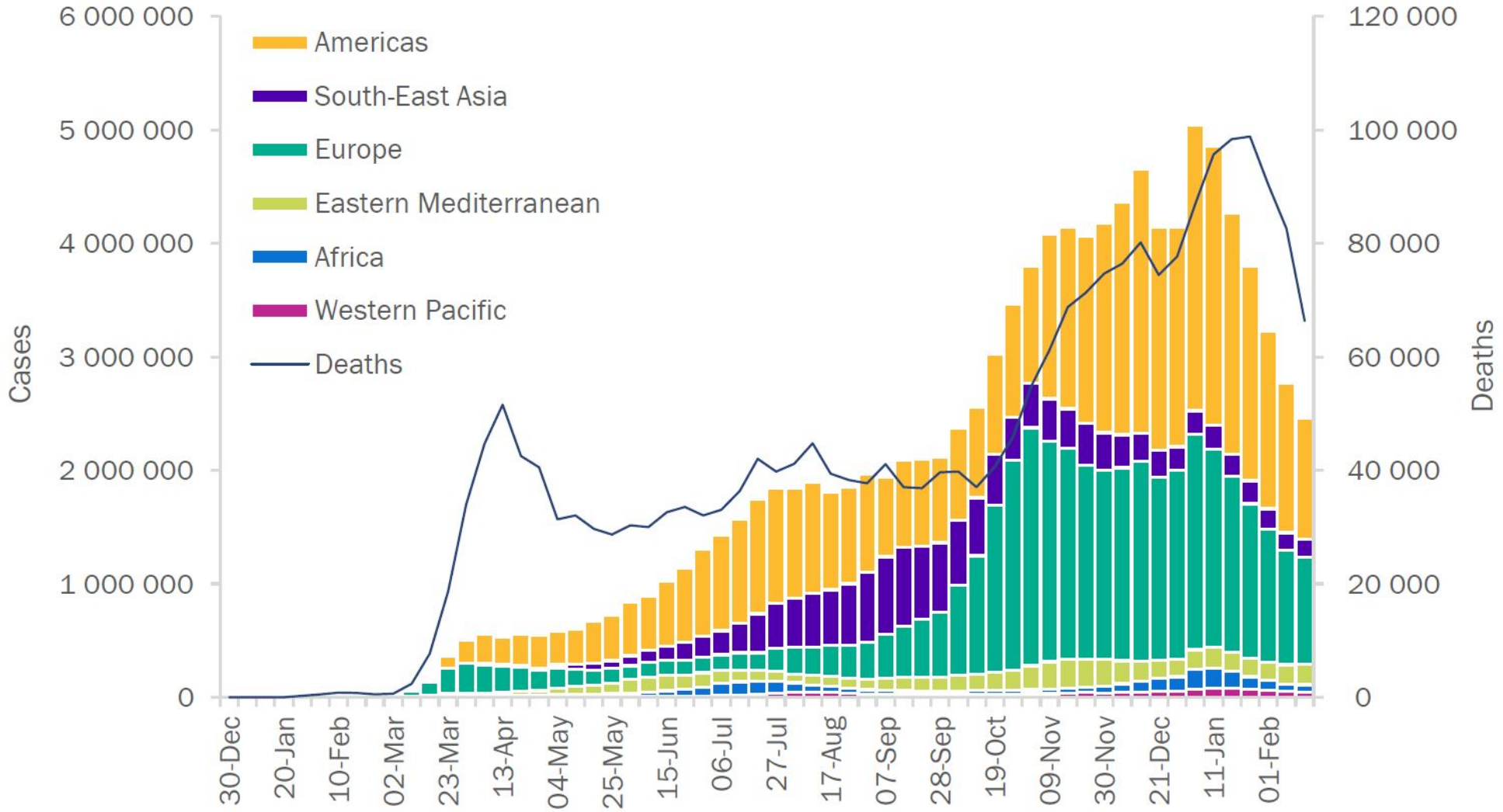
Age group (years)	Serogroup	Adjusted* total cases and average annual incidence rate/100 000 population				IRR 2010–2012 *vs.* 2000–2002	
		2000–2002		2010–2012			
		Cases (raw)	Rate	Cases (raw)	Rate	IRR	95% CI
<1	C	22 (17)	2·93	3 (3)	0·34	0·11	0·034–0·38
	Non-C	204 (161)	27·15	97 (89)	10·96	0·40	0·31–0·51
1–4	C	95 (70)	3·10	0 (0)	0	0·0	—
	Non-C	278 (204)	9·07	126 (107)	3·59	0·40	0·32–0·49
5–14	C	120 (79)	1·49	3 (2)	0·04	0·02	0·01–0·08
	Non-C	180 (118)	2·24	68 (53)	0·82	0·37	0·28–0·48
15–24	C	282 (225)	3·57	6 (6)	0·07	0·02	0·01–0·04
	Non-C	309 (247)	3·91	171 (162)	1·86	0·47	0·39–0·57
25–39	C	116 (79)	0·89	5 (5)	0·03	0·04	0·02–0·10
	Non-C	106 (72)	0·81	48 (44)	0·33	0·41	0·29–0·58
⩾40	C	114 (86)	0·46	21 (19)	0·07	0·15	0·09–0·24
	Non-C	172 (130)	0·69	144 (135)	0·47	0·68	0·54–0·85
1–24	C	497 (374)	2·61	9 (8)	0·04	0·02	0·01–0·032
	Non-C	767 (569)	4·03	365 (322)	1·73	0·43	0·38–0·49
⩾25	C	230 (165)	0·60	26 (24)	0·06	0·10	0·06–0·14
	Non-C	278 (202)	0·73	192 (179)	0·43	0·58	0·48–0·70
All ages	C	749 (556)	1·30	38 (35)	0·06	0·04	0·02–0·06
	Non-C	1249 (932)	2·16	654 (590)	0·97	0·45	0·41–0·50

SARS-CoV-2 “variants of concern” What do they mean for vaccines?

