Public Health England

ROBERT KOCH INSTITUT

Vaccine efficacy and effectiveness

[redacted] [redacted], RIVM

EPIET Vaccine Module, online, June 22

Based on a presentation by

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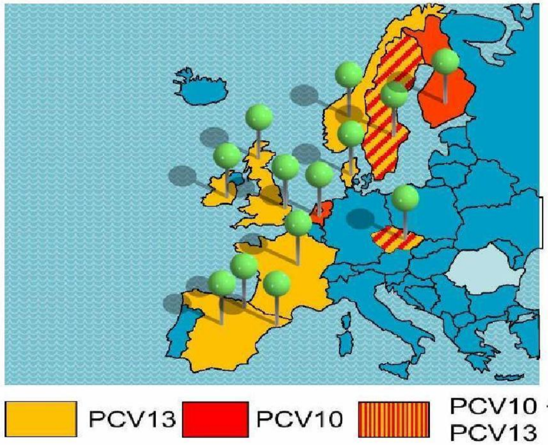
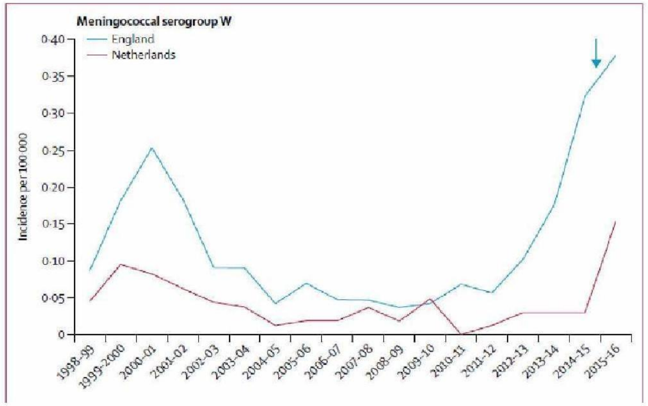
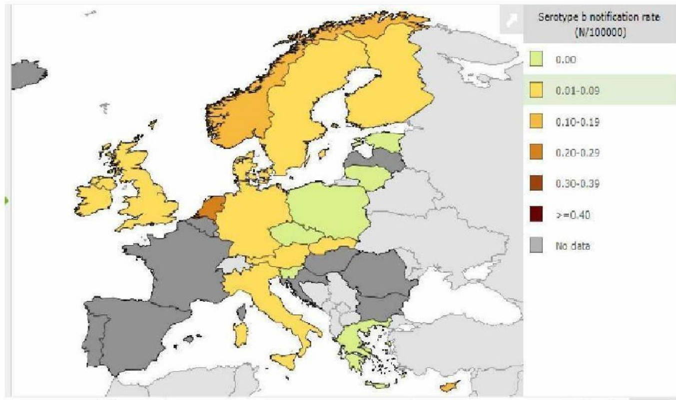
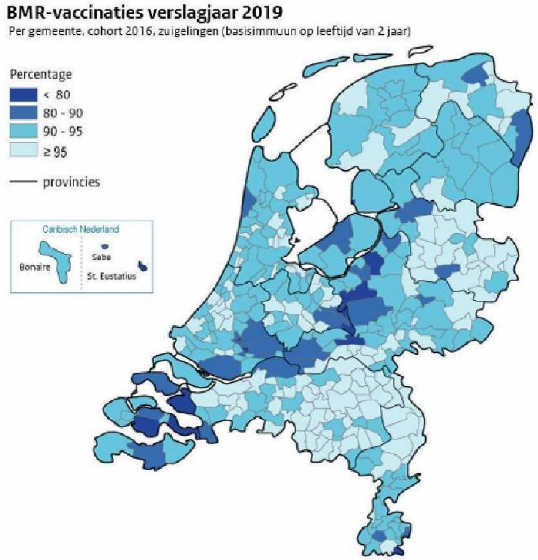
Epidemiologist VPD at RIVM









Objectives of the lecture

- to understand and be able to calculate vaccine efficacy and effectiveness (VE);
- to describe study designs for estimating VE;
- to understand potential pitfalls in estimating VE;
- to be able to interpret VE estimates.

