

# External validity of phase III trials on vaccines against SARS-CoV-2 to a middle-aged and elderly Western European population

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## Research Article

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# Abstract

**Background:** Initial results from various phase-III trials on vaccines against SARS-CoV-2 are promising. For proper translation of these results to clinical guidelines, it is essential to determine how well the general population is reflected in the study populations of these trials.

**Methods:** This study was conducted among 7162 participants (age-range: 51-106 years; 58% women) from the Rotterdam Study. We quantified the proportion of participants that would be eligible for the nine ongoing phase-III trials. We further quantified the eligibility among participants at high risk to develop severe COVID-19. Since many trials were not explicit in their exclusion criterion with respect to 'acute' or 'unstable preexisting' diseases, we performed two analyses. First, we included all participants irrespective of this criterion. Second, we excluded persons with acute or 'unstable preexisting' diseases.

**Results:** 97% of 7162 participants was eligible for any trial with eligibility for separate trials ranging between 11%-97%. For high-risk individuals the corresponding numbers were 96% for any trial with separate trials ranging from 5%-96%. Importantly, considering persons ineligible due to 'acute' or 'unstable pre-existing' disease drastically dropped the eligibilities for all trials below 43% for the total population and below 36% for high-risk individuals.

**Conclusion:** The generalisability of phase-III trials to the general population depends largely on the interpretation and application of the criterion 'acute' or 'unstable pre-existing' disease, which reduces the generalisability by half. This indicates the importance of developing clinical recommendations applicable to the appropriate target populations and cautions against ad hoc wide-spread use of any effective vaccine.

## Introduction

Several phase III trials on vaccines against SARS-CoV-2 are ongoing and initial results highly promising. A major issue of these phase III trials is to what extent the included study population is representative of the intended (or target) population, i.e. external validity.

For these trials, the intended target population is initially comprised of high-risk individuals and ultimately the entire world population. It remains unclear whether these target populations are representatively recruited into ongoing trials. This information is pivotal, since clinical recommendations for any approved vaccine should incorporate the proper target populations for which these vaccines have shown efficacy, and also determine those populations not sufficiently represented in the trials.

We sought to quantify the external validity of the various ongoing trials to a middle-aged and elderly West-European population. Specifically, we were interested to quantify what proportion of this study population would be eligible to participate in these trials and how many of those eligible are from high-risk categories.

# Methods

Extensive methods are available in the **Online Resource**.

Briefly, for this study we screened [www.clinicaltrials.gov](http://www.clinicaltrials.gov) for ongoing phase III trials focused on vaccine development against SARS-CoV-2 and COVID-19.

The group at high risk of severe COVID-19 was defined according to the criteria of the Dutch National Institute for Public Health and the Environment (RIVM) [1], and included participants aged 70 or higher, and participants with asthma and COPD, diabetes, cancer, participants with current use of antineoplastic and immunosuppressive agents, obesity, end-stage kidney disease, liver steatosis and cirrhosis, cardiac diseases.

We carried out our analyses in the population-based Rotterdam Study [2] and used data collected from 2009 to 2014, which yielded 7162 persons (mean age 70 years, 58% women) for analysis (**Online Resource Table 1**). These calendar-years were chosen such to maximize the number of living participants as well as their available data. Data on the comorbidities was ascertained during the in-person examinations complemented by automated linkage of medical and pharmacy records to our study database.

We applied eligibility criteria from each separate trial to our study population and calculated the following proportions: the proportion of participants eligible for any trial, and for each trial separately, the number of high-risk individuals in our study eligible for any trial, and for each trial separately.

