

Preliminary report and investigation into the benefit and necessity of an early phase infection unit in the Netherlands and addendum

Preliminary report and investigation into the benefit and necessity of an early phase infection unit in the Netherlands

Ploemen Life Science Consultancy

Dr. Ivo Ploemen, MBA

Note: This report is written and delivered by Ploemen Life Science Consultancy as commissioned by ZonMw. The findings of this report follow from in-depth interviews with private parties and academic experts, public sources and academic literature, as well as information received under embargo from subject matter experts. All information is gathered in good faith from these secondary sources, the accuracy of which cannot always be guaranteed. As such Ploemen Life Science Consultancy can accept no liability whatsoever for actions taken based on any information in this report. The findings and recommendations in this preliminary report reflect the combined input from the sources consulted.

Contact information:

Dr. Ivo Ploemen, MBA www.plsc.nl Ivo.ploemen@plsc.nl

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1. List of key terms, names and abbreviations used in this report

Terms, Names and Abbreviations	Definition
BAL	Bronchoalveolar lavage (BAL) (also known as bronchoalveolar washing) is a diagnostic method of the lower respiratory system in which a bronchoscope is passed through the mouth or nose into an appropriate airway in the lungs, with a measured amount of fluid introduced and then collected for examination.
BMGF	Bill and Melinda Gates Foundation.
BSL-3	Biosafety level 3: Safety regimen under which work can be performed with highly contagious pathogens.
CBG	College ter Beoordeling van Geneesmiddelen, independent agency charged with the admission of drugs and vaccines to the market.
CCMO	Centrale Commissie Mensgebonden Onderzoek; Committee charged with evaluating and guaranteeing the protection of volunteers involved in clinical trials.
CDMO	Contract Development Manufacturing Organization; a commercial service provider which offers the development and or production of biologicals from sponsors.
CEPI	Coalition for Epidemic Preparedness Innovations, a global partnership launched in 2017 to develop vaccines to stop future endemics.
CHDR	Centre for Human Drug Research, a foundation specialized in innovative clinical drug research.
CHIM	Controlled Human Infection Model: In a Controlled Human Infection Model (CHIM) study, a well-characterized strain of an infectious agent is given to carefully selected adult volunteers in order to better understand human diseases, its transmission, and find new ways to prevent and treat them.
CRO	Contract Research Organization: A commercial service provider which offers services (e.g. clinical sample analysis, data analysis) to sponsors
DBM process	Design Build Manufacture Process: Procedure in which a contractor is responsible for planning, leading, executing, supervising and inspecting a building construction project.
ELISPOT	Enzyme-linked immune absorbent spot (ELISpot) is a type of assay that focusses on quantitatively measuring the frequency of cytokine secretion in a single cell.
EMA	European Medicine Agency: regulatory agency charged with amongst the evaluation and admission of drugs and vaccines to the European market.
efficacy endpoints	A clinical or laboratory outcome measured in an individual in a clinical trial that provides information on whether the treatment or intervention has been efficacious.
FDA	United States Food and Drug Administration: Responsible for protecting the public health by ensuring amongst the safety, efficacy and security of human and veterinary drugs and biological products.
GCP	Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects.

GDPR	The General Data Protection Regulation (GDPR) is a legal framework that sets guidelines for the collection and processing of personal information from individuals who live in the European Union (EU).
GLP	Good laboratory practice (GLP) is a set of principles intended to assure the quality and integrity of non-clinical laboratory studies that are intended to support research or marketing permits for products regulated by government agencies.
GMP	Good manufacturing practice (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.
GSP	Good Scientific Practice (GSP) sets out the principles, values and the standards of behavior and practice for the Healthcare Science workforce. These standards and values must be achieved and maintained in the delivery of work activities, the provision of care and personal conduct.
hVIVO	Commercial service provider (United Kingdom) specialized in amongst CHIM studies.
Imperial College	Imperial College London is a University setting which specializes in amongst CHIM studies.
inpatient	A patient or volunteer which goes to a hospital or clinical trial unit and stays there one or more nights, for instance as part of a clinical study.
Morbidity	Refers to having a disease or a symptom of disease, or to the amount of disease within a population. Morbidity also refers to medical problems caused by a treatment.
Mortality	A term also used for death rate, or the number of deaths in a certain group of people in a certain period of time.
MRSA	Methicillin-resistant Staphylococcus aureus (MRSA) infection is caused by a type of staph bacteria that's become resistant to many of the antibiotics used to treat ordinary staph infections.
NIH	National Institute of Health in the USA; medical research agency, supporting scientific studies that turn discovery into health.
outpatient	a patient or volunteer who attends a hospital or a clinical trial unit with no plan to stay beyond the duration of the visit.
PK analytics	Pharmacokinetics is currently defined as the study of the time course of drug absorption, distribution, metabolism, and excretion. Clinical pharmacokinetics is the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient.
SGS	Commercial service provider (amongst in Belgium) specialized in amongst CHIM studies.
Study endpoint	An event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial.
WHO	World Health Organization.

2. Executive Summary

The COVID-19 pandemic has made it clear that the Netherlands was not ready to respond swiftly by testing new therapies and vaccines in the combat to the spread of the virus. One bottleneck was the absence of a clinical trial unit where specific therapeutic and preventative therapies in humans, could be studied in a suitable environment (infrastructure).

