Vaccine Effectiveness and Impact Studies

Presenter(s): Kaatje Bollaerts

Date: 18 March 2021

Plan of the presentation

1. Evaluation of vaccine benefits post-marketing
2. Potential threats to observational studies
3. Outcomes of vaccine benefits
4. Measures of vaccine benefits
5. Study designs
6. Examples of COVID-19 vaccine effectiveness studies
7. International initiatives
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Evaluation of vaccine benefits post-marketing

Vaccine benefit evaluation

Pre-licensing	Post-licensing, observational studies
Efficacy	Effectiveness, impact
Randomized, blind, controlled clinical trials (Phase 3)	Mostly observational studies, different study designs (cohort, case-control, screening)
Randomization to vaccine and control arm	Routine practice: prone to bias and confounding
Idealized conditions: limited generalizability	Real-life use
Resource intensive, expensive: typically limiting sample size	Depending on design, less resource intensive, expense: larger sample sizes possible
Simple interpretation of causality	Careful interpretation needed

Why post-licensure studies?

Why post-licensure studies?

To **complement vaccine trials**

- To assess vaccine performance in real-life (while trials are run under 'ideal conditions', often very selective on participant inclusion)
- To assess vaccine performance in specific subpopulations typically excluded from trials
- To assess protection against rare endpoints (for which sample size of the clinical trials is typically too small)
- To assess long-term protection (for which the duration of the clinical trials is too short)

To study the impact of vaccination at **population level**

- To assess indirect effects of vaccination (~herd immunity)

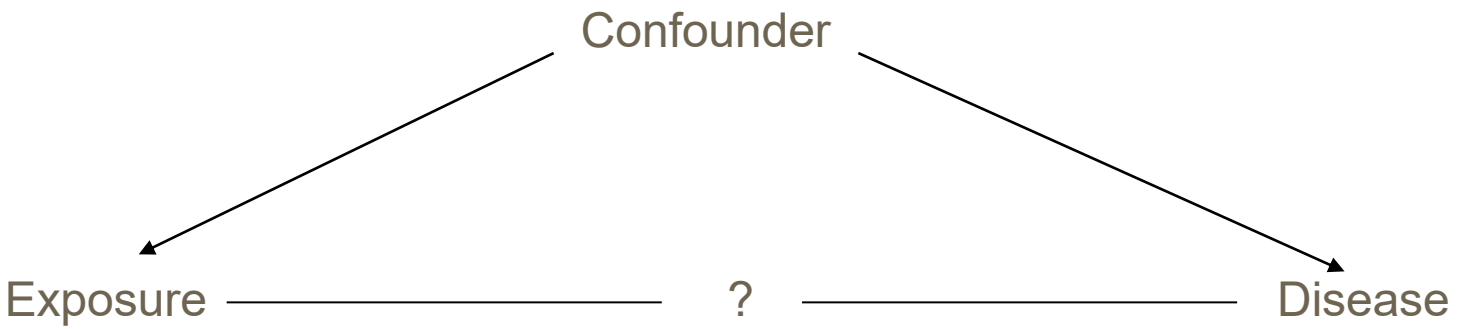
To study **vaccine programmatic choices**

- To evaluate vaccine schedules

Potential threats to observational studies

Potential threats to observational studies

- **Selection bias**: arises from systematic differences in selecting and following study groups (in case-control study if selection of cases and controls is based on differing criteria that are related to exposure status; in cohort studies if selection of exposed and unexposed in based on criteria related to developing the outcome)
- **Disease misclassification**: subjects wrongly classified as diseased or non-diseased
- **Exposure misclassification**: subjects wrongly classified as vaccinated or unvaccinated
- **Confounding**: variable that is independently related to both the risk of disease and vaccination status



The confounder is associated both with the exposure/vaccination status and the disease, but it is not an intermediate step in the casual pathway between exposure and the disease for example age, socioeconomic status, underlying conditions, health seeking behavior

TAKE HOME:

- **Vaccine efficacy is assessed in idealized conditions of RCT**
- **Observational studies are needed to assess the vaccine performance in specific subpopulations, in long term perspective and at population level**
- **Vaccine effectiveness is assessed in real-life conditions prone to bias and confounding**

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The vaccine prevents what?
Outcomes of vaccine benefit studies

Outcomes (1/2)

Protection against **disease**

- Different levels of disease severity (mild, moderate, severe disease, hospitalization, mortality)
- Typically, vaccines have a higher effectiveness against more severe disease

Protection against **infection**

- Especially important for diseases with pre-symptomatic and asymptomatic transmission
- Contributes to herd immunity

Outcomes (2/2)