Structure – Part I

- Background & definitions
- Efficacy vs effectiveness
- Study designs to estimate effectiveness

Structure – Part II

- Methodological issues in estimating VE
- Indirect protection and impact
- Vaccine failure

Vaccines

- Vaccines are used to protect individuals and populations from specific diseases;
- Vaccines need to be assessed before and after licensure;
- Assessment includes safety, (cost) effectiveness, changes to disease epidemiology & interactions with other vaccines;
- We will concentrate on how well a vaccine prevents disease – vaccine efficacy/effectiveness

Vaccine evaluation pre- and post-licensure

Pre-licensing

randomised, blind, controlled clinical trials

Vaccine efficacy:

protective effect under idealised conditions

licensing sometimes based on surrogate outcomes (immunogenicity, e.g. PCV13, MenB)

complex and costly to conduct, but simple interpretation

Post-licensing

usually observational studies

Vaccine effectiveness:

protective effect under ordinary conditions of public health programme;

could be affected by cold chain problems/bad batches/use in different populations/different schedules/changes to disease epidemiology…

prone to bias, so interpretation more complex

Vaccine efficacy

The reduction in the chance you will get disease if vaccinated compared to not vaccinated (usually given as a %).

Formula:

$$VE = 1 - RR = 1 - \frac{R_{vacc}}{R_{unvacc}} = \frac{(R_{unvacc} - R_{vacc})}{R_{unvacc}}$$

RR = relative risk

R_{vacc} = disease risk in vaccinated

R_{unvacc} = disease risk in unvaccinated

Calculation of risks

measure of risk: attack rate (AR)

$$= \frac{\text{number of cases}}{\text{number of persons at risk}}$$

measure of rate: incidence density

$$= \frac{\text{number of cases}}{\text{number of person-years at risk}}$$

$$VE = 1 - RR = 1 - \frac{R_{vacc}}{R_{unvacc}} = \frac{(R_{unvacc} - R_{vacc})}{R_{unvacc}}$$

RU (%)	RV (%)	VE (%)
10	2	
8	4	
5	5	
8	10	

$$VE = 1 - RR = 1 - \frac{R_{vacc}}{R_{unvacc}} = \frac{(R_{unvacc} - R_{vacc})}{R_{unvacc}}$$

RU (%)	RV (%)	VE (%)
10	2	80
8	4	50
5	5	0
8	10	-25

Estimating efficacy
-Randomised controlled trial (RCT)

gold standard

- evaluate optimal clinical protection of vaccine in target population (phase 2b or 3 trial)
- compare new vaccine to either placebo or control vaccine