This preliminary report set out with the aim to investigate whether there is a benefit and a need for the establishment of an early phase infection unit in the Netherlands. By interviewing key experts from academia and industry, it became evident that there is a need and a benefit for a new highly specialized facility that can perform high-quality registration-grade early phase clinical trials in infectious diseases, both for drug and vaccine development, including controlled human infection studies. Such a unit would benefit the clinical trial capacity needed to perform essential clinical studies in case of a pandemic. Furthermore, outside a pandemic this unit can facilitate clinical studies to a variety of infectious diseases.

The early phase infection unit is envisioned to be seed funded with public funds. By combining investigator-initiated studies (at cost) in addition to commercial sponsor-initiated studies, the unit is envisioned to operate financially independent, shortly after its launch. The unit could be governed as a foundation, or alternatively a commercial entity with a public task in case of pandemics. Independent of its eventual legal status, the unit is proposed to be lead by a dedicated team of specialized and business-savvy experts. For its success, and specifically for the performance of sponsor-initiated studies, it is considered essential that the unit will be run with the efficiency of a commercial entity. Given that the unit is proposed to be equipped for the performance of amongst CHIM (Controlled human Infection Models) studies, under stringent biosafety (and containment) levels, an early phase infection unit should be constructed as a new building (infrastructure). Such a unit would have both inpatient rooms under BSL-3 regimen and outpatient facilities for the performance of for instance vaccine studies. The primary focus of the unit is suggested to be on infectious disease with a pandemic potential or current pandemic effect. Furthermore, clinical studies assessing disease indications for which there is a high need for a vaccine or therapy for Public Health, or Global Health could be performed. The eventual focus of the infection unit in terms of pathogen or disease indication studied would follow the needs of Academia, Industry and Public/Global health, which might shift over time.

The eventual success of the infection unit is dependent on a broad infrastructure. For instance, the production of challenge agents (CHIM studies) is likely in need of outsourcing to expertised labs. Clinical (sample) analytics could (in part) be outsourced to either specialized Academic centers of excellence, or commercial service organizations which have established validated assays. A close relationship with other international early phase infection units such as SGS, the NIH and Imperial College, as well as non-governmental agencies such as the BMGF, CEPI and the WHO can further contribute to the establishment and benefit of an early phase infection unit in the Netherlands.

This preliminary report includes initial cost estimates for the build of a new early phase infection unit, its potential revenues and infrastructural features as well as a preliminary notion on the need for dedicated staffing and the preliminary requisites to its location. The new unit could possibly be established as a separate entity under an existing clinical trial unit, de-risking its development, piggybacking on its (immaterial) infrastructure and expertise.

This preliminary report concludes with a number of suggestions and recommendations to further propel the business case and provide guidance on the inception of an early phase infection unit in the Netherlands.

Management Samenvatting

De COVID-19-pandemie heeft duidelijk gemaakt dat Nederland niet klaar was om direct en adequaat te reageren met nieuwe therapieën en vaccins in de strijd tegen de uitbraak. Een van de knelpunten was het ontbreken van een ‘clinical trial unit’ toegerust voor de bestudering van therapeutische en preventieve therapieën bij mensen in een daarvoor geschikte omgeving (infrastructuur).

Dit rapport heeft tot doel nut en noodzaak van een vroege fase infectie unit in Nederland initieel te inventariseren en verder te onderzoeken. Uit interviews met experts uit de Academie en de Industrie wordt duidelijk dat er een behoefte is aan een nieuwe, zeer gespecialiseerde faciliteit die hoogwaardige klinische onderzoek kan uitvoeren naar infectieziekten, zowel voor de ontwikkeling van geneesmiddelen als voor vaccins, inclusief gecontroleerde humane infectiestudies. In het geval van een pandemie zouden essentiële klinische studies in deze unit kunnen worden uitgevoerd. Daarnaast kan deze unit, buiten een pandemie om, klinische studies naar een verscheidenheid aan infectieziekten faciliteren en bespoedigen.

De vroege fase infectie unit is beoogd te worden gefinancierd met publieke gelden. Hierbij kunnen studies vanuit de Academie mogelijk tegen kostprijs worden uitgevoerd naast de uitvoer van commerciële studies geïnitieerd door de industrie. De unit is beoogd om een aantal jaar na de start financieel onafhankelijk te kunnen draaien. De unit zou bijvoorbeeld bestuurd kunnen worden vanuit een stichting, of alternatief vanuit een commerciële service provider met een publieke taak in geval van pandemieën. Voor het succes van de unit is het essentieel dat het leiderschap bestaat uit een kleine groep experts, waarbij ook de commerciële kwaliteiten gewaarborgd zijn. Dit is met name essentieel voor de uitvoer van door sponsors geïnitieerde studies. De unit is beoogd te worden toegerust voor de uitvoer van gecontroleerde humane infectie studies. Dit stelt specifieke eisen aan het gebouw. De unit moet zijn toegerust voor de uitvoer van zowel intramurale als poliklinische studies. De unit zou zich primair moeten richten op het tegengaan en onderzoeken van infectieziekten met een pandemisch potentieel of anderzijds een pandemisch effect. Anderzijds kan de unit worden gebruikt voor studies naar ziekte indicaties en infecties waarbij er een hoge nood is voor een vaccin of een therapeutisch middel. De uiteindelijke focus van de unit kan verschuiven over de tijd, naargelang (nieuwe) infectieziekten meer van belang worden.