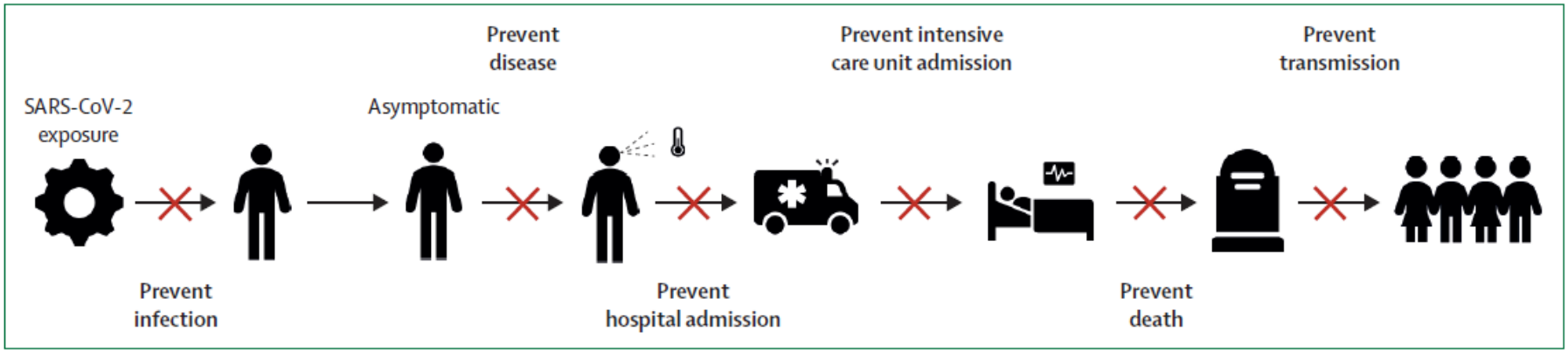
Protection against **infectiousness**

- ~ Reduced duration of infectiousness, reduced pathogen shedding
- Contributes to herd immunity

Protection against **transmission**

- Combines protection against infection and infectiousness
- Effect at population-level

Potential outcomes of COVID-19 vaccine benefit studies



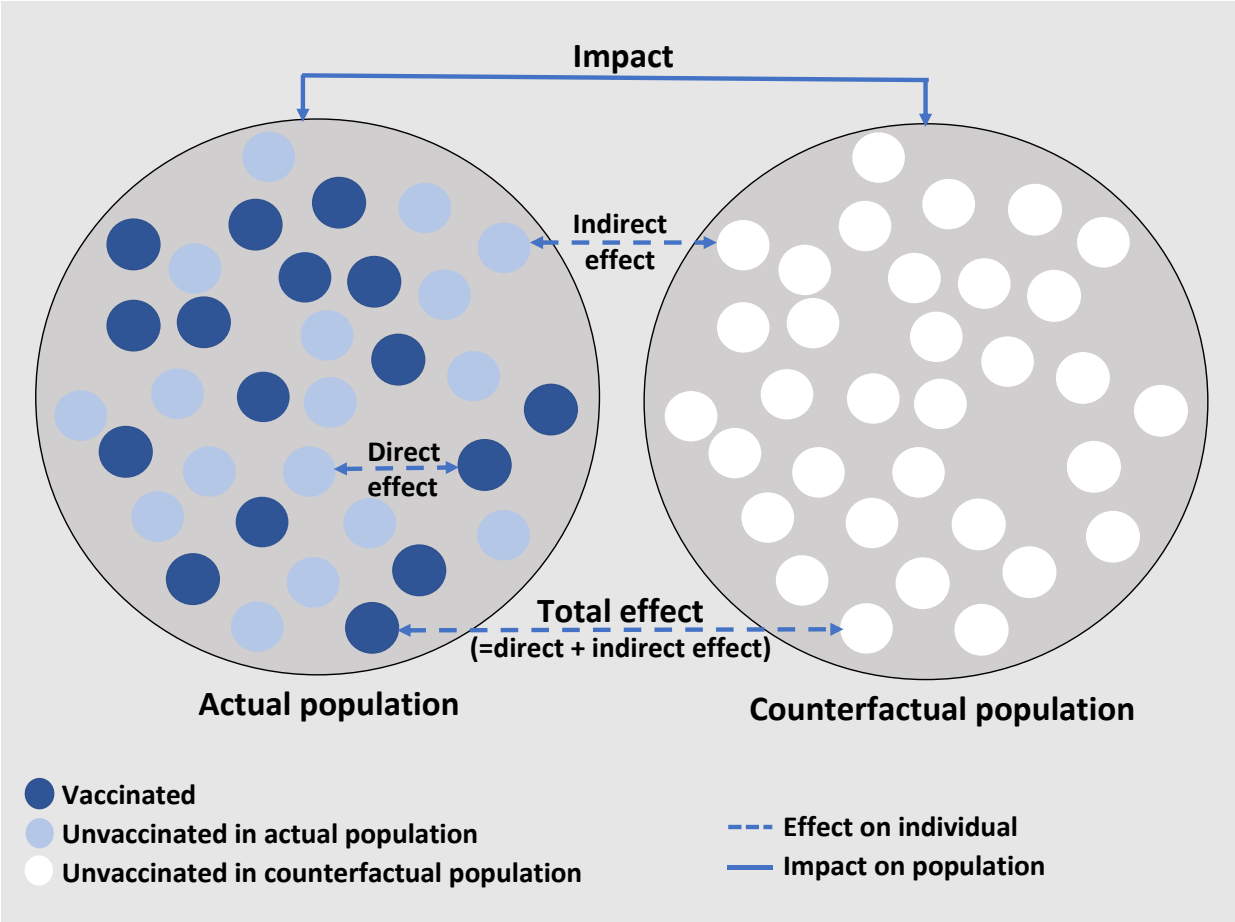
From: *Hodgson S. H. et al, Lancet ID 2021,* What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2