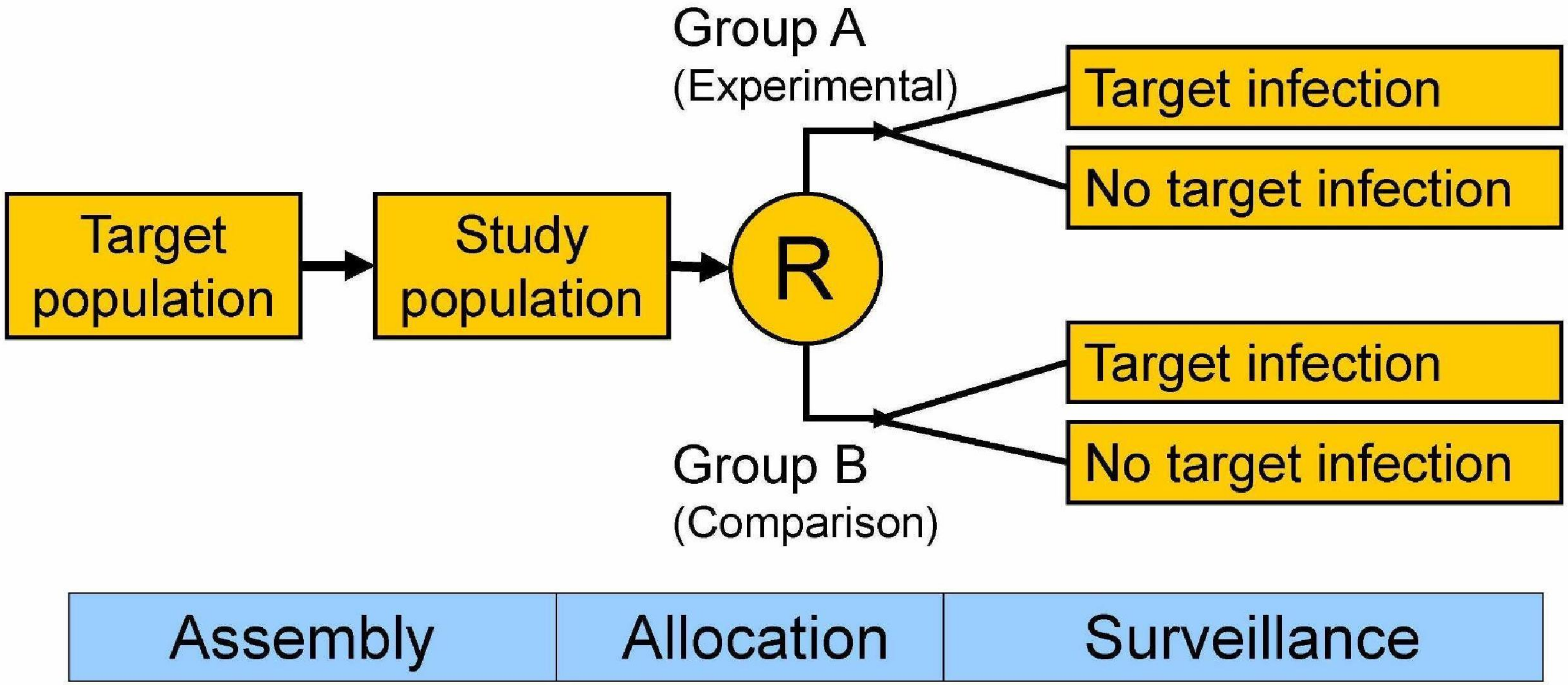
randomised, double-blind design

- only difference between individuals is vaccine status
- control for confounding and bias in study design

Issues

- expensive for rare outcomes (use correlate of protection)
- may not represent population vaccine used on
- ethical issues
- what to use as comparison group – particularly if new formulation or delivery method

Randomised controlled trial (RCT)



Example RCT – Pertussis

Clinically confirmed cases of pertussis and VE of acellular DTaP

	No. of person-days at risk	No. of cases	Incidence/ 100 person-years
DTaP	2,354,321	37	
DT	758,646	74	

(Greco et al. NEJM 1996)

Example RCT – Pertussis

Clinically confirmed cases of pertussis and VE of acellular DTaP

	No. of person-days at risk	No. of cases	Incidence/ 100 person-years
DTaP	2,354,321	37	0.56
DT	758,646	74	3.5

VE = 1-RR = 1- (0.56/3.5) = 0.84 (84%)

(Greco et al. NEJM 1996)

Estimating vaccine effectiveness
-observational studies

- cohort study;
- case control study;
- screening method (case / population).

Cohort Design

- Usually retrospective as part of an outbreak investigation or using database such as GP data;
- Define discrete population at risk (cohort) e.g. school;
- Obtain vaccination status;
- Compare risk of disease in vaccinated and unvaccinated groups, VE = (1 –RR);
- If vaccination status changes during the study period then use the person-time approach
- Key Issue: not good for rare diseases as unlikely to have sufficient power or expensive.

Example – Retrospective cohort

VE of RV against acute gastroenteritis in children

Used Health maintenance data:
comparing attack rates for 2008/09 in children "purchasing" vaccine pre 2008/09 rotavirus season with those who did not.

ARU= 8801/18591 (47.3%)

ARV= 1758/7586 (23.2%)

RR = 23.2/47.3 = 0.49

VE = (1-RR) = 0.51 (51%)

(Muhsen et al. Vaccine 2010)

Example – Prospective cohort

VE of HPV vaccination against HPV infection

Cohort set up at the time of vaccine implementation

54% of the study population was vaccinated

Type	Vaccinated	Unvaccinated	RR	VE
HPV16	0.3/1000 py	9.5/1000 py	0.032	96.8%
HPV18	0.0/1000 py	4.0/1000 py	0.000	100%

(Donken et al. JID 2018)

Case Control Design
(and variants on this)

$$OR = \frac{\text{odds of vaccination in cases}}{\text{odds of vaccination in controls}}$$

Controls should be representative of the population from which cases arose;

Get vaccine history from both groups:

VE= 1 – OR

Key Issue: Selection of controls may be difficult

→ bias

Example – Case Control study
– varicella vaccine 1997-2000

	Cases	Controls
Vaccinated	46 (a)	237 (b)
Unvaccinated	156 (c)	152 (d)

