COVID-19 Vaccine Effectiveness in Health Workers (HW)

WHO Protocol overview

Capacity Building Session for Eastern Mediterranean Region
COVID-19 Vaccine Effectiveness Study
13 December 2021

Source:
https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/publications-and-technical-guidance/2021/cohort-study-to-measure-covid-19-vaccine-effectiveness-among-health-workers-in-the-who-european-region-guidance-document-2021

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Objectives

- **Primary objective:** To measure overall and **product-specific** COVID-19 VE among HW eligible for vaccination against **laboratory-confirmed SARS-CoV-2 symptomatic infection** (if resources permit, against all infection)
- **Secondary objectives***: To measure VE:
  - Against disease by severity: asymptomatic, symptomatic, severe
  - SARS-CoV-2 genetic variants
  - Infection and re-infection
  - Time since vaccination (duration of protection)
  - Groups by age, gender and health conditions (chronic / comorbidities)
  - HW roles and types of exposure / activities

* To be considered depending on sample size and resources available

STUDY DESIGN and population

Study design

- Prospective cohort study at hospital level

Proposed study period

- 6 months minimum – 12 months ideal

Study population

- HW includes all categories (e.g. clinical, ancillary etc) eligible for vaccination
- Recruitment from hospital settings
- Enrolment all HW at each study site

Inclusion criteria

- HWs (all types) eligible for COVID-19 vaccination
- HWs who are **unvaccinated or within 7 days of vaccination***

Exclusion criteria

- HWs not eligible for vaccination
- 6 month follow-up is not possible
- HWs vaccinated in COVID-19 vaccine clinical efficacy trials

*HWs vaccinated >7 days before can be included if good retrospective data (serology, vaccination) is available and high quality (info before vaccination and between vaccination and enrolment)

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Exposure and outcome

Exposure: vaccination

- Definition of vaccinated depends on the vaccine
- Number doses (fully v partially vaccinated)
- Date vaccinations
- Brand
- Batch
- Highlights importance of good quality data collection and need to confirm vaccination data

Outcome

- Infection of symptomatic infection: positive result RT-qPCR of naso-pharyngeal samples
- Alternative sampling (e.g. saliva) to promote regular follow-up
- Symptomatic disease (mild vs severe)
- Genetic variant

Sample size

Estimates for 6 months follow-up

Hazard rate /year	VE (%)	Vaccine coverage (%)	Total sample size	Unvaccinated		Vaccinated	
				N	# events	N	# events
0.2	90	90	388	39	4	349	3
		80	258	52	5	206	2
		70	222	67	6	155	2
		60	214	86	8	128	1
	80	90	609	61	6	548	11
		80	383	77	7	306	6
		70	319	96	9	223	4
		60	300	120	11	180	4
	70	90	939	94	9	845	25
		80	570	114	11	456	13
		70	464	139	13	325	10
		60	429	172	16	257	8
	60	90	1,468	147	14	1,321	52
		80	872	175	17	697	27
		70	697	209	20	488	19
		60	637	255	24	382	15
	50	90	2,380	238	23	2,142	104
		80	1,392	279	27	1,113	54
		70	1,098	330	31	768	37
		60	992	397	38	595	29
0.1	90	90	765	77	4	688	765
		80	508	102	5	406	508
		70	437	131	6	306	437
		60	420	168	8	252	420
	80	90	1,199	120	6	1,079	1,199
		80	753	151	7	602	753
		70	626	188	9	438	626
		60	589	236	12	353	589

Hazard rate /year	VE (%)	Vaccine coverage (%)	Total sample size	Unvaccinated		Vaccinated	
				N	# events	N	# events
0.1	70	90	1,850	185	9	1,665	1,850
		80	1,123	225	11	898	1,123
		70	912	274	13	638	912
		60	843	337	16	506	843
	60	90	2,888	289	14	2,599	2,888
		80	1,714	343	17	1,371	1,714
		70	1,369	411	20	958	1,369
		60	1,250	500	24	750	1,250
	50	90	4,678	468	23	4,210	4,678
		80	2,733	547	27	2,186	2,733
		70	2,155	647	32	1,508	2,155
		60	1,945	778	38	1,167	1,945
0.05	90	90	1,518	152	4	1,366	3
		80	1,008	202	5	806	2
		70	866	260	6	606	2
		60	832	333	8	499	1
	80	90	2,380	238	6	2,142	11
		80	1,493	299	7	1,194	6
		70	1,242	373	9	869	4
		60	1,167	467	12	700	3
	70	90	3,672	368	9	3,304	25
		80	2,227	446	11	1,781	13
		70	1,809	543	13	1,266	9
		60	1,672	669	17	1,003	7
	60	90	5,729	573	14	5,156	51
		80	3,399	680	17	2,719	27
		70	2,714	814	20	1,900	19
		60	2,475	990	24	1,485	15