Measures of vaccine benefits

Efficacy, effectiveness, impact, and indirect effects

- **Efficacy**: direct protection to a vaccinated individual as estimated from a clinical trial
- **Effectiveness**: direct protection to a vaccinated individual as estimated under real-life conditions
- **Impact**: population level effect of a vaccination programme, expressed as the proportionate reduction in disease burden comparing the (partially) vaccinated population to the unvaccinated population.
- **Indirect effect** (herd protection, herd immunity): indirect, effect of vaccination due to reduced disease transmission

Individual effects and population impact of vaccination

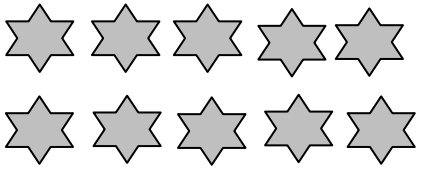


Basic calculation of vaccine benefit measures

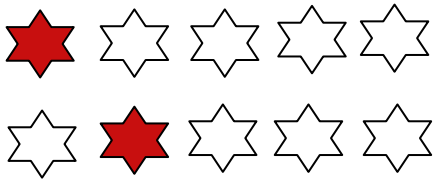
Impact	Efficacy/effectiveness
Impact = $\frac{IR_{pre-vacc} - IR_{post-vacc}}{IR_{pre-vacc}}$ x 100% Impact = $1 - IRR$ x 100%	VE= (1- $\frac{Iv}{Iu}$) x 100% VE = (1 – RR) x 100%
$IR_{post-vacc}$ = population incidence rate post vaccination $IR_{pre-vacc}$= population incidence rate pre vaccination IRR = incidence rate ratio	Iv = incidence in vaccinated group Iu = incidence in unvaccinated group RR is relative risk of disease in vaccinated compared to unvaccinated

Vaccine effectiveness: worked-out example

vaccinated

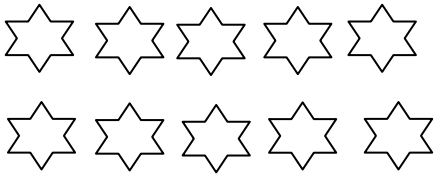


outcome?

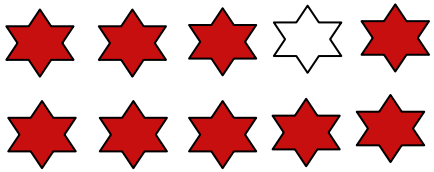


Iv =2/10=0.2

unvaccinated



outcome?



Iu =9/10=0.9

$$VE=\frac{0.9-0.2}{0.9} \times 100\% = 78\%$$

TAKE HOME:

- **Vaccine can be assessed against different outcomes such as disease and transmission**

- **Vaccine impact includes direct and indirect effect of vaccines**

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Study designs for vaccine benefit evaluation post-licensing