Voor het uiteindelijke succes is de infectie unit afhankelijk van een brede infrastructuur. Zo moeten er ‘challenge agents’ worden gemaakt voor de humane infectie studies wat waarschijnlijk zal moeten worden uitbesteed bij gespecialiseerde laboratoria. Klinische sample analyse kan tevens (deels) worden uitbesteed bij gespecialiseerde universiteiten of commerciële partijen. Een hechte relatie met andere internationale infectie units zoals SGS, de NIH en Imperial College London, evenals NGO’s zoals de BMGF, CEPI en de WHO zal verder bijdragen aan het succes van de unit.

Dit rapport bevat initiële kostenramingen omtrent de bouw van een nieuwe infectie unit, de essentiële middelen, de potentiële revenuen, en infrastructurele kenmerken. Waar mogelijk zou de unit kunnen worden opgericht onder een bestaande clinical trial unit., waarbij deze kan meeliften op de reeds bestaande infrastructuur en expertise.

Dit rapport sluit af met een aantal suggesties en aanbevelingen voor de verdere ontwikkeling van de business case en geeft richting aan de start van een vroege fase infectie unit in Nederland.

3. Background

The assignment

As put forward by ZonMw, in the assignment from which this preliminary report and investigation results, the current COVID-19 pandemic has made it clear that the Netherlands was not ready to respond immediately with adequate therapies for patients who became infected with the virus or to vaccinate preventively. There are many causes to this. One bottleneck was the absence of a clinical trial unit where specific therapeutic and preventative therapies in humans, could be studied in a suitable environment (infrastructure). Such a unit would ideally have met the requirements of the safety for the research participants with secured processes for the relevant laws and regulations and/or protocols/guidelines to set up such studies quickly. Due to the lack of such a unit, which would be equipped to scale up immediately in case of need (pandemic preparedness), Dutch inventions were studied abroad and there was no important connection with companies and knowledge institutions.

This report serves to investigate and advice on the benefit and necessity for the establishment of an early phase clinical infection unit in the Netherlands. Central to the preliminary study is mapping the need and necessity of an infection unit, its requisites and features, scenario's for business models and governance.

This report

The interest in infectious disease, the mitigation of its spread, the development of new therapies and vaccines has become a widely debated topic following the SARS-CoV-2 pandemic. Prior to investigating if, and by which means the establishment of an early phase infection unit in the Netherlands is of essential importance to the Dutch population, Academia and Industry, it is essential to set the scene to which the question for the need of an infection unit was most recently raised. To this end, the report starts by briefly providing some background on the COVID-19 pandemic, therapeutic drugs and vaccines and their development, the manner by which SARS-CoV-2 vaccines have been granted emergency licensure, the role of the Netherlands in COVID-19 clinical trials thus far, the current and historic role of the Netherlands in the field of infectious disease, and the use of Controlled Human Infection Models (CHIM). CHIM studies are in many ways unique and different from classical clinical field trials. The requisites of performing a CHIM study might justify a case for the establishment of an early phase infection unit. Notwithstanding, a justification for such a unit might also results from a broader need from clinical trials in infectious disease, aimed at either understanding the pathogenesis of disease, methodology or development of drugs and vaccines and the correlates of protection.

The COVID-19 pandemic

The pandemic of coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, poses an extraordinary threat to global public health, socioeconomic stability, food security and other social goods (World Health Organisation, 2021). COVID-19 has shown how an infectious disease can sweep the globe in weeks and, in the space of a few months, set back sustainable development by years (The Independent Panel, 2021). By all measures, the impact of the pandemic on a global scale, has been massive:

- 196 million people were confirmed infected and more than 4 million have died in 223 countries territories and areas (World Health Organisation, 2021)

- At least 17,000 health workers died from COVID-19 during the pandemic first year (Amnesty International, 2021)
- US \$ 10 trillion of output is expected to be lost by the end of 2021, and US \$ 22 trillion in the period 2020-2025 – the deepest shock to the global economy since the Second World War and the largest simultaneous contraction of national economies since the great Depression of 1930-32.
- At the highest point in 2020, 90% of schoolchildren were unable to attend school.
- 10 million more girls are at risk of early marriage because of the pandemic.
- 115-125 million people have been pushed into extreme poverty.

In the Netherlands, a total of

- 17,815 COVID-19 patients died as from the start of the measurement by July 29 2021 (source RIVM)
- 1,859,199 infections have been reported by July 29 2021 total (source RIVM)

In terms of the impact of the COVID-19 pandemic on society, the Netherlands has not been spared. According to a recent report from NL Health Holland (NL Health Holland, 2021) the Dutch society spends a staggering 100 million euro's on managing the crisis every day.

