

COVID-19 sub-programme vaccine studies

Summary of the advice on the utility and necessity of a CHIM for COVID-19 in the Netherlands

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Colophon

ZonMw is The Netherlands Organisation for Health Research and Development



Progress requires research and development. ZonMw funds health research and stimulates use of the knowledge developed to help improve health and healthcare.

ZonMw's main commissioning organisations are the Ministry of Health, Welfare and Sport and the Netherlands Organisation for Scientific Research.

For further information on this publication or the programme, visit the [website](#) or contact through e-mail covid19@zonmw.nl.

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ZonMw (the Netherlands Organisation for Health Research and Development) has written this advisory report on behalf of the Ministry of Health, Welfare and Sport (VWS). It describes the advice about the utility of and necessity for a controlled human infection model (CHIM) for COVID-19 in the Netherlands. The report was written based on the advice given by a committee explicitly appointed for this objective from the COVID-19 programme. The advice is based on WHO documents and the input of international experts. The committee has weighed up the scientific and societal benefits of a CHIM for COVID-19 against the risks and consequences associated with a deliberate infection of healthy study subjects with the SARS-CoV-2 virus.

The committee members are unanimously of the opinion that a CHIM can provide valuable information with a greater level of detail in a relatively efficient manner. Considering the current state of the pandemic, alternative possibilities to acquire knowledge, available knowledge about COVID-19 and the possibilities for treating a SARS-CoV-2 infection, the committee members are divided about the question as to whether there is sufficient need to develop a CHIM for COVID-19 at this moment in time.

The balance between utility and necessity can change, dependent on the developments with respect to the pandemic. Therefore, the committee is of the opinion that ongoing attention is required regarding the setting up of a CHIM. That entails starting to make preparations now. This is a vital step to ensure that immediate action can be taken in the event that a CHIM will have a convincing added value and its necessity is evident and undisputed.

1 Introduction

1.1 Commission Ministry of Health, Welfare and Sport

On 8 December 2020, the Ministry of Health, Welfare and Sport requested ZonMw, the Dutch organization for Health research and development, to make preparations for the development of a CHIM for COVID-19. ZonMw works on improving prevention, healthcare and health by encouraging and funding research, development and implementation. The request was realised by the subprogramme vaccine studies of the larger COVID-19 programme, which is aimed at developing the knowledge needed in the Netherlands for the optimum deployment of COVID-19 vaccinations.

As part of the preparations, the Ministry of Health, Welfare and Sport requested ZonMw to elaborate on the utility and necessity of a CHIM. ZonMw was also requested to include the possibilities of the model for future outbreaks. The Ministry of Health, Welfare and Sport considers that the development of a CHIM fits within its policy of facilitating a Clinical Trial Network. The intention is that all knowledge institutions in the Netherlands can work with such a model; the model facilitates clinical research in the area of therapy and vaccine development. Currently for COVID-19 and in the future, possibly for other diseases too.

As a result of this request, an advisory report was written about the general utility of and necessity for a CHIM in the Netherlands. A separate ZonMw committee was appointed for the formulation of this advice.

1.2 Controlled Human Infection Model

In a CHIM, healthy study subjects are deliberately exposed to an infectious agent under controlled conditions. In the first phase of the study, healthy study subjects are infected with increasing doses of the SARS-CoV-2 virus, which provides the basis for follow-up research. With a CHIM, the pathophysiology of the infection can be accurately described, and the kinetics of virus particle excretion can be characterised and related to symptoms and transmission potential. In addition, the build-up of protective antibodies (and cellular immunity) can be followed. Ultimately, this model can be deployed to determine more quickly which vaccines and treatments work. The model can also generate knowledge for, amongst other things, defining antibody titers and the degree of cellular immunity, which provide protection as an “immunity passport”. These can also be used as a guideline value for vaccine development.

A CHIM offers a unique opportunity to collect valuable information about various aspects of infectious diseases by using a small group of participants in a controlled manner. However, the use of a CHIM leads to various dilemmas in the area of safety, because study subjects are deliberately exposed to an infectious agent. That presents the risk of severe complications. One way of minimising this risk is a rescue treatment, but no rescue treatment for COVID-19 is currently available.

2 Outcomes ZonMw process

2.1 Relevance

Within the committee, various opinions exist concerning the relevance of developing a CHIM for COVID-19 in the Netherlands at this moment in time. The argumentation is as follows:

Societal value

The committee is of the opinion that, in principle, a CHIM for COVID-19 is a good way of rapidly filling gaps in our knowledge while using relatively few participants. However, the added value for medical research and the necessity of a CHIM are not self-evident for all committee members.

With a CHIM, knowledge questions such as the kinetics of virus particle excretion, correlates of protection and vaccine-induced immunity can be described in greater detail in a relatively efficient manner than would be the case with an epidemiological study. The committee nevertheless doubts whether this knowledge can be implemented in practice. Furthermore, the committee is not

unanimously convinced that these knowledge questions, such as the kinetics of virus particle excretion, correlates of protection and vaccine-induced immunity, can only be answered satisfactorily and in sufficient detail by means of a CHIM.