Importance of disease severity

Global Epidemiology – Cases and Deaths

Figure 1: COVID-19 cases reported weekly by WHO Region, and global deaths, as of 21 February 2021**



Variants of concern

Concern =

1. increased transmission
2. increased severity
3. Escape from vaccine-induced immunity

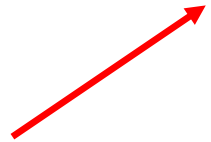
Current variants of concern

Table 3: Overview of emerging information on key variants of concern, as of 23 February 2021*

Nextstrain clade	20I/501Y.V1	20H/501Y.V2†	20J/501Y.V3
Pango lineage	B.1.1.7	B.1.351	B.1.1.28.1
GISAID clade	GR	GH	GR
Alternate names	VOC 202012/01†	VOC 202012/02	P.1†
First detected by	United Kingdom	South Africa	Brazil / Japan
First appearance	20 September 2020	Early August 2020	December 2020
Key spike mutations	H69/V70 deletion; Y144 deletion; N501Y; A570D; D614G; and P681H	L242/A243/L244 deletion; N501Y; D614G; E484K; and K417N	N501Y; D614G; E484K; and K417N
Key mutation in common	S106/G107/F108 deletion in Non-Structural Protein 6 (NSP6)		
Transmissibility*	Increased[1] (36%-75%)[2], increased secondary attack rate[3] (10% to 13%)	Increased [1.50 (95% CI: 1.20-2.13) times more transmissible than previously circulating variants][4,5]	Suggested to be increased
Severity*	Possible increased severity and mortality[6]	No impact reported to date[4,5], no significant change in-hospital mortality[7]	Under investigation, no impact reported to date
Neutralization capacity*	Slight reduction but overall neutralizing titers still remained above the levels expected to confer protection[8]	Decreased, suggesting potential increased risk of reinfection[4,9,10]	Potential decrease, small number of reinfections reported[11,12]

Vaccines preventing what?
Importance of disease severity

Vaccine	Cases/Total in placebo	Severe	Cases/Severe as % of Total Placebo
AZ simian adenovirus	101/5829	10	1.7%/0.17%
Janssen Adeno type 26	348/21888	29	1.6%/0.13%
Pfizer BNT162b2	169/18846	9	0.9%/0.04%
Moderna mRNA 1273	269/15181	30	1.8%/0.19%

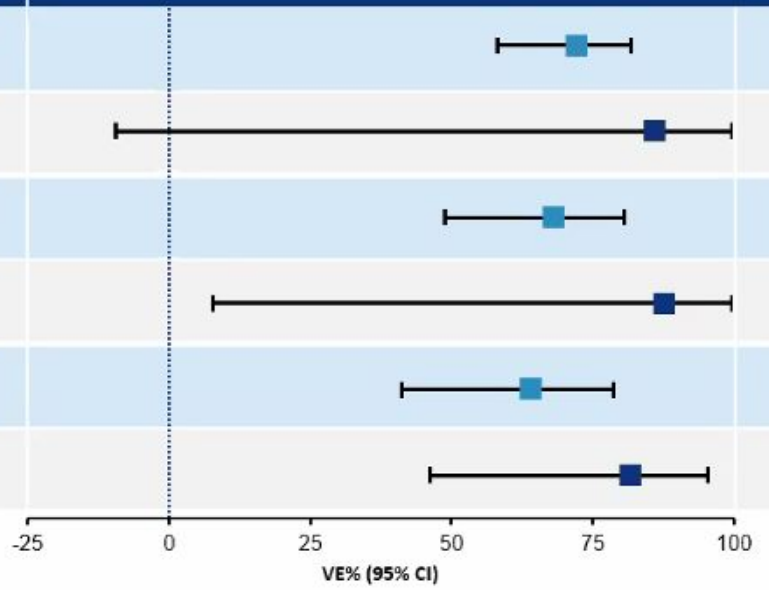


Pfizer trial placebo group had half as many cases as other trials and 1/3 to 1/5 severe cases

J&J Trial first to have data on the South African and Brazilian variants

Vaccine Efficacy Consistently High Across Key Countries > Days 28

Country *% Variant*	Severity	# Events / N Ad26.COV2.S N = 19,306	# Events / N Placebo N = 19,178	> Day 28 Vaccine Efficacy (95%CI)
United States 96% D614G 3% CAL.20C	Moderate-Severe/Critical	32 / 8,958	112 / 8,835	72.0% (58.2, 81.7)
	Severe/Critical	1 / 8,958	7 / 8,835	85.9% (-9.4, 99.7)
Brazil 69% P.2 lineage 31% D614G	Moderate-Severe/Critical	24 / 3,354	74 / 3,312	68.1% (48.8, 80.7)
	Severe/Critical	1 / 3,354	8 / 3,312	87.6% (7.8, 99.7)
South Africa 95% B.1.351 3% D614G	Moderate-Severe/Critical	23 / 2,449	64 / 2,463	64.0% (41.2, 78.7)
	Severe/Critical	4 / 2,449	22 / 2,463	81.7% (46.2, 95.4)



Equivalent efficacy vs severe/critical disease for variants

Summary

- Issues in measuring vaccine impact
  - Direct vs Indirect effects
  - Vaccine-Preventable Disease Incidence (VPDI)
  - Disease severity

- Case studies
  - Declines pre-vaccine: pertussis, meningococcal disease
  - Changes in laboratory measures: meningococcal disease, IPD
  - Importance of disease severity: COVID variants