Therapeutic drugs and vaccines

Infections can be combatted by two main types of (biological) interventions. A vaccine, typically provides protection to healthy individuals so that these may not get infected (or ill) from the pathogen. A therapeutic drug (e.g either directly acting on a pathogen, its replication, or through for instance an immunomodulatory effect) is aimed at combatting the infection and/or its symptoms. Although vaccines and therapeutic drugs are the main approaches in the combat with infectious disease, prophylactic drugs and compounds classified as medical devices might also contribute in combatting the infection. For the development of vaccines and therapeutic drugs, it is essential to take note of the clinical development phases. Specifically, a Phase I comprises a dose ranging of the compound in healthy volunteers for safety. A Phase II study comprises the testing of the compound on participants to assess efficacy and side effects and a Phase III study assesses the testing of drugs on participants to assess efficacy, effectiveness and safety. When dealing with a pathogen, and certainly with a pathogen with a high risk of inflicting morbidity (serious sickness) and mortality (death), it is evident that clinical studies, in support of the development of new vaccines and compounds against that pathogen, involve the (potential) follow up of infectious individuals. Depending on the pathogen, there would be a risk for the performance of these studies if these were to be executed in a hospital setting in proximity to patients with underlying disease.

SARS-CoV-2 vaccines

The vaccination of the population with SARS-CoV-2 vaccines, starting with the immunization of the elderly and gradually moving to the younger population, has substantially decreased the incidence of COVID-19. A large number of (candidate) vaccines have been developed in record time aimed to provide protection against the disease. At the moment (July 2021), the Dutch population can be vaccinated with a number of vaccines which received emergency use licensure.

Some of these vaccine concepts are built on the mRNA platform. A platform which, prior to the SARS-CoV-2 pandemic, had never been used in the general population. The speedy development of the SARS-CoV-2 (mRNA) vaccines has been unprecedented. It is important to note that a number of the platforms were built with (partial) public funding (e.g. through CEPI) to battle novel pandemic diseases, then referred to by as Disease X. When it became apparent that COVID-19 would become the Disease X of recent time, the companies which had developed their platforms - aimed at a rapid development of effective and scalable vaccine candidates, thereby supported with public funding - stepped in and developed vaccine concepts in record time. In their development these companies were supported by large amounts of public funding through for instance Operation Warp Speed in the USA. Without public funding, SARS-CoV-2 vaccines would not have been developed in the same timeframe.

The imminent threat of the SARS-CoV-2 infections might have waned somewhat in the Western industrialized world, given the (relatively) high level of protection in the population. Still, with the emergence of new SARS-CoV-2 variants, (existing) vaccines might need to be improved. Furthermore, not all people can be (or want to be) immunized (effectively) and there is a need for (antiviral) medication to combat the infection and decrease the severity of the disease.

CHIM studies and its application in SARS-CoV-2 infection

With the spread of SARS-CoV-2, rigorous public health measures were taken which resulted in low transmission. This brought with it the fear in 2020 that, Phase III clinical trials for vaccines in development would not bring sufficient infection cases to showcase efficacy of the vaccine concept. A world-wide inventory of trial centers with capacity to perform studies in a controlled human infection model, often simply referred to as human challenge studies, was undertaken to assess the potential of organizing challenge trials with hundreds of participants to prove efficacy for a number of vaccines. Suchlike trials would require in-patient facilities with sufficient capacity to house SARS-CoV-2 challenge participants individually for at least 14 days. In the end, this proved not to be necessary as sufficient cases of infection and transmission (mainly in the US and Brazil), warranted efficacy data from Phase III studies.

CHIM studies have been in use for quite some time and they have proven their value in studies assessing therapies and new vaccine concepts for amongst others human rhinovirus, Paratyphoid (enteric fevers), Influenza, Malaria, Pneumococcal carriage, Shigella, E-Coli, Campylobacter, Norovirus, Cholera, Cryptosporidium, Respiratory Syncytial Virus, Dengue, Pertussis, and Mycobacteria (BCG). (Wellcome Trust , 2017). One key feature of a CHIM study, is that a well characterized strain of an infectious agent is administered at a controlled dose and by a specific route to carefully selected adult volunteers. Volunteers are closely monitored for evidence of carriage or infection under medical supervision to anticipate or manage symptoms of disease (Wellcome Trust , 2017).

A report of the WHO from 2020, describing the key criteria for the ethical acceptability of COVID-19 in human challenge studies, highlights that CHIM studies in general have been reported to be particularly valuable for testing vaccines. They can be substantially faster to conduct than vaccine field trials, in part because far fewer participants need to be exposed to experimental vaccines in order to provide (preliminary) estimates of efficacy and safety. Such studies can be used to compare the efficacy of multiple vaccine candidates and thus select the most promising vaccines for larger studies. Well-designed challenge studies might thus not only accelerate COVID-19 vaccine development, but also make it more likely that the vaccines ultimately deployed are more effective.

Challenge studies are also used to study processes of infection and immunity from their inception. They could thus be used to (a) validate tests for immunity (e.g. antibody testing to check if a person has been exposed to the pathogen and is in fact immune) to SARS-CoV-2, (b) identify correlates of immune protection, and (c) investigate the risks of transmission posed by infected individuals. The benefits and use of challenge studies is not restricted to vaccines. Certainly these studies have value in assessing the efficacy of new (therapeutic) drugs. In addition, challenge studies can play an essential role in the study of the interaction between the pathogen and the host. Results from challenge studies could, according to the report from the WHO from 2020, significantly improve the overall public health response to the pandemic. (World Health Organisation, 2020 (May 6)).