Study design is chosen in function of the outcome and measure of vaccine benefit

Common post-licensing designs include for effectiveness

Cohort studies

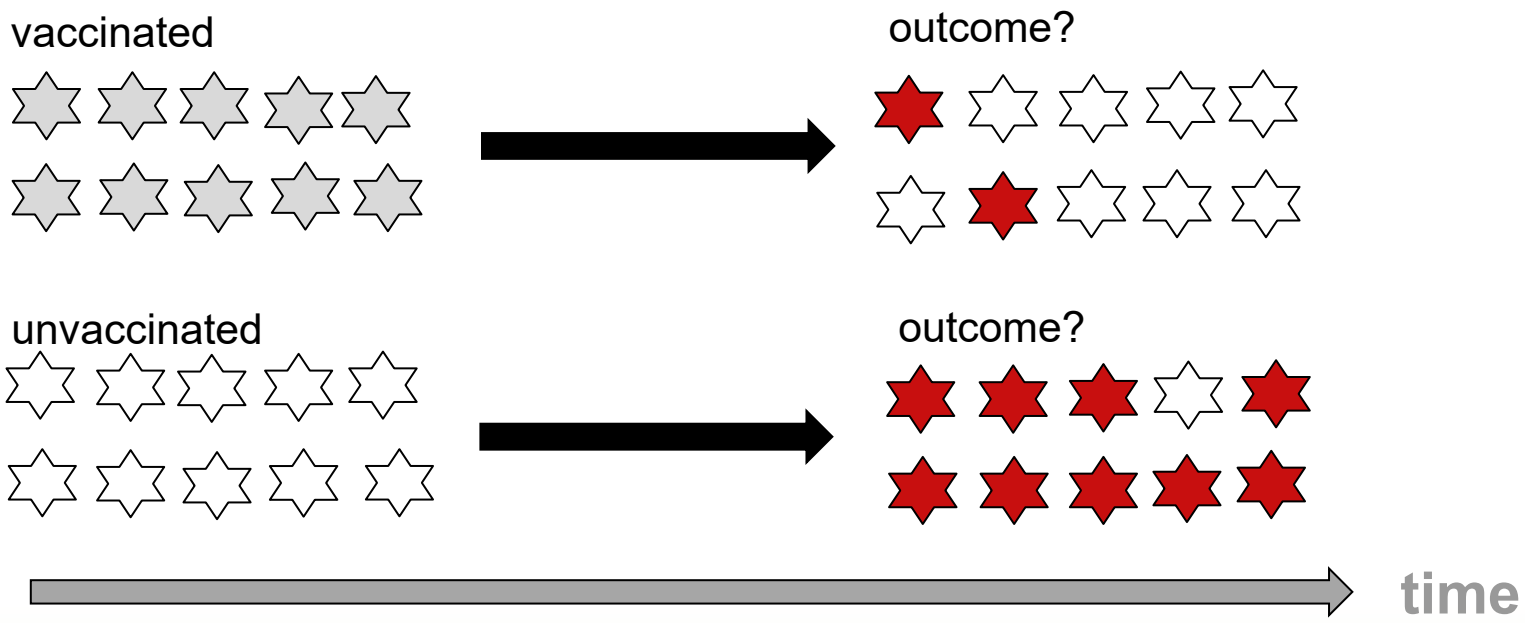
Case-control studies

- 'Standard' case-control
- Test negative case-control
- Screening methods

Household studies

Cohort studies

- Compares outcomes in a vaccinated cohort to the same outcomes in a non-vaccinated cohort
- Either primary data collection or secondary use of existing healthcare databases



Cohort studies: advantages and challenges

Advantages:

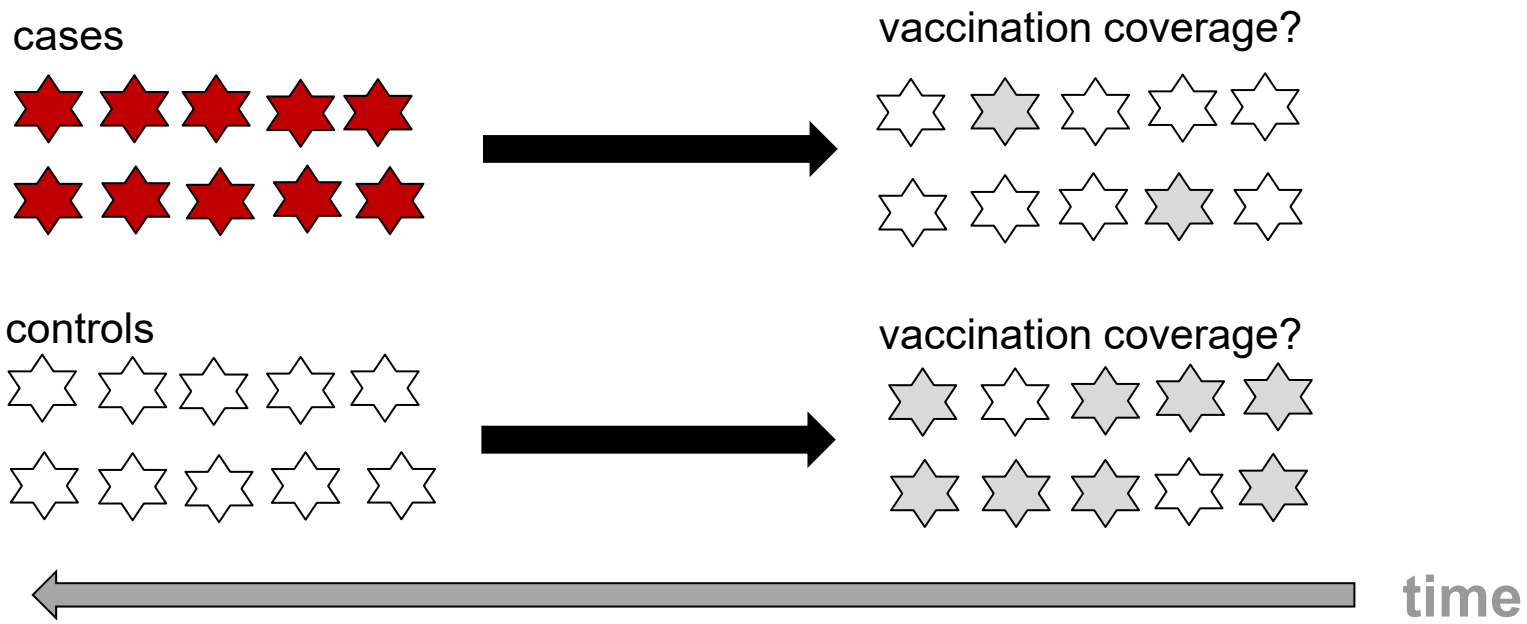
- Easy to explain (follows natural 'time' direction)
- Easy to collect all information on exposure
- Can be used to study multiple outcomes
- Can be used to obtain **'absolute' risk estimates**

Disadvantages:

- Potential for missing study outcomes
- Potential for bias due to differences in healthcare seeking behavior
- Might be time and resource consuming (for primary data collection)
- Insufficient to study rare outcomes (for primary data collection)
- Long time to results (for primary data collection)

Case-control studies

- Compares the vaccination coverage in a group of ‘cases’ to the vaccination coverage in the control group
- Several options to select an appropriate control group



Case-control studies: options for controls

Controls to be selected to obtain an unbiased estimation of the exposure in the population given rise to the cases