We performed two complementary analyses and calculated the abovementioned proportions in each analysis separately. These two analyses differed with respect to the interpretation of an eligibility criterion that was not always explicitly specified in the various trial protocols. This criterion was often stated as follows: *'preexisting (un)stable disease', 'an acute course of disease', or 'other medical or psychiatric condition or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study'*. In our dataset, we operationalized this criterion as follows: diagnosis of dementia, diagnosis of moderate to severe COPD, current clinically significant depressive symptoms, abnormal kidney function, current liver disease (defined as liver steatosis, and liver cirrhosis) or a new diagnosis within the preceding three months for the following conditions: stroke, cancer, (including antineoplastic agents), diabetes mellitus, COPD, cardiac disease (heart failure, myocardial infarct, atrial defibrillation, and revascularisation). In the first analysis, we included everyone as eligible, who met this operationalization and in the second analysis, we excluded anyone who met this operationalization.

Finally, in sensitivity analyses we incrementally restricted the study population to persons aged over 60, 70, and 80 years.

# Results

**Table 1** presents the exclusion criteria from the 9 included trials, and we note that seven of these mentioned the eligibility criterion of ‘acute’ or ‘unstable preexisting’ disease without further specification.

97% (N=6945) of the total Rotterdam Study participants would be eligible for any trial in the first analysis, while this percentage dropped to 43% (N=3107) in the second analysis. Among the 5781 participants at high-risk of severe COVID-19, 96% (N=5564) would be eligible for any trial in the first analysis and 36% (N=2102) in the second analysis (**Figure 1**).

**Figure 2A** shows the percentages for the two analyses for each trial separately. Whereas in the first analysis the proportion included for the most inclusive trial was 97%, this number dropped considerably in the second analysis to 43%. **Figure 2B** shows the corresponding numbers from participants at high-risk of severe COVID-19. Finally, sensitivity analyses revealed similar patterns at various age cut-offs (**Online Resource Figure 1**).

## Discussion

In a middle-aged and elderly population in the Netherlands from predominantly West-European descent, we found that 97% of this population would be eligible to participate in any of the nine currently ongoing vaccine trials against SARS-CoV-2. For persons at high-risk of severe COVID-19, the eligibility for any trial was 96%. Importantly, applying stricter exclusion based on the criterion ‘acute’ or ‘unstable preexisting’ disease drastically reduced the eligibility for any trial to 43% of the entire study population and 36% of the high-risk individuals.

External validity is the extent to which findings from one study are applicable to target populations not included in the actual study. For currently ongoing vaccine trials, it remains unclear to what extent their included study population actually intended populations for these vaccines. In our community-based sample of middle-aged and elderly, we found that 97% of our total study population and among these, 96% of the high-risk population would be eligible for at least one ongoing phase III vaccine trial against SARS-CoV-2. Moreover, most trials individually had eligibility proportions exceeding 75%, with the exceptions of the Biotec and Petrovax trials, primarily due to their stricter exclusion criteria which were exactly specified in detail. Importantly, the other seven trials with seemingly high eligibility applied a similar exclusion criterion, but did not explicitly specify this further. In our first analysis, we therefore counted as eligible all participants if their possible exclusion could not be pinpointed towards an *explicitly specified* exclusion criterion. For our second analysis, however, we operationalized these unspecified criteria and excluded participants meeting this operationalization. We then found that eligibility proportions for individual trials dropped drastically to at most 43%. These findings demonstrate that any trial showing efficacy of their vaccine should take utmost care to detail exactly which persons were recruited into the trial and more importantly which persons were not included or remained underrepresented.

The population of the Rotterdam Study is a lower-middle class population of primarily European descent. Previously, this population has shown good generalizability to the population of the Netherlands [3-5].

Another important metric in this regard is the response rate, which has continuously exceeded 70% for the Rotterdam Study [2]. This is a major strength of our study which makes it not only population-based but also population-representative, and far exceeds response rates for other larger efforts ongoing worldwide [6]. Notwithstanding these considerations, the drastic drop in eligibility for the stricter criterion in the second analysis would likely have been of the same magnitude in any other population, irrespective of geographical or ethnic setting or response rate.

In conclusion, we found that eligibility for ongoing vaccine trials against SARS-CoV-2 can reduce by half depending on interpretation and application of a single unspecified exclusion criterion. This indicates the importance of developing clinical recommendations that are applied to the appropriate target populations, including or excluding high-risk populations, and cautions against ad hoc wide-spread use of any effective vaccine.