COVID-19 risks and CHIM

When considering the use of CHIM studies, it is essential to offset the risks for the patients, to the (potential) gains of performing the study. For COVID-19, although the disease burden on the general population has been high, the morbidity and mortality have been greatly skewed over the age groups. Overall, younger people are less affected by an infection compared to people of (high) age. For example, in those aged 18-30 years (whether healthy or not), hospitalization rates for COVID-19 were estimated to be around 0.6-1% and fatal infection rates around 0,007 – 0,031% (R. Verity, 2020). In comparison, the overall case fatality rate in the Netherlands (percentage of people who die) is currently 1%. The incidence of morbidity and mortality decreases as a large part of the Dutch population is becoming fully vaccinated. Therewith, and with a vaccination campaign that has focused on immunizing the population by age groups, new infections are (in July 2021) mostly seen in the younger population. Although this population is less affected by the infection and the risk of hospitalization is low, there is a risk of developing so-called Long COVID (or PASC; Post-Acute Sequelae of SARS-CoV-2 Infection).

After the emergency licensure of several preventive vaccines, many experts felt that the risks of controlled human infection with SARS-CoV-2 could not be justified by the potential scientific gain, which is why controlled infection studies never started in the Netherlands. Controlled human infection studies were conducted in the UK but not in the Netherlands.

The Netherlands - Missed opportunities to support clinical COVID-19 trials

Not only were CHIM studies not performed in the Netherlands, the overall capacity in the Netherlands to contribute to the clinical development of vaccine candidates and therapies (e.g. novel drugs), could not fulfill the demand of public and private entities.

In the years 2020 and 2021 there was a high demand for clinical trial capacity which was highly competed. There was a lot of interest in developing novel vaccines and drugs for infectious diseases, which was often prioritized over other research. Before (and even now after) the pandemic, research areas that lead to a higher potential return of investment (e.g. oncology, transplantation) or are otherwise more in line with strategic interest are generally favored over clinical studies in infectious disease.

For instance, one University Medical Center (UMC) was requested to participate in a Phase III clinical trial, for one of the leading mRNA vaccine concepts. Due to the lack of capacity, the UMC could not

participate in this pivotal Phase III clinical study. Neither did the same UMC participate in a Phase II trial to test a novel drug for COVID-19, as a result of insufficient capacity. The space for testing symptomatic individuals included in vaccine trials was very limited and, combined with hospital crowding, the UMC could not participate in these essential studies.

Although the needs and benefits of installing an early phase infection unit that can perform CHIM studies is discussed at length in this report, it is essential to note that the infection unit could be used for early phase infection studies in general. In the context of a strained health care system (as is the case in a pandemic) the product development and clinical testing of compounds by Academia and Industry is severely hampered in the absence of a dedicated unit.

The Netherlands – a history in infectious disease

According to a recent publication (Invest In Holland, 2021) written by InvestinHolland,

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The coronavirus pandemic has ushered in a new era of vaccine development worldwide, and the Netherlands is a hotbed of vaccine production and research. This is reportedly not by coincidence, as the Dutch have a rich history in life sciences, including vaccine development, which predates the COVID-19 pandemic by decades.

“Collaboration is part of the Dutch DNA. The collaborative spirit between academia, industry, government and end-users is inspiring and has led to breakthrough innovations in life sciences, including in the field of vaccines.” – Hans Schikan, Special Envoy for vaccines at the Dutch Ministry of Health, Welfare and Sport

Beyond the current vaccine juggernauts like Janssen and Lonza, the Netherlands is home to some of the largest and oldest pharmaceutical companies developing other vaccines. Abbott has been operating in the Netherlands for over 60 years and is now producing its influenza vaccine for South America in the Netherlands. Bilthoven Biologicals (BBio) has also played a large part in vaccine development, now being a crucial supplier of the Inactivated Polio Vaccine (IPV) for the World Health Organization’s Global Polio Eradication Initiative (GPEI). An estimated 30% of vaccines produced globally are made with technology developed in Bilthoven, according to BBio.

Such success of vaccine development and related pharmaceutical breakthroughs and distribution in the Netherlands reflects the combined power of companies, researchers and institutions working together in the Dutch life sciences & health ecosystem.

More than 300 public-private life sciences & health partnerships exist within the Netherlands, including several focused on developing vaccines against COVID-19.

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A recent report by LSH, and the ‘Future, Affordable, Sustainable Therapies’ (FAST) task force, highlighted the benefit and necessity of a program stimulating the treatment of infectious diseases

and vaccine development. HollandBio, the Dutch interest group for Biotech, has pleaded for a strong ecosystem supporting vaccine development from production to preparedness. (HollandBio, 2021).

The plea for stronger ecosystems that build for a future in which the Netherlands is better prepared for future pandemics and is able to contribute its share to the development of novel therapies and vaccines has been echoed in multiple policy documents and initiatives. Other countries, such as Belgium, have stepped up and are investing in a state-of-the art facility in Antwerp, the Vaccinopolis. (Universiteit Antwerpen, 2021). Whereas there seems to be a strong ecosystem supporting the development of vaccines, there seems to be a lack for clinical infrastructure to produce these vaccine products (certainly in case of a pandemic) as exemplified by the examples in the section above. In the Netherlands one of the key hurdles has been the lack of sufficient and dedicated clinical trial capacity to perform essential SARS-CoV-2 clinical studies in the recent year. Historically, there has been a lack of sufficient clinical trial capacity for infectious disease.

