

COVID-19 Vaccine Effectiveness in Health Workers (HW)

Expert meeting
Epiconcept
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Objectives VE in HW

- **Primary objective**
 - To measure overall and **product-specific** COVID-19 VE among **HW eligible for vaccination** against **laboratory confirmed SARS-CoV-2** infection
- **Secondary objectives**
 - Report VE estimates by:
 - Vaccination: product, number doses, time since dose
 - Disease severity: asymptomatic v symptomatic v severe
 - SARS-CoV-2 variant
 - Individual: age, gender and health (chronic illness, previous infection)
 - Professional: roles (speciality, ward), activities (type of exposure)
- **Further secondary objectives not addressed in circulated draft protocol**
 - VE against transmission
 - Describe immunogenetic profiles of vaccinated groups

Study design and population

- Study design
 - Prospective cohort study at hospital level
- Study population
 - HW includes all categories (e.g. clinical, ancillary etc) eligible for vaccination
 - Recruitment from hospital settings
 - Enrolment all or random sample HW at each study site

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: RT-qPCR of naso-pharyngeal samples
 - Alternative sampling (e.g. saliva) to promote regular follow-up
 - Symptomatic disease (mild v severe)
 - Genetic variant

Sample sizes

Follow up 1 year

Hazard rate (/yr)	Total size	N unvac	Event unvac	N vac	Events vac	VC	VE
0.05	1350	135	7	1215	6	90	90
	1913	191	9	1722	17	90	80
	3860	386	19	3474	69	90	60
	5842	584	28	5258	130	90	50
	3153	630	31	2523	62	80	50
0.1	680	68	6	612	6	90	90
	966	96	9	870	17	90	80
	1356	135	13	1221	36	90	70
	1957	195	19	1762	69	90	60
	2968	296	28	2672	130	90	50
	333	99	9	234	5	70	80
	1179	353	34	826	40	70	50
	1001	400	38	601	29	60	50
0.2	492	49	9	443	17	90	80
	694	69	13	625	36	90	70

Follow up 3 months

Hazard rate (/yr)	Total sample	N unvac	Events unvac	N vac	Events vac	VC	VE
0.05	3740	748	9	2992	7	80	80
	5465	1093	14	4372	16	80	70
	8084	1616	20	6468	32	80	60
	12455	2491	31	9964	62	80	50
	23088	2308	29	20780	129	90	50
0.1	697	278	7	419	1	60	90
	1075	430	11	645	3	60	80
	1623	649	16	974	7	60	70
	2472	988	24	1484	15	60	60
	7667	766	19	6901	69	90	60
	11590	1159	29	10431	130	90	50
0.2	2681	268	13	2413	36	90	70
	3860	386	19	3474	69	90	60
	5842	584	28	5258	130	90	50

Stata code: `stpower exponential 0.1, power(0.8) loghazard hratio(0.1)(0.1)(0.5) fperiod(0.25) p1(0`

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

Follow up

- Enrolment
 - Respiratory specimen
 - Serology
 - Questionnaire: baseline characteristics, vaccination, exposures 14 days before (hospital and community), previous SARS-CoV-2
- Follow up
 - Weekly PCR irrespective of symptoms
 - Weekly questionnaire for changes in symptoms, vaccination status and exposures (professional and personal)
 - Further serology
- Duration of follow-up considering limited time for study
 - Sample size considerations
 - Limited study time (maximum 6 months?)
 - Continuation of cohorts beyond study period

Effect modifiers/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?
- Blood group?
- 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 dependent)
 - Household composition
 - Contact with cases
 - Use of public transport
 - Social events
 - Use of masks

Discussion points (1)

- Objective: Estimate VE infection transmission
 - VE against infection adequate?
 - Reporting of viral load assuming \uparrow viral load = \uparrow risk of transmission
 - Household transmission study to estimate secondary attack rates?
 - Recruitment of (random?) sample of HW and their households
 - Random versus volunteer HW enrolled
 - Distinguish infections acquired from HW and from community
 - Alternative designs?
- Objective: description immunogenetic profiles
 - Sub-study of B and T cell responses in vaccinated populations
 - Key research questions to be addressed
- Objectives: any research questions being overlooked?

Discussion points (2)

- Genetic sequencing of infections to estimate VE by variant
 - Capacity and resource intensive – random selection of samples to sequence
 - Role of study as sentinel surveillance of VE in emerging variants?
- Follow-up of HW
 - Enthusiasm of HW to participate (e.g. high service demand)
 - Duration of follow-up (3-6 months) and acceptability weekly swabbing
 - Current testing regimen and alternatives of self-swabs or saliva
- HW vaccination programme with rapid and high uptake
 - Unvaccinated may have unique characteristics (e.g. previous infection, exposures)
 - HW vaccinated before study initiation (infected between time points)
 - Data collection at T_0 to identify previously infected
 - Serology to discriminate natural and acquired immunity
 - Differential profiles assessed with 2 tests for anti-N and anti-S antibody
 - Questionnaire to collect retrospective symptom information
 - Sensitivity analysis of individuals with evidence of infection

Discussion points (3)

Accounting for biases/effect modifiers/confounders

- Prevent or minimise biases in design and analysis?
 - Known v unknown previous infection
 - Confirmation of vaccination status
 - Differential exposure between vaccinated and unvaccinated
 - Collection of national/site meta data to inform analysis
 - COVID19 incidence in community and study site
 - Site data on PPE availability and use to triangulate self-reported use
 - Differential ascertainment of outcome
 - Reporting of viral load for PCR+
 - Lower viral loads in vaccinated?
- Unmeasured variables?
- Other limitations?