OR = [a/c] / [b/d] = [46/156] / [237/152] = 0.19

VE = 1-OR

VE = 1-0.19 = 0.81 (81%)

(Vazquez et al. NEJM 2001)

Example – Test negative case-control design – pandemic Influenza VE

Sentinel GPs swab influenza-like-illness cases and send for laboratory confirmation:

	FLU +	FLU-
Vaccinated	7 (a)	113 (b)
Unvaccinated	877 (c)	2225 (d)

OR = [a/c] / [b/d] = [7/877] / [113/2225] = 0.16

VE = 1-OR

VE = 1-0.16 = 0.84 (84%)

Key Issue: needs a sensitive assay or cases become controls = Bias

(Hardelid et al. Eurosurveillance 2011)

Example – Broome method case-control design

– Pneumococcal VE against Invasive Pneumococcal disease.

Non PCV7 vaccine serotypes used as controls

TYPE	PCV7 TYPE	NON-PCV7
Vaccinated (2doses)	9 (a)	96 (b)
Unvaccinated	7 (c)	8 (d)

OR = [a/c] / [b/d] = [9/7] / [96/8] = 0.11

VE = 1-OR

VE = 1-0.11 = 0.89 (89%)

Key Issue: Vaccine should not partially protect against non-vaccine types.

Screening Method

For use with surveillance data, population vaccine coverage known

→ Compare coverage in cases with coverage in population

- VE is 1 – odds of vaccination in cases compared to population
- $$\mathrm{VE} = 1 - \frac{\frac{\mathrm{PCV}}{1-\mathrm{PCV}}}{\frac{\mathrm{PPV}}{1-\mathrm{PPV}}} = \frac{PPV - PCV}{PPV(1-PCV)}$$

PCV = proportion of cases vaccinated,

PPV = proportion population vaccinated

Coverage must relate to the same population as cases

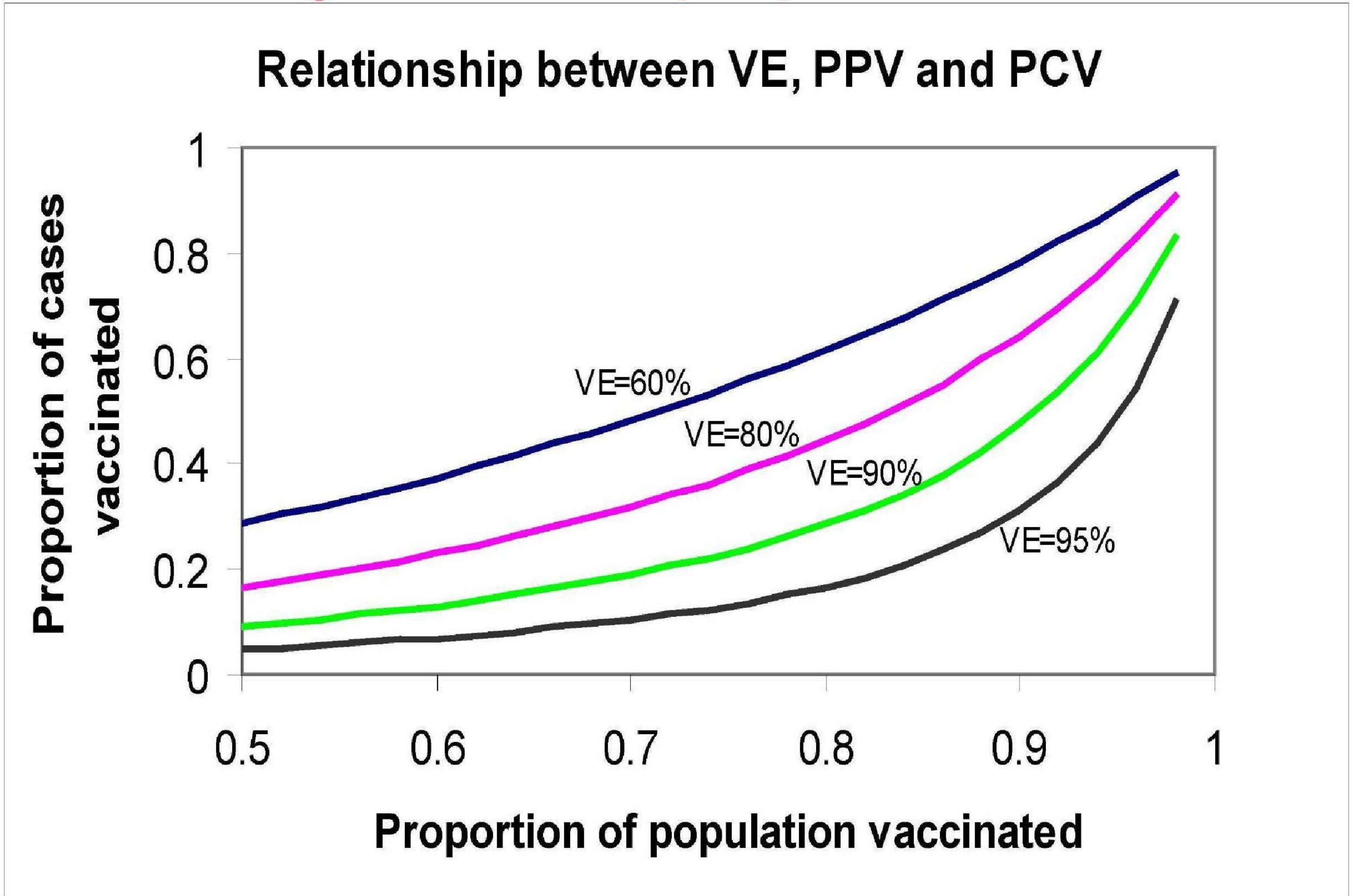
→ so stratify by age etc.