Whereas this preliminary report finds its origin in the lack of an infection unit in the COVID-19 pandemic, an infection unit can benefit clinical studies to a variety of infectious diseases, including early clinical studies into the safety and efficacy of new therapies and vaccines, as well as challenge studies wherewith healthy volunteers are actively infected with a pathogen.

Key question and methodology

The key question to this report is to investigate the benefit and necessity of the establishment of an early phase infection unit in the Netherlands. Whereas suchlike an infection unit might be instrumental in the performance of CHIM studies, the potential scope of the studies performed in such a unit might be broader and could for instance also comprise studies of a methodological nature, studies assessing the interaction between the pathogen and the host or studies enrolling patients to a highly pathogenic disease assessing the effect of a new treatment. Certainly in the case of a pandemic, where the health care system might be strained, sufficient dedicated capacity to perform clinical trials seems essential. Although the COVID-19 pandemic is certainly at the basis for the assessment of the benefit and necessity to establish an early stage infection unit, it is important to note that, by the time such a unit will be established, there might no longer be a need for an infection unit to combat COVID-19 or SARS-CoV-2 infection. This report focusses on the benefit and necessity of building an early phase infection unit, thereby taking COVID-19 as an example, whilst focusing on its broader application. Next to COVID-19, the utility of the potential future unit for other infectious diseases, will be assessed.

With the help of commonly used models such as the Osterwalder Business Model Canvas and the Value Proposition Canvas and by means of focused interviews (example of Questionnaire in Annex 1) with Key Opinion leaders from Academia and Industry (list of key people interviewed in Annex 2) this report aims to provide insights into the benefit and the necessity of an early stage infection unit.

4. The benefit and necessity of an early phase infection unit in the Netherlands

Needs of the Dutch population, the Academia and the industry.

When considering the potential use and necessity for the establishment of an early phase infection unit in the Netherlands it is essential to take into consideration the so-called ‘pains and gains’ of the various stakeholders. In this report, we focus on three groups of stakeholders; the Dutch population, the Academia and the private Industry in the Netherlands.

Needs and benefits of the Dutch population

The needs for the Dutch population are the clearest headed. The (speedy) development of prophylactic and therapeutic drugs or vaccines, directed against infectious disease, will save lives, decrease disease in the overall population and in the case of a pandemic, influence the duration of the socioeconomic burden the mitigation of a (new) pathogen might bring. In addition, insights into for instance the transmission of a pathogen, or the viral shedding, gathered under controlled conditions in a scientific environment, might provide (essential) insights that could be used to guide the response to the containment of the infectious disease. Clinical research into the effect of new COVID-19 therapies, in which a large amount of data is gathered, requires performance in a controlled setting.

In CHIM studies the effect of pathophysiology of an infection can be studied in depth. For instance, the viral shedding can be characterized and related to symptoms and viral transmission. The study of the precise buildup of the humoral and cellular immune response will benefit the development of new drugs and vaccines in case of a pandemic, or for current infectious diseases.

CHIM studies can provide essential insights

- for the expedited testing of the clinical efficacy of vaccines and therapies
- in the relation between symptomatic and asymptomatic infections
- in the kinetics of (viral/ bacterial/parasite) shedding and therewith transmission
- in the kinetics and buildup of immune responses.

Notwithstanding the insights CHIM studies can bring, it is essential to note that it is (only) a ‘fit for purpose’ model. Its use is dependent of amongst others, the pathogen studied, the option to perform field studies, the transmission, the scientific question etc. It is not the ‘Alpha and the Omega’ to vaccine development and will not (completely) replace the traditional Phase I-III clinical trials.

To summarize the potential gains for the Dutch population of an early phase infection unit, one could argue that, if such an infection unit would provide either a faster access to or a better understanding of i) drugs directed against the pathogen ii) the development of vaccines iii) drugs preventing disease iv) transmission or infection of the pathogen or v) the pathogenesis of disease, there would be a benefit for the Dutch population. Furthermore, an early infection unit would possibly contribute to the investment climate in the Netherlands, in support of the overall economic vigor and employment.

Needs and benefits for the Academia

The content and information of this report is partly retrieved from interviews with key experts from Academia and Industry. From Academia, the pool comprised experts from the University of Amsterdam, the Radboud University Medical Center, the Leiden University Medical Center, the

University Medical Centre Utrecht and the Erasmus Medical Center from Rotterdam. All experts were, in general, supportive to the use and need for a (new to be formed) early phase infection unit. The Netherlands is privileged to have a high number of excellent (including young) researchers in the infectious disease space. Whereas the need for a separate infection unit and its requisites, depends amongst others on the pathogen researched, the transmission of that pathogen in the population at the time of clinical study and the need for an inpatient or an outpatient setting, the overall thought of the Academics was that an early phase infection unit would be (most) welcomed. The need for an early phase infection unit is illustrated by the examples above, in which the demand for the support of (SARS-CoV-2) clinical trials could not be met. In general, certainly during a pandemic, there is a need to perform clinical trials into novel drugs and vaccines. Clinical studies (including outpatient studies) often comprise symptomatic (infected) volunteers. These studies could not be performed in the 'regular' hospital / clinical trial center settings during (part of) the pandemic as symptomatic patients could not enter the location or for instance nasopharyngeal swabs could not be taken and processed. The need for an early phase infection unit, dedicated and equipped to perform outpatient and inpatient clinical trials, is therewith evident. Further, outside a pandemic, the benefit of having a dedicated early infection unit might be advantageous for the various academic centers working on infection trials. For instance, a unit with an expertised staff, working under a well-defined quality system, with GCP procedures in place, is proposed to de-risk, benefit and expedite the clinical studies from Academia. Therewith, findings from Academia could become more readily available, which could in turn benefit the Dutch population.