## **Declarations**

### **Funding**

The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. The authors are grateful to the study participants, the staff from the Rotterdam Study and the participating general practitioners and pharmacists.

### **Conflicts of interest**

Authors declare no conflicts of interests.

### **Availability of data and material**

Data can be obtained upon request. Requests should be directed towards the management team of the Rotterdam Study ([secretariat.epi@erasmusmc.nl](mailto:secretariat.epi@erasmusmc.nl)), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

### **Authors' contributions**

Albert Hofman, Jaap Goudsmit and M. Arfan Ikram conceptualized the analysis. N. Terzikhan and M. Arfan Ikram did the data analysis and prepared the first draft of the manuscript. All authors were involved in the interpretation of the results and revision of the final manuscript.

### **Ethical statement**

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration number EMC1712001. The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; [www.trialregister.nl](http://www.trialregister.nl)) and into the WHO International Clinical Trials Registry Platform (ICTRP; [www.who.int/ictrp/network/primary/en/](http://www.who.int/ictrp/network/primary/en/)) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

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## Table

**Table 1. Overview of the included trials with the selection of exclusion criteria per trial, for which data from the Rotterdam Study was available.**

**Trial sponsor** (Collaborator)  
*Clinical Trials.gov identifier*

<b>ModernaTX, Inc.</b> (Biomedical Advanced Research and Development Authority and NIAID)	<b>Janssen Vaccines &amp; Prevention B.V.</b>	<b>Butantan Institute</b> (Sinovac Life Sciences Co., Ltd.)
<i>NCT04470427</i>	<i>NCT04505722</i>	<i>NCT04456595</i>
Immunodeficient state and therapy* Acute or unstable disease, not further specified	Immunodeficient state and therapy* Acute or unstable disease, not further specified	Immunodeficient state and therapy* Current diagnosis/treatment for cancer Alcohol dependency Depressive symptoms Dementia diagnosis Acute or unstable disease, not further specified
<b>AstraZeneca</b> (Iqvia Pty Ltd)	<b>BioNTech SE</b> (Pfizer)	<b>Novavax</b>
<i>NCT04516746</i>	<i>NCT04368728</i>	<i>NCT04583995</i>
Immunodeficient state and therapy* History of malignancy‡	Immunodeficient state and therapy* Age >85 years	Immunodeficient state and therapy* Current diagnosis/treatment for cancer Alcohol dependency
Acute or unstable disease, not further specified	Dementia diagnosis Depression Acute or unstable disease, not further specified	Continuous use of anticoagulants¶ History of chronic neurological disorders that have required prior specialist medical review† Age >84 years Acute or unstable disease, not further specified
<b>Gamaleya Research Institute &amp; Health Ministry of the Russian Federation</b> (Government of the city of Moscow and CRO)	<b>China National Biotec Group Company Limited</b> (G42 Healthcare company, Abu Dhabi Health Services Company, Wuhan Institute of Biological Products Co., Ltd and Beijing Institute of Biological Products Co., Ltd)	<b>NPO Petrovax</b> (CanSino Biologics Inc.)
<i>NCT04530396</i>	<i>NCT04510207</i>	<i>NCT04540419</i>
Immunodeficient state and therapy* History of neoplasms Alcohol	Immunodeficient state and therapy* DiaBP >90 mmHg SysBP >150 mmHg	Immunodeficient state and therapy* History of malignancies   Age >85 years

dependency		
Acute stroke the previous year	Dementia diagnosis	History of Diabetes Mellitus
Acute cardiac disease in the previous year	Acute or unstable disease, as specified in the footnote §	18.5 < BMI >30
Acute or unstable disease, not further specified		SysBP >139 mmHg DiaBP >90 mmHg
		SysBP <100 mmHg DiaBP <60 mmHg
		Acute or unstable disease, as specified in the footnote §

BMI: Body mass index; DiaBP: Diastolic blood pressure; SysBP: Systolic blood pressure

\*Immunosuppressive and immunomodulatory medications: Immunosuppressive medications, corticosteroid use and antineoplastic agents; ICD10-codes: L04, L01, H01.

