Cohort study into COVID-19 vaccine effectiveness (COVE study)

Collaboration RIVM, UMC Utrecht, Julius Clinical

Agenda

- Study team / division of tasks
- METC protocol
  - Objectives / endpoints
  - Study design
  - Study population
  - Sample size
- Timeline
- Action points

Study team / division of tasks

Tasks	RIVM	UMC Utrecht	Julius Clinical
Sponsor/opdrachtgever	X		
Protocol writing	X	X	X
Data collection/logistics			X
Data management			X
Data analysis (lab+stat)	X (PhD)		
Data reporting	X (PhD)		
Project management	x (5.1.2e 5.1.2e)		X
…			

Involve Lareb?, involve other people UMC: 5.1.2e 5.1.2e , 5.1.2e 5.1.2e ?

Primary objective

- To estimate product-specific VE of COVID-19 vaccines used in the Dutch national vaccination program against laboratory-confirmed SARS-CoV-2 infection at 9 months after implementation of vaccination by age and medical risk groups

Primary endpoint

- Laboratory-confirmed SARS-CoV-2 infection (asymp or symp)
  - Positive SARS-CoV-2 test
  - Based on testing policy in NL, so not active testing
  - Should we then call it positive test result? Or COVID-19?
  - Self-testing may become available

Secondary objectives

- Product-specific VE against severe COVID-19 (hosp. and death)
- Product-specific VE by time since vaccination and nr doses
- Relative VE of different vaccines (in primary objective?)
- Monitoring (long-term) adverse events following immunization
  - (definition, Lareb?)
- Substudies → in separate protocol/amendment?:
  - Immunogenicity / immunologic parameters
  - Regular (self) testing to detect asymptomatic infections
  - Correlation of protection → blood sample at regular points → analyze when relevant

Study design

- Prospective observational cohort study with 5 years follow-up
- Inclusion participants preferably at least 2-4 weeks before invitation COVID-19 vaccine
- COVID-19 vaccination given according to prioritization national vaccination program, not as part of the study
- Participants can contribute unvaccinated as well as vaccinated time (time varying exposure)
- Recruitment through BRP by age group and through GP for medical risk group