- **'Standard' case-control:** controls are community based or other hospital controls
- **Case-coverage, screening method** as a special case: vaccination coverage in the total population (external source) is used to compare the vaccination coverage in the cases with (only works for rare outcomes).
- **Test-negative case-control:** controls are subject that fulfill the expected case definition but eventually test negative for the laboratory test to confirm disease (e.g. cases of severe acute respiratory disease that test negative for influenza)

Case-control studies: advantages and challenges

Advantages:

- Can be used to study rare outcomes
- Fast to results
- Less resource intensive
- Smaller sample size required compared to cohort study

Disadvantages:

- Difficult to explain (does not follow natural ‘time’ direction)
- Potential for errors in vaccination exposure ascertainment
- Cannot be used to obtain absolute risk estimates
- Selection of controls not always easy

Household studies

- The relative risk of developing disease in vaccinated is compared to unvaccinated susceptible exposed to cases in their household
- Each household with a primary case can be treated as mini-cohort
- Used to study transmissibility, incubation periods, duration of the infectiousness and vaccine effect
- Can be used as a natural challenge study
- Family, classrooms, schools, workplaces can be convenient units of the study

Household studies: advantages and challenges

Advantages:

- Vaccinated and unvaccinated have a similar opportunity for an exposure
- Allows easy identification of contacts between a case and susceptible

Disadvantages:

- Ascertainment bias: higher number of cases in household result in a higher probability of ascertainment
- Households may not be representative of the general population

TAKE HOME:

- **Study design should be chosen in function of outcome and measure of vaccine benefit**
- **Cohort studies are relatively easy to explain and communicate to the public**
- **Case-control studies with different type of controls, are commonly used for estimating vaccine effectiveness**

Examples of COVID-19 vaccine effectiveness studies

Currently planned COVID-19 VE assessments

VE priority	Prospective data collection	Electronic health record (EHR) and claims analyses (coordination across US government)
Immediate priority		
Does vaccine work as expected to prevent symptomatic disease?	Test-negative design case-control among healthcare personnel	
Subsequent priorities		
Older adults, including residents of long-term care facilities (LTCF)	Case-control among adults ≥65 years (COVID-NET linked to CMS); National Healthcare Safety Network	CMS cohort (FDA, CMS) EHR datasets (CDC, VA, FDA)
Infection and transmission	Prospective longitudinal cohorts, including among healthcare personnel & frontline workers; case-ascertained household cohorts for transmission	
Severe disease/hospitalization	Test-negative design (for adults and children); conventional case-control using hospitalized controls; screening method	EHR datasets (CDC, VA, FDA): Retrospective cohort or test-negative design
Non-severe disease	Test-negative design among outpatients	Potentially using EHR datasets
Those with key underlying conditions (e.g., immunocompromised)	Captured in above studies	CMS (FDA,CMS); EHR datasets (CDC, VA, FDA)
Disproportionately affected racial/ethnic groups	Captured in above studies; test-negative design in American Indian/Alaska Native population	CMS (FDA, CMS); EHR datasets (CDC, VA, FDA); Exploring IHS EHR (IHS)
Vaccine impact	Ecologic analyses of disease incidence/seroprevalence and vaccine coverage; comparisons of expected vaccine impact from models with observed impact	

Source: **CDC**, https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-01/09-COVID-Fleming-Dutra.pdf

Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in the UK: a test negative case control study

Jamie Lopez Bernal[1,2,3], Nick Andrews[1,2], Charlotte Gower[1], Chris Robertson[4], Julia Stowe[1], Elise Tessier[1], Ruth Simmons,[1] Simon Cottrell[5], Richard Roberts[5], Mark O'Doherty[6], Kevin Brown[1], Claire Cameron[7], Diane Stockton[7], Jim McMenamin[7], Mary Ramsay[1,2]

- **Study design**: observational study test-negative case control study
- **Data sources**: national COVID-19 testing, national vaccination register, Emergency care dataset, covariates extracted from the national testing data set
- **Study population**: England, national
- **Exposure definition**: 1st and 2d dose of BNT162b2 mRNA COVID-19, 1ste dose of ChAdOx1
- **Outcome definitions**: symptomatic COVID-19 disease confirmed by positive PCR test, hospitalization, death
- **Potential confounders**: age, sex, ethnicity, elderly home resident