†History of chronic neurological disorders that have required prior specialist medical review: Dementia, Parkinson Disease, Stroke in the previous year.

‡Except childhood and prostate cancer and uterine cervical carcinoma

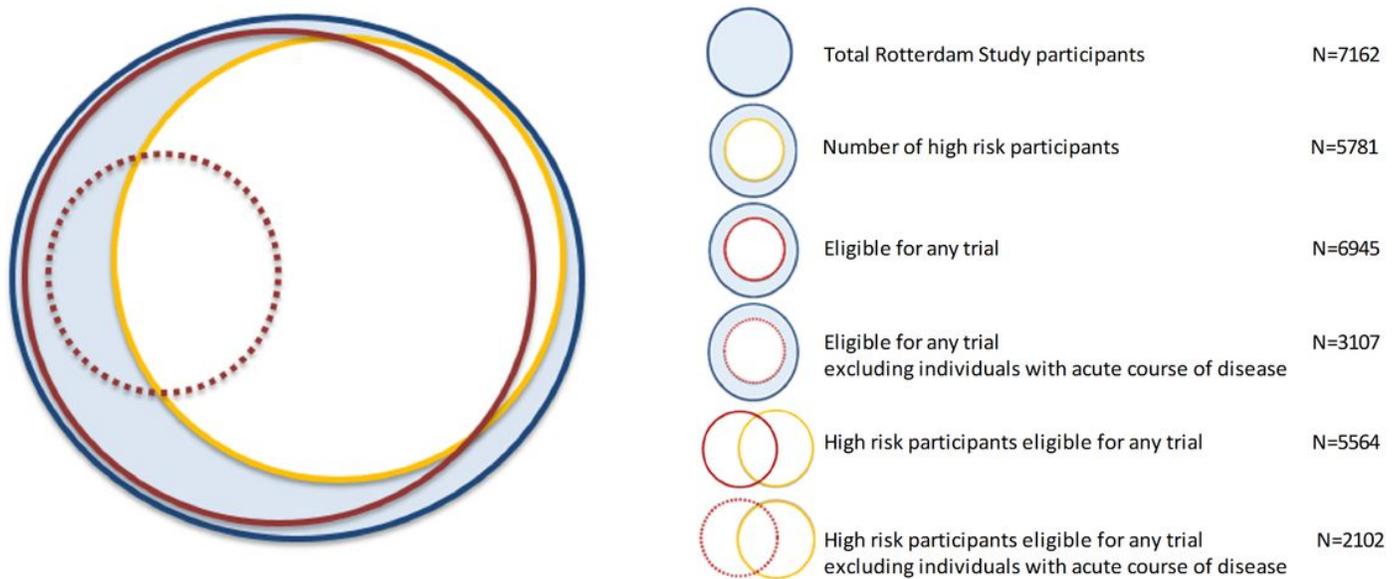
|| Including history of lymphoma and history of haematopoietic cancer

¶ ICD10- codes: B01AA and B01AE.

§Acute or unstable disease is defined as: Dementia diagnosis, diagnosis of moderate to severe Chronic obstructive pulmonary disease (COPD), current depressive symptoms, abnormal kidney function (defined as estimated Glomerular Filtration Rate <60 millilitre/minute), current liver disease (defined as liver steatosis, and liver cirrhosis).