Cannot adjust for confounding variable

→ unless population coverage stratified by that variable

 Key issue: Coverage data must be accurate

Screening Method – properties



Structure – Part II

- Methodological issues in estimating VE
- Indirect protection and impact
- Vaccine failure

Methodological Issues

- case definition;
- case ascertainment;
- vaccine history;
- comparability of vaccinated and unvaccinated groups.

Methodological issues

- case definition (1)

Different endpoints may have different true VE:

- clinical disease
- hospitalised case (severe)
- carrier state

Methodological issues
-case definition (2)

Specificity and sensitivity of the case-definition

<u>Specificity:</u> case definition based only on clinical criteria may result in *false-positive* diagnoses

→ ARV increases relatively more than ARU

→ artificial reduction in VE

<u>Sensitivity:</u> case definition with low sensitivity usually only lowers precision (except test-negative case control design)

<u>Differential sensitivity</u>: If more sensitive in the unvaccinated then VE estimate will be higher than true VE.

Methodological issues
-case definition (3)

Changes in mumps vaccine effectiveness

	Case definition
	Diagnosis by school nurse
ARV	18% (12/67)
ARU	28% (77/272)
VE	37%

(5.1.2e 5. 5.1.2e et al. AJE 1985)

Methodological issues
-case definition (3)

Changes in mumps vaccine effectiveness

	Case definition	
	Diagnosis by school nurse	Parotitis > 2 days
ARV	18% (12/67)	12% (8/67)
ARU	28% (77/272)	25% (68/272)
VE	37%	52%

[redacted] et al. AJE 1985)

Methodological issues

-case ascertainment (1)

Case ascertainment must be independent of vaccination history

→ vaccinated and unvaccinated populations may not have equal access to health care services;

Two types of case finding used:

<u>population based</u>

- avoids differential use of health care services
- useful for common, less serious diseases
- use in local outbreaks

<u>health care provider</u>

- good for rare, severe diseases e.g. meningitis
- provides laboratory confirmation (increases specificity)

Methodological issues
-case ascertainment (2)

Effect of complete case finding on mumps VE

	Case finding
	School nurse
ARV	12% (8/67)
ARU	25% (68/272)
VE	52%

([redacted] [redacted] et al. AJE 1985)

Methodological issues

-case ascertainment (2)

Effect of complete case finding on mumps VE

	Case finding	
	School nurse	Parents
ARV	12% (8/67)	13% (9/67)
ARU	25% (68/272)	36% (97/272)
VE	52%	64%

(5.1.2e 5.1.2e et al. AJE 1985)

Methodological issues

-vaccine history ascertainment

Avoid misclassification of vaccination status

- will bias VE to be lower than true VE e.g. due to recall bias

Equal effort to confirm vaccination status amongst cases and non-cases

- vaccination histories should be documented using GP, clinic or computer records