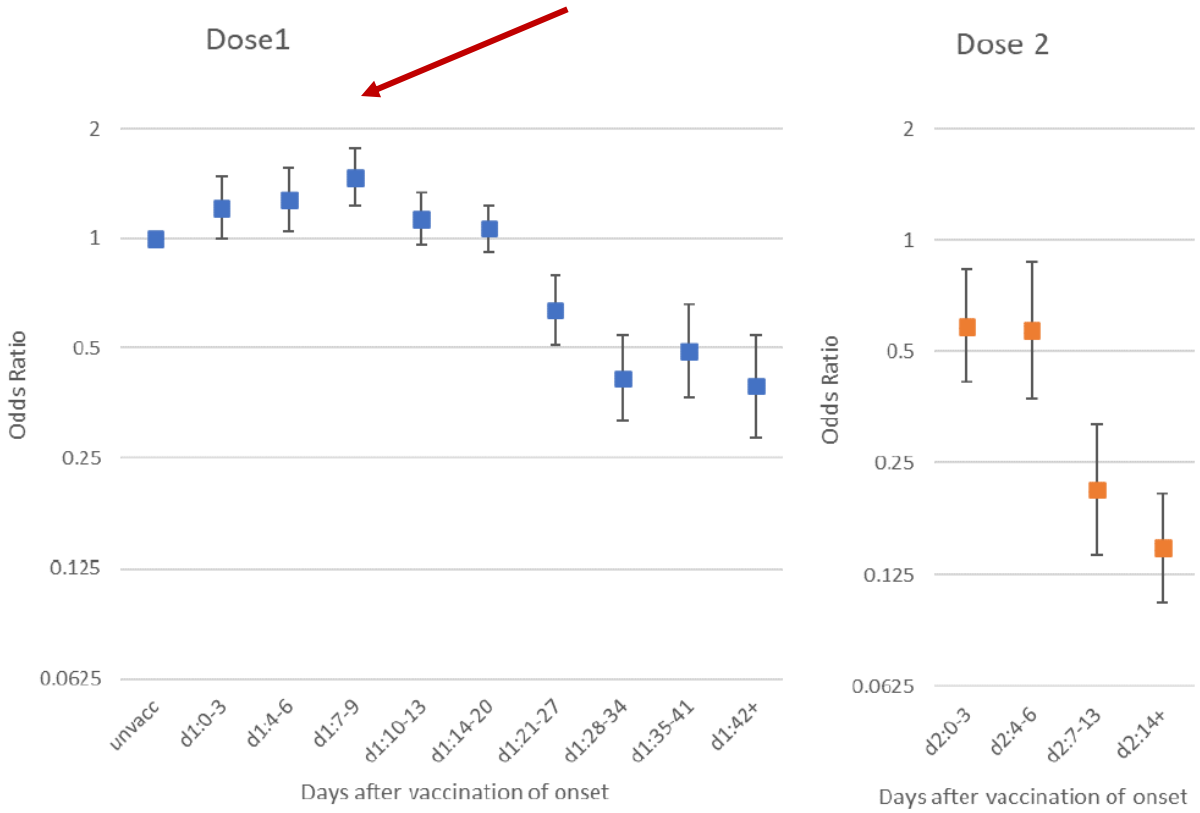


Figure 2: Adjusted odds ratios for confirmed case by interval after vaccination for BNT162b2, vaccinations administered prior to 4th January 2021, age >=80 years

Table 5:Risk of death within 21 days of testing positive in vaccinated and unvaccinated cases aged over 80 years, BNT162b2

	Deaths within 21 days			
Vaccination status	**Total cases**	**Deaths**		**Hazard ratio**
		n	**%**	
Unvaccinated	8096	1063	13.13%	1.00
Test date less than 14 days after first dose	1096	114	10.40%	0.74 (0.62-0.90)
Test date 14 days or more after first dose	750	51	6.80%	0.49 (0.38-0.63)
Total	9942	1228	12.35%	

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting

Noa Dagan, M.D., Noam Barda, M.D., Eldad Kepten, Ph.D., Oren Miron, M.A., Shay Perchik, M.A., Mark A. Katz, M.D., Miguel A. Hernán, M.D., Marc Lipsitch, D.Phil., Ben Reis, Ph.D., and Ran D. Balicer, M.D.

ABSTRACT

BACKGROUND

As mass vaccination campaigns against coronavirus disease 2019 (Covid-19) commence worldwide, vaccine effectiveness needs to be assessed for a range of outcomes across diverse populations in a noncontrolled setting. In this study, data from Israel's largest health care organization were used to evaluate the effectiveness of the BNT162b2 mRNA vaccine.

- **Study design**: observational study (matched cohort), all new vaccinated persons were matched with a 1:1 ratio to unvaccinated controls
- **Data sources**: secondary use, data from Clalit Health Services (CHS)-largest health care organization Israel
- **Study population**: 4.7 million patients (53% of the population)
- **Exposure definition**: 1st and 2d dose of BNT162b2 mRNA COVID-19 vaccine (Pfizer vaccine)
- **Outcome definitions**: documented SARS-Cov-2 infection confirmed by positive PCR test, documented symptomatic COVID-19, hospital admission for COVID-19, severe COVID-19, death from COVID-19
- **Potential confounders**: age, sex, sector (general Jewish, Arab,ultra-Orthodox Jewish), neighborhood of residence, history of influenza vaccination, pregnancy, total number of co-existing conditions

Table 2. Estimated Vaccine Effectiveness against Covid-19 Outcomes during Three Time Periods.*