NB: - Sample size can be smaller if follow-up period extended e.g. >6 months

- Must take into account expected drop-out rate, adjustments and stratifications

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Data analysis

Cohort study design

- Person-time analysis allows individuals to move between “states”
- Unvaccinated → vaccinated; high ↔ low exposures
- Poisson regression assumes constant rates over time
- Split time and allow for piece-wise different rates
- Cox regression assumes constant hazard ratio over time (but not hazard)

Pooling data

- Use of standardised protocol to pool at regional/national levels
- Obtain higher precision estimates
- Multilevel modelling to account for clustering of data by site or country

Cox regression: VE = 1 – hazard ratio [HR]

Poisson regression: VE = 1 – rate ratio [RR]

Follow up

Enrolment

- Collection of respiratory specimen
- Serology
- Questionnaire: baseline characteristics, vaccination, exposures 14 days before (hospital and community), previous SARS-CoV-2

Active follow-up

- Weekly questionnaire for changes in symptoms, vaccination status and exposures (professional and personal)
- RT-PCR upon development of compatible symptoms
- Weekly/biweekly RT-PCR irrespective of symptoms (if estimating VE against infection)
- Additional serological testing (for VE against asymptomatic infection)

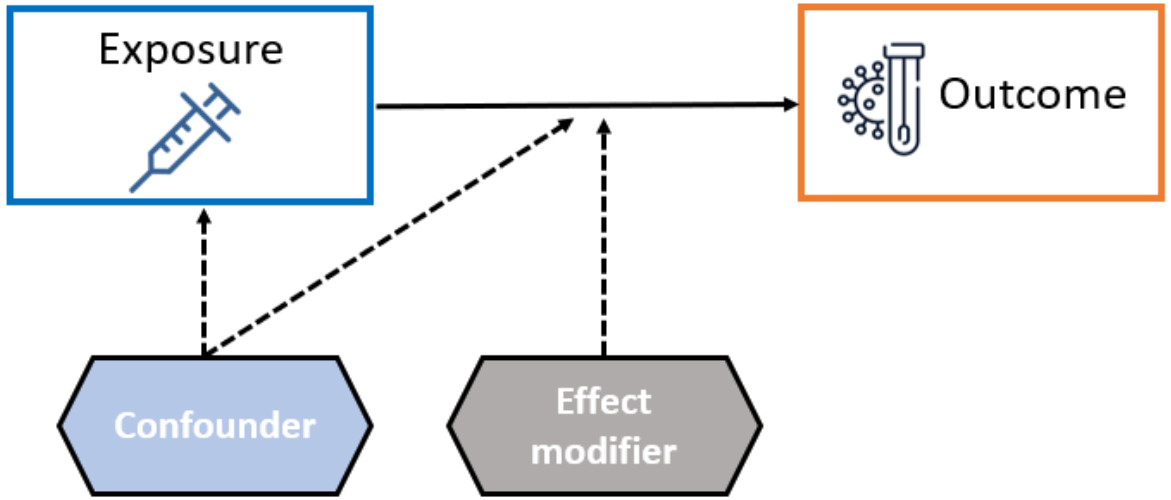
Duration of follow-up considering limited time for study

- Sample size considerations
- Limited study time (6 months or 12 months?)
- Continuation of cohorts beyond study period

Effect Modifiers and confounders

Essential variables to collect and how to best document

- Demographic: age, sex, ethnic group, socio-economic status
- Chronic conditions and relevant medication
  - Time dependent (i.e. regular update) or collect just at enrolment?
- Exposures in the hospital/ward (time dependent)
  - Aerosol generating procedures performed
  - Number of COVID patients contacted and average time per patient
  - PPE, IPC indicators (Availability? Use? Both?)
- Exposures in the community (time depe
  - Household composition
  - Contact with cases
  - Use of public transport
  - Social events
  - Use of masks



Considerations

Timing and progress of vaccination campaign among HWs

- Random versus volunteer HW enrolled
- High exposure of HWs may lead to high seropositivity rate at enrollment (essential to document)
- Inclusion of HWs vaccinated more than 7 days prior to enrolment is possible but vaccination (type and date) must be documented. To be considered depending on context and added value.

Testing capacities:

- For repeat testing if measuring VE against infection
- For sequencing
- For repeat serological testing

Documenting previous infection and infection during study

- Serological testing at enrolment : detection of anti-S and anti-N
- Repeat serological testing for detection of asymptomatic infections → remove from at risk population
- Type of vaccine used in country (inactivated vaccines include both N and S antigens)

Funding availability and options

Pooling data across countries

Why pool data?