The committee thinks it is a good choice to only include healthy young study subjects in a CHIM, because this group has the least risk of complications as a consequence of COVID-19. The committee is of the opinion that it is important to be able to extrapolate the research results, because the results should be relevant for clinical practice. However, it depends upon the research question posed as to whether the results can indeed be extrapolated to the target group and are, in fact, applicable to it. Not all results in healthy young study subjects can be extrapolated to elderly people and risk groups.

The committee has doubts about the relevance of a CHIM considering a situation where the population is vaccinated or is (increasingly) being vaccinated and the number of infections is relatively low.

Variants

A CHIM offers the possibility of answering questions concerning new variants of the SARS-CoV-2 virus, so-called variants of concern. However, developing an agent for a new variant currently takes 3 to 4 months. The committee doubts whether a CHIM can play a valuable role in research into new variants given the speed and diversity with which new virus variants appear and the rate at which mRNA and viral vector vaccines can be adjusted. Another complicating factor is that too little is known about the variant's clinical presentation, which entails risks.

Long COVID

The committee has concerns about the uncertainty with respect to the development of Long COVID. At present, there is limited scientific research available concerning the risk of Long COVID and about the consequences of Long COVID for human health. Whereas on the basis of the available data, some estimate that the risk to young adults is low and therefore acceptable, the committee weighs these facts differently with respect to the risks for Long COVID and the possible health damage this causes.

2.2 Further considerations

Following the relevance determination, the committee also offers the following considerations:

Social context

Controlled trials yield relevant information if the conditions in the laboratory approach those in everyday circumstances. The extent to which the SARS-CoV-2 virus must be biologically, socially and politically contained for it to be investigated in a controlled trial would mean that the research results might not be relevant for current and future measures to prevent, limit and manage COVID-19. For science to be relevant to the public, a more adaptive approach is required than is possible in a CHIM.

Timing

The committee argues that the development of a CHIM for COVID-19 at this moment in time possibly has a limited relevance. At the same time, the committee sees potential in the development of a CHIM for the future. The committee is aware that delaying the setting up of a CHIM is associated with risks, for example if a new severe variant develops. If there are urgent questions that must be rapidly answered while a CHIM still needs to be set up, then this would mean that those urgent questions cannot be answered quickly. Furthermore, a CHIM for COVID-19 would teach us a lot that is applicable for other infectious diseases. Yet, the considerable amount of diligence necessary for setting up a CHIM for COVID-19 could be diametrically opposed to the required speed with which studies need to be performed to bring the pandemic situation under control.

National embedding

Important aspects of a CHIM for COVID-19 in the Netherlands is that it is nationally embedded, there is sufficient collaboration with other institutes and the data is made available. As the funding comes from public funds, it is important that the setup and funding are transparent and provide room for the various actors in the Netherlands.

Positioning compared to other studies

An important question for the committee is how such a model must be positioned in the pandemic setting. This is particularly the case if a dynamic occurs in which developments proceed very quickly and when sufficient time and space is made available to answer certain urgent questions but not others. How can a CHIM be ideally positioned in the context of future studies? It is important to ensure that we learn from the current process and that in future studies or in the case of other infections, efficient decision-making is possible.

Need to communicate with the public

Involving the community is vitally important for the acceptance of the model. Due to the lack of a rescue treatment, the committee expects that realising a CHIM for COVID-19 will be controversial and that could lead to a lot of media attention. Therefore, it is crucial that issues concerning a CHIM for COVID-19 do not influence the willingness to be vaccinated. This means that researchers, funding bodies and the government need to develop a good communication strategy for informing the general public.

3 Advice to Ministry of Health, Welfare and Sport

Based on existing WHO documentation and the input of international experts, the committee has made a deliberation about the utility of and necessity for a CHIM for COVID-19 in the Netherlands.

The committee members are unanimously of the opinion that a CHIM can provide valuable information with a greater level of detail in a relatively efficient manner. The committee members are divided about the question as to whether there is, at present, sufficient need to develop a CHIM for COVID-19, given the current state of the pandemic, alternative possibilities to acquire knowledge, available knowledge about COVID-19 and possibilities for treatment of a SARS-CoV-2 infection. Various committee members hold the view that the scientific and societal value of a CHIM for COVID-19 at this moment in time does not outweigh the risks and consequences associated with a deliberate infection of healthy study subjects with the SARS-CoV-2 virus. In combination with the risk of Long COVID, important other considerations in this deliberation are the committee's doubts about the urgency of the research results and about the possibilities to extrapolate the results that can be obtained with this model and the available alternatives. Other committee members, however, are of the view that, at this moment, the scientific and societal value of a CHIM for COVID-19 does outweigh its risks and consequences. The contribution of a CHIM in developing the knowledge needed for future follow-up studies with new vaccines and new variants and in preparing for future pandemics weighs heavily in the opinion of these committee members.

The balance between utility and necessity can change, dependent on the developments with respect to the pandemic. Therefore, the committee is of the opinion that ongoing attention is required regarding the setting up of a CHIM. That entails starting to make preparations now. This is a vital step to ensure that immediate action can be taken in the event that a CHIM will have a convincing added value and its necessity is evident and undisputed.

Progress requires research and development. ZonMw funds health research and also facilitates the use of the knowledge developed so that care and health can be improved. The principal commissioners of ZonMw are the Ministry of Health, Welfare and Sport and NWO.

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