Needs and benefits for the Industry

Industry has a unique perspective to the needs of an early phase infection unit. As an example from information gathered through focused interviews, a start-up working on new antivirals against Dengue supported the idea of an early phase infection unit in the Netherlands. A start-up focusing on antibiotics for antimicrobial resistance (AMR), supported the idea of an early infection unit but stressed at the same time that for AMR, there is a general need for overall funding of initiatives that aim to tackle future AMR (a topic of high importance but not further discussed in this report). Larger companies in the Netherlands with a broader pipeline, and often experience in the clinical development of compounds and dealings with regulators, stressed that in principle, an early phase infection unit would be welcomed and used. The use of the infection unit for challenge studies would be depending on the pathogen (e.g. currently not for COVID-19 due to the absence of rescue medication, the chance of developing LONG COVID). The key experts from industry stressed that, in order for an early phase infection unit, and specifically a CHIM model, to be attractive for Industry, the infection unit would need to be part of a larger infrastructure (as discussed more in depth below and confirmed by Academia). Furthermore, a challenge study might, in accordance to some companies, only be useful when a field study (e.g. Phase III clinical study) could not be performed. Furthermore, rescue medication would have to be available to the pathogen to safeguard the health status of the volunteers in a CHIM study. Also, the regulatory environment (e.g. EMA) would have to be supportive of the performance of CHIM studies for the acceptance and eventual (faster) licensure of a drug or vaccine to the market.

Regulatory view on CHIM studies

Regulatory agencies seem to be supportive of CHIM studies in that these studies include evaluable efficacy endpoints that then guide decisions on how to optimize subsequent field studies, as

recommended by the FDA and thus licensing studies that follow. Such a strategy optimizes the benefit of the studies and identifies possible threats early on, minimizing the risk to subsequent volunteers but also maximizing the benefit of scarce resources available to the research group investing in the research. Inspired by the principles of the 3Rs (Replacement, Reduction and Refinement) now commonly applied in the preclinical phase, CHIM studies allow refinement and reduction of the subsequent development phase, accelerating progress towards further statistically powered Phase IIb studies. The breadth of data generated from challenge studies allows for exploration of a wide range of variables and endpoints that can then be taken through to pivotal Phase III studies.

Summary to the needs and benefits of an early phase infection unit for the Dutch Population, Academia and Industry.

From the interviews with key experts from Academia and Industry, it became evident that there is support for the establishment of an early phase infection unit in the Netherlands, benefiting the needs from Academia, Industry and the Dutch population. On the one end, the value of an early phase infection unit for Academia and the Dutch population might be in the performance of studies with a (partial) focus on amongst methodological and fundamental studies and possible development of new therapies and vaccines to diseases with a low interest from Industry (e.g. malaria, AMR). For Industry, methodology studies and fundamental studies are of less interest and the use of an early phase infection unit, and CHIM models in particular, would in part, pending of the pathogen and disease of interest, dependent on the utility of the data these studies would yield for the dossier building of the respective compound, the time it would take to perform suchlike studies and the cost of opportunity with respect to the performance of other studies. Academic experts working with for instance RSV have corroborated the idea that CHIM studies are supported and welcomed by regulatory agencies such as the EMA. Overall, there seems to be an increasing interest in CHIM studies and the general idea is that the classical clinical development path of Phase I studies, followed by Phase II studies, followed by Phase III studies will become outdated. While a dedicated infection unit (infrastructure) is not present in the Netherlands for studies with (up to) BSL-3 pathogens, it is important to note that the essential expertise to work with various pathogens and infectious diseases is present in the Netherlands. Academia and private industry have initiated a high variety of clinical studies into infectious disease. While some of these studies, e.g. CHIM studies with influenza or RSV, have previously been outsourced abroad, an approximate 600 volunteers have been enrolled in malaria CHIM studies in the Netherlands in the last 20 years. Further exemplifying the availability of the key expertise to perform for instance CHIM studies in the Netherlands.

There are ample examples of requests for essential (non CHIM) clinical studies in which the Netherlands could not participate based on the lack of capacity. An early phase infection unit could support these studies. For instance a leading company with a mRNA vaccine against SARS-CoV-2, in need for a location to support a Phase III clinical trial, could not be served in certain clinical centres. Also, a company working on a new therapeutic for the treatment of COVID-19, with the potential of influencing the burden on the IC occupancy if proven effective, could not be served. These examples illustrate the need for an infection unit in the Netherlands.