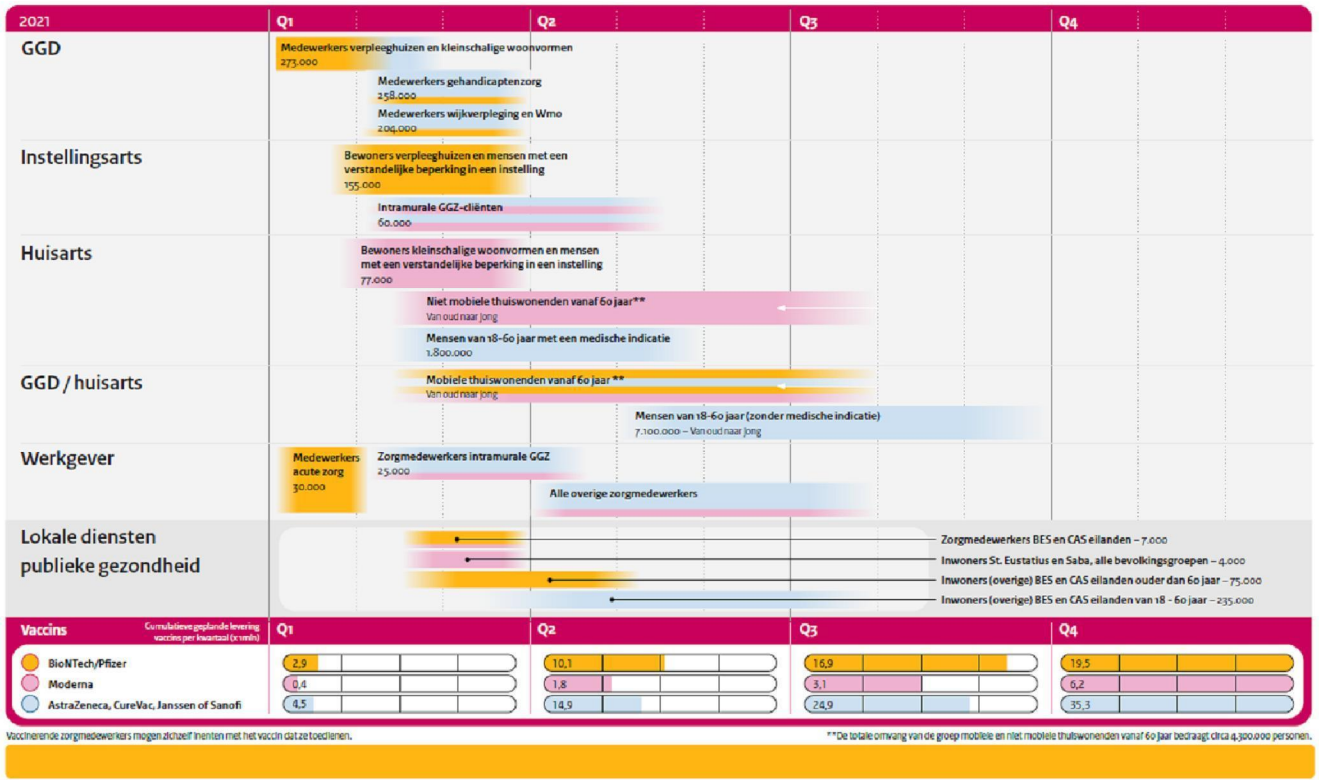
Study design / population

Target group	Estimated size in NL	Scheduled vaccination period (ref to latest strategie)	Scheduled vaccines used	Recruitment	Needed sample size (see section 4.4)
Community dwelling persons aged 60-80 years	~4 million	Feb-July 2021	BioNTech/Pfizer Moderna Other	Random sample BRP based on age	21,000 (medical risk group yes/no, 3 vaccines)
Persons aged 18-59 years with medical indication	~1.8 million	Feb-May 2021	Other	20% from random sample from BRP 80% from selective recruitment GP	14,000 (2 age strata, 2 vaccines)
Persons aged 18-59 years without medical indication	~7.1 million	May-Sept 2021	Other	Random sample BRP based on age (80% of this sample is without medical indication)	14,000 (2 age strata, 2 vaccines)

Vaccinatiestrategie*

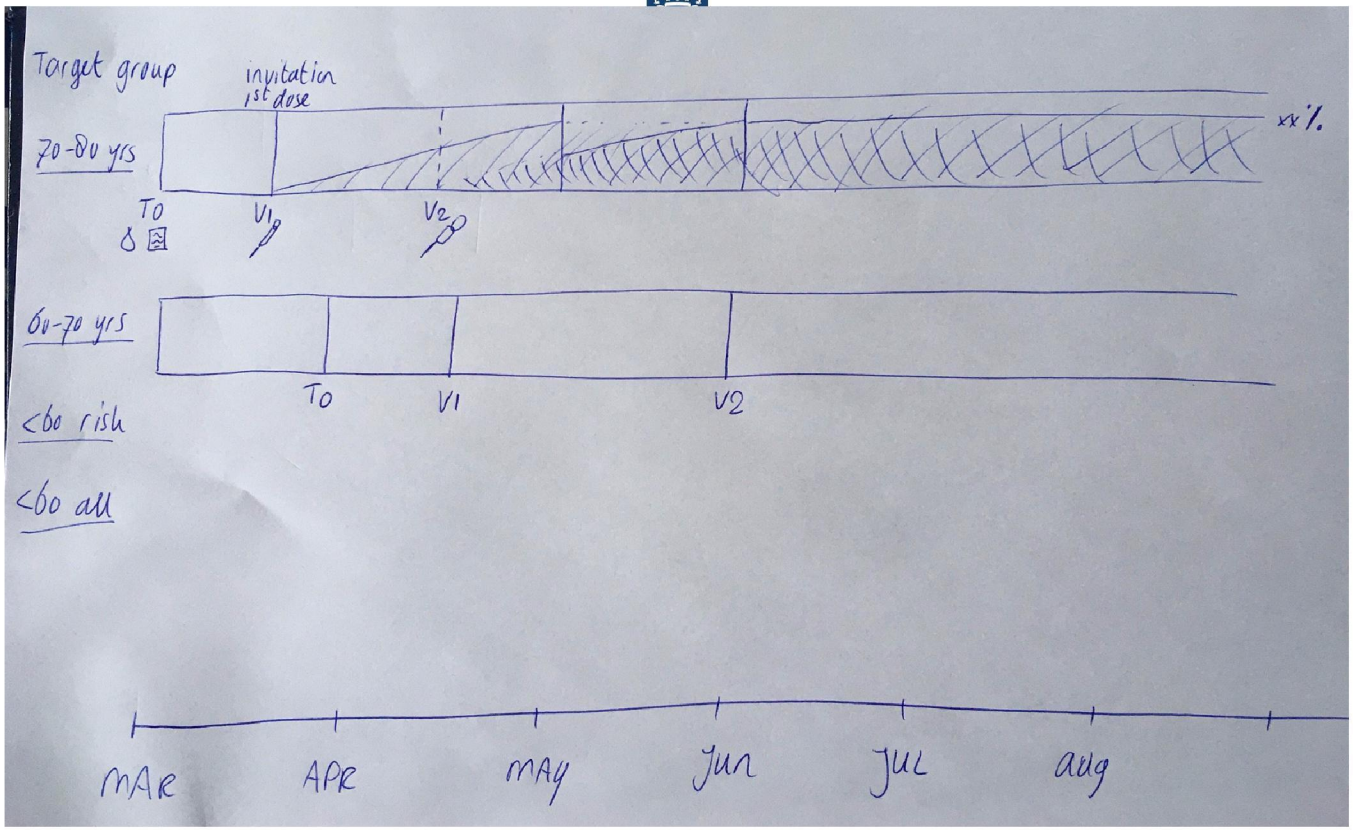
Afbeelding 1

*Let op! De gegevens waarop deze afbeelding is gebaseerd veranderen continue. Start en snelheid van vaccineren zijn voortdurend aan veranderingen onderhevig. De planning is afhankelijk van o.a. goedkeuring, werking, levering en distributie van de vaccins. Op basis van ontwikkelingen en adviezen kan ook veranderen welke groep welk vaccin krijgt.