Period	Documented Infection		Symptomatic Illness		Hospitalization		Severe Disease		Death	
	1–RR	Risk Difference	1–RR	Risk Difference	1–RR	Risk Difference	1–RR	Risk Difference	1–RR	Risk Difference
	% (95% CI)	*no./1000 persons (95% CI)*	*% (95% CI)*	*no./1000 persons (95% CI)*	*% (95% CI)*	*no./1000 persons (95% CI)*	*% (95% CI)*	*no./1000 persons (95% CI)*	*% (95% CI)*	*no./1000 persons (95% CI)*
14 to 20 days after first dose	46 (40–51)	2.06 (1.70–2.40)	57 (50–63)	1.54 (1.28–1.80)	74 (56–86)	0.21 (0.13–0.29)	62 (39–80)	0.14 (0.07–0.21)	72 (19–100)	0.03 (0.01–0.07)
21 to 27 days after first dose	60 (53–66)	2.31 (1.96–2.69)	66 (57–73)	1.34 (1.09–1.62)	78 (61–91)	0.22 (0.13–0.31)	80 (59–94)	0.18 (0.10–0.27)	84 (44–100)	0.06 (0.02–0.11)
7 days after second dose to end of follow-up	92 (88–95)	8.58 (6.22–11.18)	94 (87–98)	4.61 (3.29–6.53)	87 (55–100)	0.22 (0.08–0.39)	92 (75–100)	0.32 (0.13–0.52)	NA	NA

* Confidence intervals were estimated using the percentile bootstrap method with 500 repetitions. Estimates were calculated only for cells with more than 10 instances of an outcome across the two groups. NA denotes not available, and RR risk ratio.

This is a preprint and has not yet been peer reviewed

Effectiveness of first dose of COVID-19 vaccines against hospital admissions in Scotland: national prospective cohort study of 5.4 million people

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Professor Colin R Simpson PhD, School of Health, Wellington Faculty of Health, Victoria University of Wellington, NZ and Usher Institute, University of Edinburgh, Edinburgh, UK*

Professor Chris Robertson PhD, Department of Mathematics and Statistics, University of Strathclyde, Glasgow, UK and Public Health Scotland, Glasgow, UK*

- **Study design**: national prospective cohort study
- **Data sources**: secondary data use, linked vaccination, primary care, laboratory testing, hospitalization, mortality data
- **Study population**: 5.4 million people in Scotland (app. 99% population)
- **Exposure definition**: 1st dose of the BNT162b2 mRNA COVID-19 vaccine (Pfizer vaccine) or ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca)
- **Outcome definitions**: hospital admission with COVID-19 as the main cause of admission or hospital admission within 28-days of positive RT-PCR test for SARS-CoV-2
- **Potential confounders**: age, sex, socio-economic status, residential settlement, number and type of comorbidities

Vaccination status	Person years	Number of events	Age-adjusted Hazard Ratios (95% CI)*	Full-adjusted Hazard Ratios (95% CI)**	Full and inverse propensity adjusted Hazard Ratios (95% CI)***	Vaccine effect (95% CI)
Vaccinated overall						
Unvaccinated	787518	7472	1	1	1	NA
Vaccine dose 1 (7-13 days)	13487	212	0.73 (0.64 to 0.84)	0.74 (0.64 to 0.86)	0.53 (0.47 to 0.61)	47% (39 to 53)
Vaccine dose 1 (14-20 days)	9191	120	0.61 (0.5 to 0.73)	0.63 (0.52 to 0.76)	0.4 (0.34 to 0.48)	60% (52 to 66)
Vaccine dose 1 (21-27 days)	6343	52	0.43 (0.33 to 0.56)	0.44 (0.33 to 0.58)	0.3 (0.23 to 0.38)	70% (62 to 77)
Vaccine dose 1 (28-34 days)	3867	20	0.34 (0.22 to 0.52)	0.31 (0.2 to 0.48)	0.16 (0.1 to 0.26)	84% (74 to 90)
Vaccine dose 1 (35-41 days)	2326	17	0.6 (0.38 to 0.97)	0.46 (0.28 to 0.76)	0.39 (0.26 to 0.58)	61% (42 to 74)
Vaccine dose 1 (42+ days)	3843	21	0.52 (0.34 to 0.81)	0.51 (0.33 to 0.79)	0.42 (0.3 to 0.61)	58% (39 to 70)

From: https://www.ed.ac.uk/files/atoms/files/scotland_firstvaccinedata_preprint.pdf

Effectiveness of BNT162b2 mRNA vaccine against infection and COVID-19 vaccine coverage in healthcare workers in England, multicentre prospective cohort study (the SIREN study)

Authors:

Hall V FFPH[1,2], Foulkes S MSc[1], Saei A PhD[1], Andrews N PhD[1,5], Oguti B[1,3], Charlett A PhD[1,4,5], Wellington E MSc[1], Stowe J PhD[1], Gillson N BA[1], Atti A MSc[1], Islam J PhD[1], Karagiannis I PhD[1], Munro K MSc[1], Khawam J BSc[1], The SIREN Study Group∞, Chand MA FRCPath[1,6], Brown CS FRCPath[1], Ramsay M FFPH[1,5], Lopez-Bernal J PhD[1], Hopkins S FRCPath[1,2]*.