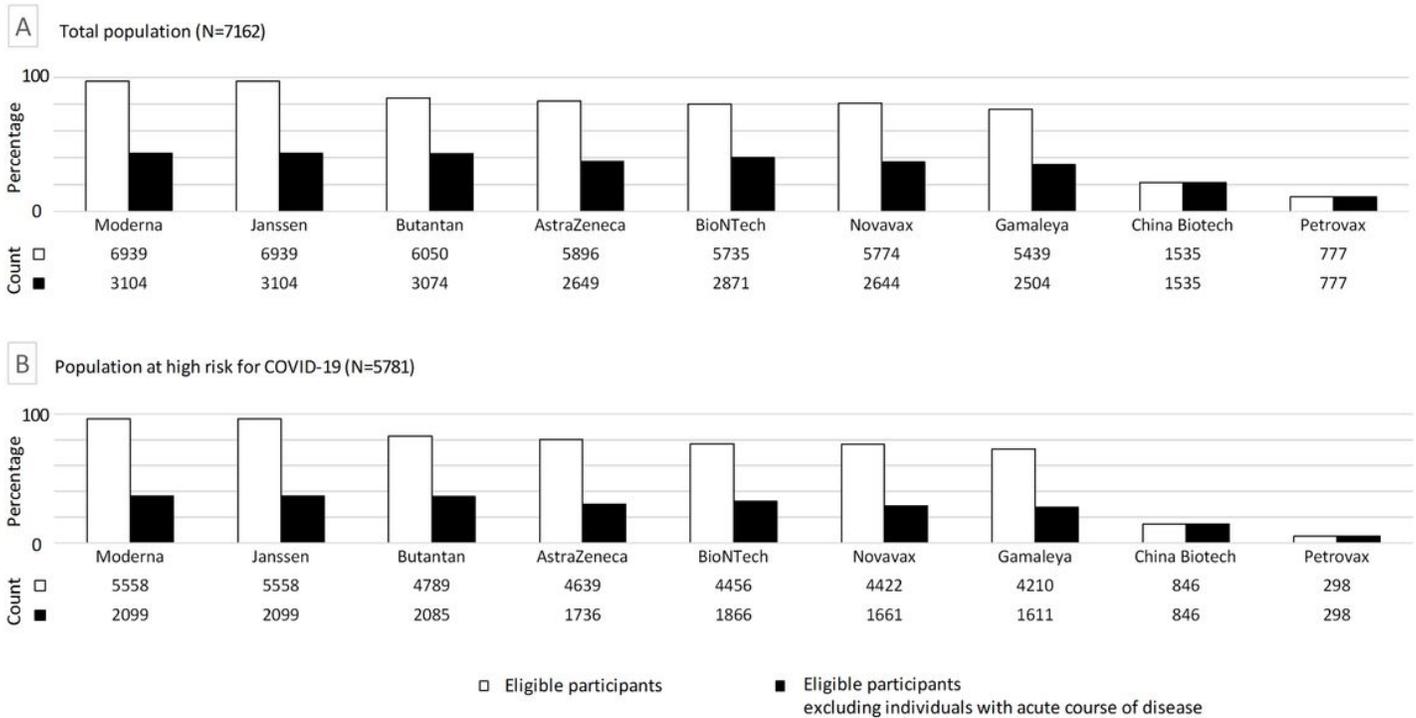
Diagnosis of the following within the previous 3 months: stroke, cancer (including antineoplastic agents), diabetes mellitus, COPD, cardiac disease (heart failure, myocardial infarct, atrial defibrillation, and revascularisation).

## Figures



**Figure 1**

Venn diagram for the proportion of eligible Rotterdam Study participants for any trial. The colours are coded as follows: blue circle: total study population; yellow circle: persons at high risk of severe COVID-19; red circle: persons eligible for any trial in the first analysis; red dotted circle: persons eligible for any trial in the second analysis, in which individuals with acute course of disease were excluded.



**Figure 2**

The number and proportion of eligibility from the Rotterdam Study population for ongoing clinical phase III trials on a vaccine against SARS-CoV-2. Black bars indicate data from the first analysis; white bars indicate data from the second analysis. The difference between these two analyses is the operationalization, and thus inclusion or exclusion, of the eligibility criteria '(un)stable disease', 'acute course of disease', or 'other condition increasing risk of participation'. A) total population of the Rotterdam Study and B) individuals at high risk of severe COVID-19.