Challenges for COVID-19 vaccine effectiveness:
Different vaccines by:

- country
- age-group
- risk group
- time

Different vaccine schedules/days between doses
Variants
Will sample size at study site level big enough?
Pooling → larger sample size

- increase VE precision
- conduct sub-group analyses
- stratify by effect modifiers
- control for confounders

Pooling VE data: Network Collaboration

Agreed WHO generic protocol

- Plan of analysis

Generic protocol adapted to each site

- Site specific protocol

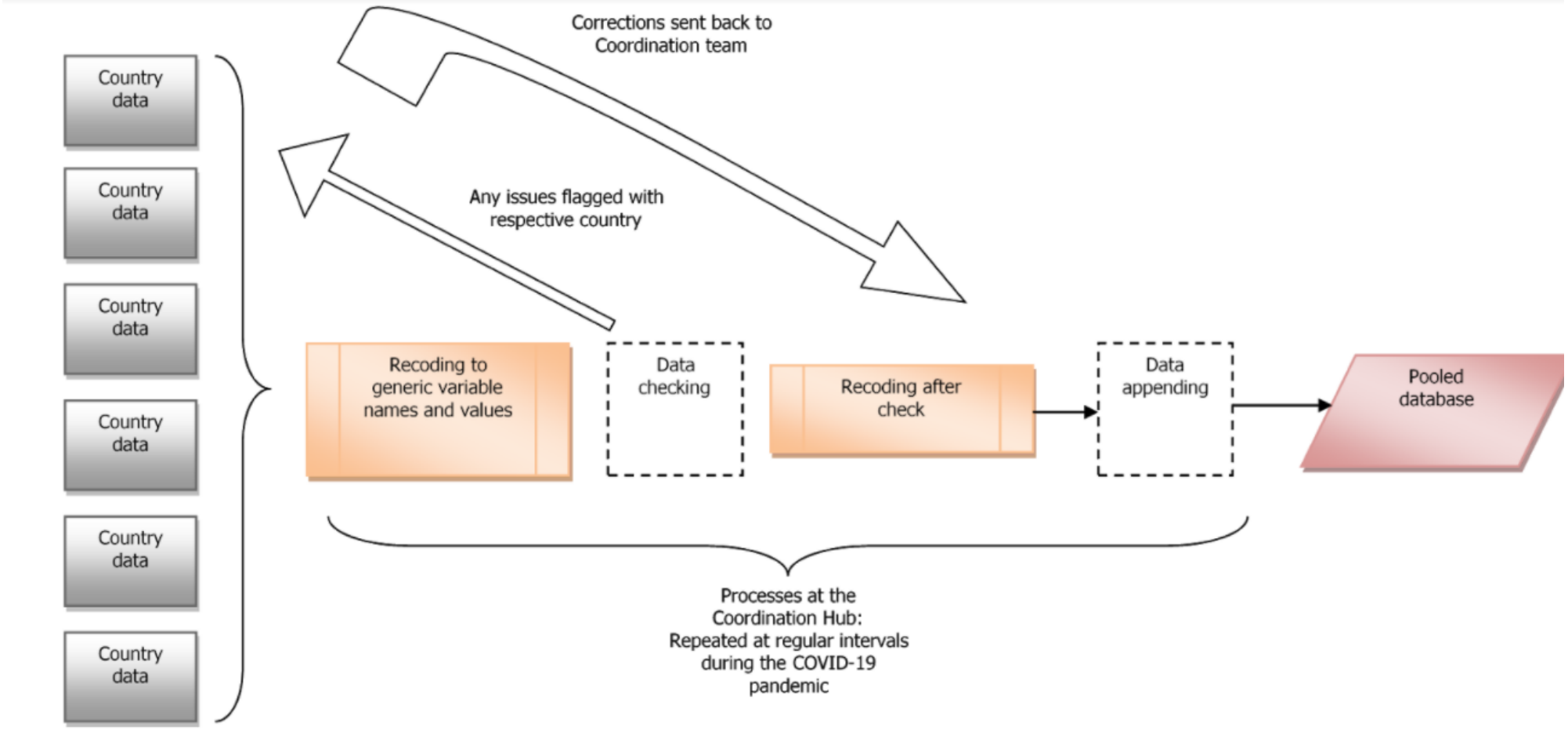
Coordinating hub

- Organises data management at central level
- Develops data analysis scripts
- Validates data for each site
- Analyses pooled data

Discuss interpretation of pooled analysis / results

Key: constant exchange coordinating hub / study sites

EMRO COVID-19 / Pooled analysis data flow



Data management and sharing for pooled analyses
Common data entry system?

Thank you

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Testing algorigthm N-S

- At enrollment: Serology at baseline
  - anti-S detection among unvaccinated HCW at inclusion
  - anti-N detection among those already vaccinated to distinguish between vaccination and infection immunity response.
  - Follow up of antibodies level is not necessary to estimate VE against lab confirmed COVID19 infection
  - Note that for individuals vaccinated with inactivated vaccines, it would not be possible to disentangle if the antibodies are due to vaccination or to infection.