Vaccinerende zorgmedewerkers mogen zichzelf inenten met het vaccin dat ze toedienen.

**De totale omvang van de groep mobiele en niet mobiele thuiswonenden vanaf 60 jaar bedraagt circa 4.300.000 personen.


Target group
invitation 1st dose
70-80 yrs
xx %
T0
V1
V2
60-70 yrs
T0
V1
V2
<60 risk
<60 all
MAR
APR
MAY
Jun
JUL
aug

Sample size calculation

Parameter	Estimate (range)
Infection rate	22 per 100,000 per day (0.04 over 6 mo)
Follow up period	6 months
Vaccination coverage	80%
Vaccine effectiveness	70%; H0: 0%
Relative effectiveness	2.5 fold difference? (80% vs 50%)
Power	90%
Alpha	5%
Sample size	~3500 per stratum

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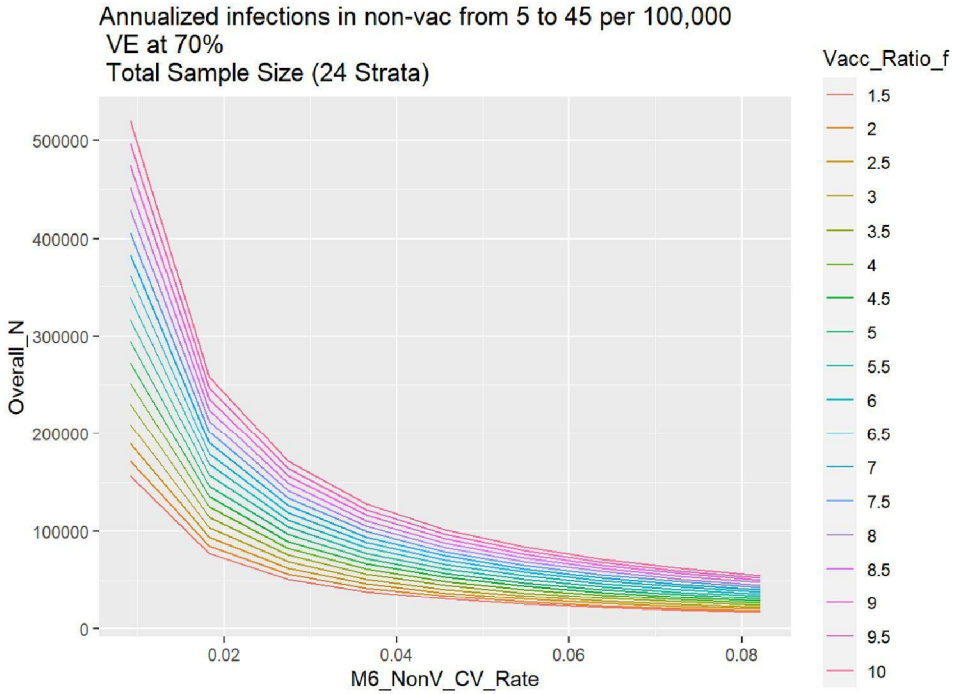
Annualized infections in non-vac from 5 to 45 per 100,000
VE at 70%
Total Sample Size (24 Strata)
Overall_N
500000
400000
300000
200000
100000
0
0.02
0.04
0.06
0.08
M6_NonV_CV_Rate
Vacc_Ratio_f
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
8.5
9
9.5
10

Data collection

- At baseline
  - Questionnaire including sociodem, health status, behavior regarding COVID-19 measures
  - Self-administered fingerprick blood sample for SARS-CoV-2 antibodies
  - Baseline PCR?
- Vaccination data through self-report and/or check/linkage with vaccination register
- Follow-up for endpoints for 4/5 years?:
  - Monthly online questionnaire → self reported positive SARS-CoV-2 test, AEFI and covariates
  - GP dossier?
  - Hospital data?
  - App, SMS?
- Regular blood sample, e.g. every 6 months? (PICO?)
- Which AEFI to follow up? → SAE or AE not mentioned in the SPC

Study population

- Community dwelling adults 18-80 years who become eligible for COVID-19 vaccination
- Exclusion:
  - Contraindication for COVID-19 vaccination?
- Children could be added when this becomes relevant

Statistical analysis

- Cox regression to compare incidence of infection in unvaccinated and vaccinated person time
- By vaccine product, age group, medical risk group
- Adjustment/stratification for calendar time
- Adjustment/stratification for region, sociodem, health status, behavior regarding measures (at time of vaccination?), e.g. using propensity score matching
- Exclude participants with SARS-CoV-2 antibodies at baseline in sensitivity analysis

Timeline

- Projected start inclusion in March (first groups vaccinated in Feb)
- Stichting BEBO – independent METC
  - Meeting 2-2, deadline 27-1 → feasible?
  - Next meeting (25-2) or other METC?

Action points

- METC
  - Protocol + ABR formulier
  - Questionnaire
  - Participant information + IC
  - Information website
- ...