  Parental recall → overestimate vaccine coverage

  Written records → underestimate vaccine coverage

- individuals with missing vaccination records should be excluded from the analysis

Methodological issues

-multiple doses

- May need >1 dose of vaccine for full protection
- Partial vaccination may afford some protection

–If classify partially vaccinated as unvaccinated
→ decrease ARU

–If classify partially vaccinated as vaccinated
→ increase ARV

If require effectiveness of full course of vaccination
→ exclude partially vaccinated cases or stratify by complete/incomplete

Example – VE by vaccine dose

-measles VE during an outbreak

TABLE 2. Attack Rates Among 1,014 Students* According to Vaccination Status and School Cohort (School X, Duisburg, January to May 2006)

Grade	No. of Students	No. of Acute Measles Cases (Attack Rates in %)			
		No MCV	Only 1 MCV Dose	At Least 2 MCV Doses	Vaccination Status Unknown
5–7	451	11 (61.1)	1 (1.1)	2 (0.6)	10 (21.3)
8–10	424	7 (46.7)	1 (0.9)	0 (0)	15 (15.5)
11–13	139	1 (33.3)	0 (0)	0 (0)	5 (6.8)
Total	1,014	19/36 (52.8)	2/199 (1.0)	2/561 (0.4)	30/218 (13.8)

*n = 22 students with receipt of MCV during the outbreak and n = 62 with measles history are excluded.

796 school students with vaccination records

VE_{1Dose} = 98,1% (95%CI: 92-100)
VE_{2Doses} = 99,4% (95%CI: 97-100)

([redacted] et al. PIDJ 2007)

Methodological issues
-confounding

both exposure to infection and vaccination coverage may vary by age, location, socio-economic factors

→ confounding

controlling for age is important as disease incidence and vaccine coverage are often both age-dependent.

potential solutions:

- stratified analysis
- multivariable regression analysis – logistic regression

Methodological issues

-past exposure

If, prior to a study (e.g. outbreak), unvaccinated individuals have been exposed to the disease more than vaccinated individuals then they may have increased natural immunity.

This will result in a biased lower VE unless those with evidence of past disease are excluded.

Methodological issues

-differential exposure

During the study, exposure should be similar in vaccinated and unvaccinated groups.

If less exposure in vaccinated then you will overestimate VE.

Need to address this is the design (e.g. household contact) or measure confounders

VE measles outbreak Netherlands

Variable	Laboratory-Confirmed Measles		Self-Reported measles	
	Vaccinated (n = 3)	Unvaccinated (n = 10)	Vaccinated (n = 20)	Unvaccinated (n = 37)
Observation time, d	106 631	23 769	140 075	72 993
Unadjusted analyses				
HR (95% CI)	0.06 (.02–.21)	Reference	0.33 (.18–.60)	Reference
VE, % (95% CI)	94 (79–98)		67 (40–82)	
Adjusted analyses				
HR (95% CI)[a]	0.292 (.05–1.72)	Reference	0.573 (.29–1.12)	Reference
VE, % (95% CI)	71 (−72–95)		43 (−12–71)	

([redacted] et al. JID 2017)