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From: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3790399

- **Study design**: a prospective cohort study
- **Data sources**: vaccination data obtained directly from participants completing the enrolment and follow up questionnaires and from linkage on personal identifiable information to the registry of COVID-19 vaccination in England
- **Study population**: staff working in publicly funded hospitals
- **Exposure definition**: receiving at least one dose of vaccination
- **Outcome definitions**: PCR confirmed SARS-CoV-2 infection
- **Potential confounders**: having a prior infection, gender, age, ethnicity, IMD score (indices of multiple deprivation), staff group

Table 2: Effectiveness of the BNT162b2 COVID-19 vaccine against infection in SIREN participants, stratified by cohort, between 7 December 2020 and 5 February 2021, (n=23,324)

Vaccine group	Total person time (days)	Number of PCR positives	Incidence Density per 10,000 person days	Unadjusted Hazard Ratio (95% CI)^	Adjusted Hazard Ratio (95% CI)*
Full cohort					
Unvaccinated	710587	977	14	Reference	Reference
d1 ≥21	87278	71	8	0.43 (0.23-0.64)	0.30 (0.15-0.45)
d2 ≥7	20978	9	4	0.23 (0.06-0.40)	0.15 (0.04-0.26)
Negative cohort					
Unvaccinated	442605	902	20	Reference	Reference
d1 ≥21	59748	66	11	0.33 (0.17-0.49)	0.28 (0.14-0.42)
d2 ≥7	14746	8	5	0.18 (0.04-0.31)	0.14 (0.03-0.24)
Positive cohort**					
Unvaccinated	267982	75	3	-	-
d1 ≥21	27530	5	2	-	-
d2 ≥7	6232	1	2	-	-

^Unadjusted includes vaccine effect (period) only; *the full model was adjusted for site as a random effect, period, and fixed effects: age, gender, ethnicity, comorbidities, job role, frequency of contact with COVID-19 patients, employed in a patient facing role, occupational exposure. **there was insufficient information to model the positive cohort separately so stratified hazard ratios are not available for the positive cohort.

From: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3790399

International initiatives

- **I-MOVE-COVID-19**

  adaptation and expansion of the existing, long-running, Europe-wide influenza surveillance network (I-MOVE) to include COVID-19. The network includes primary care networks, hospitals, and national laboratory reference centres in 10 countries across the WHO European Region.

- **CDC**

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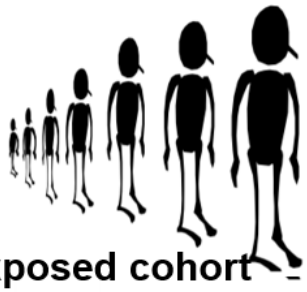
Publicly available protocols

	Aim	Study design	Link
CDC	VE among adults age 65 years and older using CMS data	Retrospective case-control	https://www.cdc.gov/vaccines/covid-19/downloads/cms-covidnet-case-control-protocol.pdf
CDC	VE among Health Care Personnel During Early Phase Vaccination	Test-negative prospective case control	https://www.cdc.gov/vaccines/covid-19/downloads/hcp-early-phase-protocol-508.pdf
CDC	VE in preventing secondary infections within households	Prospective cohort	https://www.cdc.gov/vaccines/covid-19/downloads/recover-household-transmission-study-protocol-508.pdf
CDC	VE to prevent medically attended influenza and COVID-19 among the US population	Test-negative prospective case control	https://www.cdc.gov/vaccines/covid-19/downloads/us-flu-vaccine-effectiveness-network-protocol-508.pdf
	VE to prevent hospital admission among Scottish population	Prospective observational	https://bmjopen.bmj.com/content/10/6/e039097
ACCES	VE based on existing HCD	Cohort study	http://www.encepp.eu/encepp/openAttachment/documents.otherDocument-0/39287
ACCES	VE against hospital admission	Test-negative	http://www.encepp.eu/encepp/openAttachment/documents.otherDocument-1/39288

Thank you for your attention

Counterfactuals

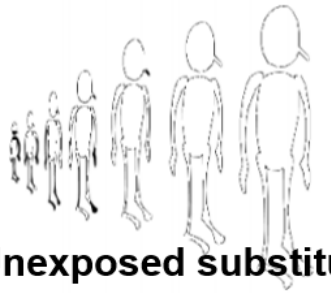


Exposed cohort

→ Observed
Incidence in exposed

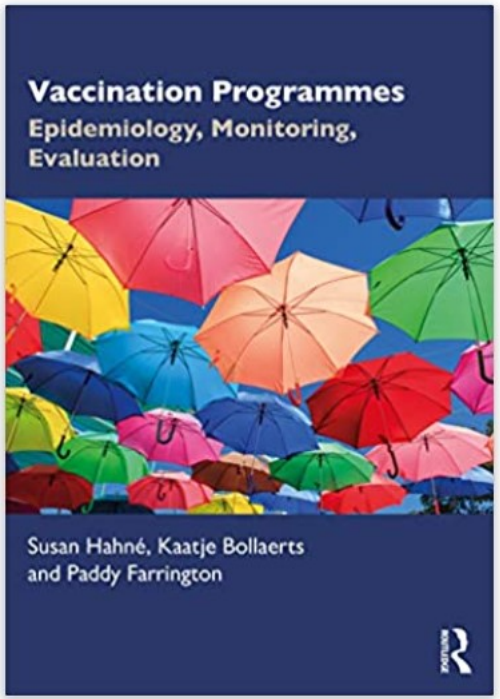
Same cohort, but unexposed

→ Counterfactual
(unobserved)



Unexposed substitute cohort

→ Observed
Incidence in unexposed



https://www.routledge.com/Vaccination-Programmes-Epidemiology-Monitoring-Evaluation/Hahne-Farrington-Bollaerts/p/book/9781138054851