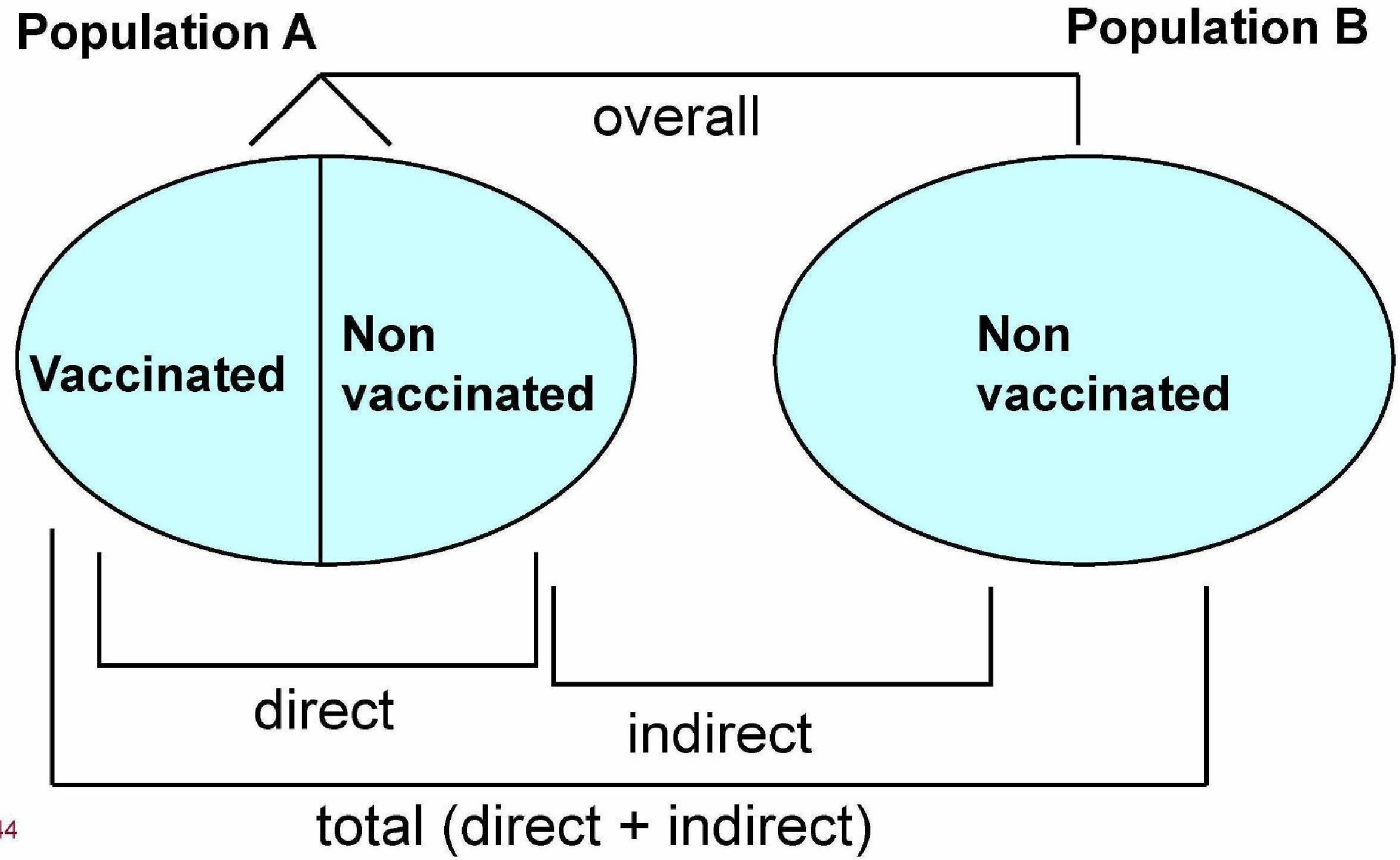
Interpretation of VE estimates

- Individual and indirect (herd) effects
- Primary and secondary vaccine failure

Terminology

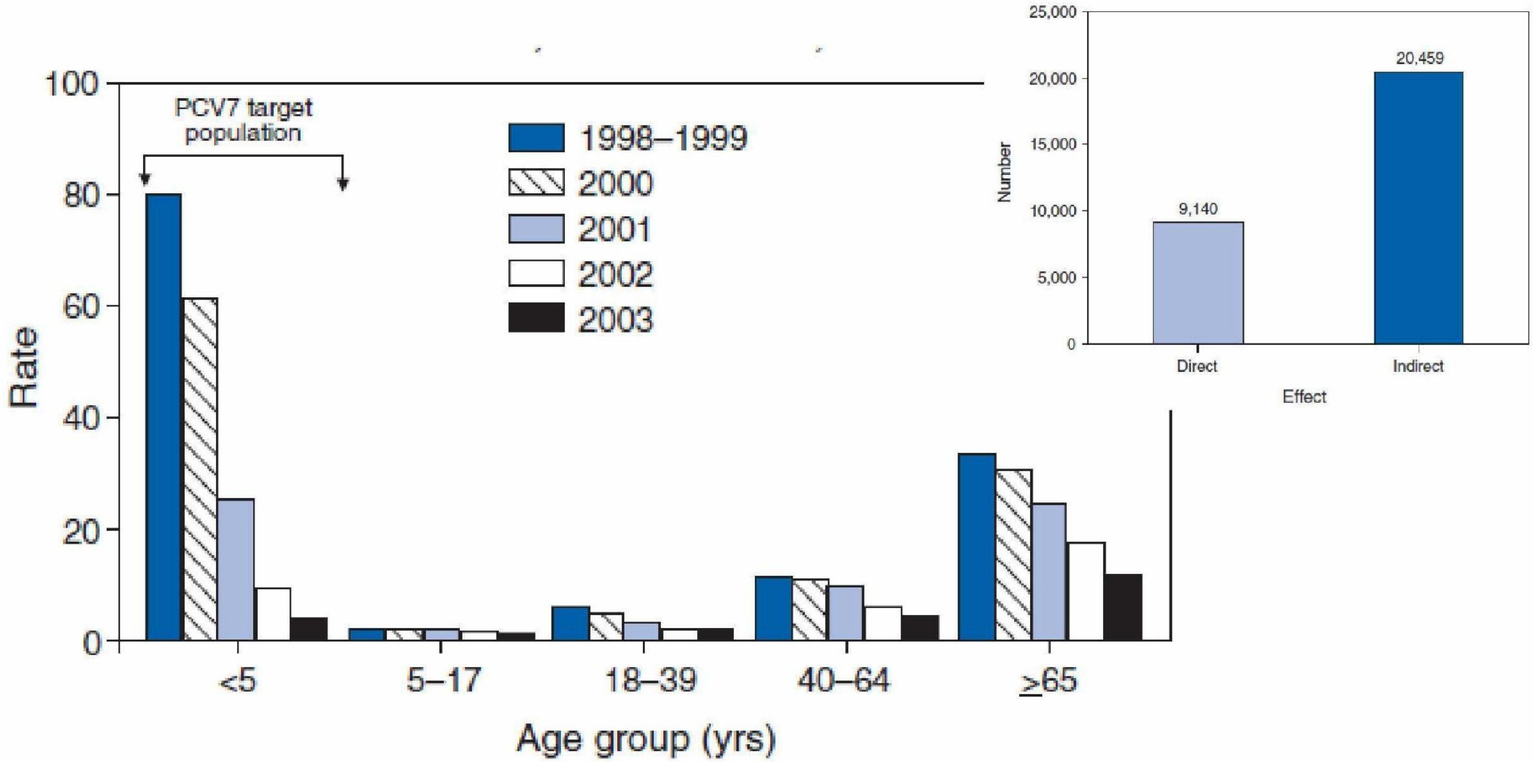
- **Herd protection** (herd immunity): indirect effect of vaccination due to reduced disease transmission
  - Benefits both vaccinated and unvaccinated individuals!
- **Impact:** population level effect of a vaccination campaign. This will depend on many factors such as vaccine coverage, herd protection and vaccine effectiveness.

Types of effects of vaccination



Herd protection – example 1

-invasive pneumococcal disease, USA



* Per 100,000 population.

† For each age group, the decrease in VT IPD rate for 2003 compared with the 1998–1999 baseline is statistically significant ($p<0.05$).

(CDC. MMWR 2005)

Herd protection – example 2

-invasive meningococcal disease, UK/NL

Incidence of serogroup W invasive meningococcal disease by age group in the Netherlands, 2015–2017 (n = 139)

MenACWY vaccination in 14-18 yr olds to decrease: carriage → transmission → disease in all age groups

([redacted] et al. Eurosurv 2015; [redacted] et al. Eurosurv 2018)

Primary and secondary vaccine failure

Primary vaccine failure
– failure to seroconvert after vaccination

Secondary vaccine failure
– waning immunity after seroconversion

Study design

- Calculate VE for different time frames after vaccination
- Example: Pertussis in children aged 4-10 years
  - VE within 12 months after 5^{th} DTaP dose: 98%
  - but drops ≥60 months after 5^{th} DTaP dose to 71%

(Misegades et al. JAMA 2012)

Summary

Vaccine efficacy and effectiveness

- Vaccine efficacy is estimated in an RCT;
- Vaccine effectiveness is estimated in observational studies (cohort, case-control, screening method);
- Monitoring vaccine effectiveness is an integral part of epidemiological surveillance of vaccination programmes;
- Interpretation of VE should take into account possible biases;
- Outbreak investigations provide an excellent opportunity to estimate VE to investigate local and general issues;
- Indirect effects can be estimated in cluster designs;
- Indications for secondary vaccine failure can be obtained from VE studies

Main References

General (Library Box)

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