While the benefit and need for an early phase infection unit is clear from the viewpoint of the Dutch population, the Academics and the Industry, not all experts were aligned on the benefit and necessity of a CHIM model in case of a new pandemic caused by a new pathogen. All experts interviewed emphasized that, in order for a new early phase infection unit to be successful, it would have to be embedded in an ecosystem that is beyond the direct capabilities of the clinical infection unit itself. This

will be discussed more in depth in following sections. Specifically, CHIM studies come with specific requisites.

In the next section the ethical considerations of performing a CHIM study in volunteers (in case of a new pandemic) and the need for challenge stocks, the regulatory process and a (fast) decision process will be discussed.

Ethical considerations in a CHIM model

With respect to the benefits and needs for an early phase infection unit in case of a new pandemic outbreak (e.g SARS-CoV-3, avian influenza with person to person transmission) the experts of Academia and Industry are not in full agreement whether it would be justified to perform CHIM studies in the early days of a pandemic outbreak. In the absence of rescue medication, the risk of inflicting harm to the volunteers might, according to some experts from Academia and Industry, outweigh the scientific gain of these studies in the early phase of a pandemic.

Ethics form a very important aspect of CHIM studies. To provide more background on this important topic it is of value to refer to a text from a paper by Amy Sherman et al (Amy Caryn Sherman, 2019), in their 2019 paper in *Frontiers in cellular and Infection Microbiology*

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In human subject research, the risk-to-benefit ratio is usually favorable to the subject before the risk-to-benefit ratio is weighed for the broader society. For example, an individual with a rare and life-threatening disease may choose to participate in a trial that tests a novel therapy, because they personally may benefit from a cure for an otherwise untreatable condition. However, for the human challenge model, the participant is not directly gaining anything for their health, and the risk-to-benefit ratio leans toward the side of risk. Therefore, an acceptable challenge model must have risks that are reasonable to the participants, because the challenge model can be justified only by the benefits to society and not to the individuals. To mitigate risk to the participants, certain criteria should be evaluated. The study hypothesis must only be answerable by challenging human subjects; if the question and endpoint of the study could be determined by animal models or *in vitro* techniques, the human challenge model should not be used. Infected subjects should also have therapy available (in the case of influenza, antivirals such as oseltamivir or peramivir) in the event that they develop severe infection during the experimental challenge. ‘

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The ethical considerations in performing CHIM studies are of the utmost essence. Not only do these considerations guide the risks for the healthy volunteers, the inadvertent disease or death of a healthy volunteer in CHIM studies, would cause serious damage to the acceptance of the CHIM models in general.

Requisites to a challenge stock in a CHIM model

Besides the ethical consideration in the performance of a CHIM study in particular, an early phase infection unit in which challenge trials can be performed needs one key ingredient. There is a need for (GMP grade, GMP like or GMP compatible) challenge stocks, which are produced, analyzed and stored under the correct conditions (including quality assurance, stability, biobanking). In the case of SARS-

CoV-2, by the time the challenge agent would be ready for use in a CHIM study, a new variant (e.g. the delta variant) might have emerged which decreases the relevance for a challenge study with the initially produced challenge stock. This redundancy of challenge stocks is explicitly relevant in case of a (fast) mutating new pathogen in a pandemic.

Requisites to the regulatory and decision process in CHIM studies

Although there is no consensus amongst the experts to the question whether a CHIM study in an early pandemic phase would have been of use and of need, most experts agreed that, in case some conditions are to be met, such as the presence of rescue medication, the (speedy) production of challenge stocks and a swift decision process by assessment committees such as the *Centrale Commissie Mensgebonden Onderzoek* (CCMO) and or the '*College ter Beoordeling van Geneesmiddelen*' (CBG) an early phase infection unit might be of merit in the early days of a future pandemic with a new pathogen. As for the longer term, once rescue medication for COVID-19 would become available and other conditions as stipulated would be met, most experts foresee a use for an early phase infection unit in SARS-CoV-2. Here it is important to note the United Kingdom, has decided to proceed and has set up a CHIM for COVID-19. With that the UK has rated the risk and benefit as acceptable. In Belgium, Vaccinopolis is being built with public funds to combat future pandemics, preparing for situations of need while acknowledging that in order for CHIM studies to be performed with SARS-COV-2, rescue medication needs to be available.

The value of CHIM studies besides COVID-19.

Besides the use of an early phase infection unit in the Netherlands for the study of a new (pandemic) pathogen in the early days following its emergence, the experts from Academia and Industry agreed on the value of CHIM studies and the infection studies for work with pathogens such as Influenza, RSV, Malaria, AMR, rhinovirus etc. The requisites to the eventual early phase infection unit are largely dependent on a great number of factors such as the pathogen of interest, its transmission rate, the need for inpatient or outpatient studies, the immune status to that pathogen in the population etc. To explain a bit more on the value of a CHIM study besides its use in the extensively debated COVID-19 model, it is of worth to illustrate the benefit and need of the model for another disease, influenza.

The influenza CHIM model, an example of its merits for the Dutch Population, Industry and Academia.

One of the examples for which there is a need of an early infection unit and a challenge model comes from influenza. While transmission of influenza has been low for the past season based on the rigorous health measures taken to mitigate the transmission of SARS-CoV-2, influenza is generally of a serious concern. The WHO estimates that annual influenza epidemics cause 3–5 million cases of severe disease, with 290,000–650,000 of these severe cases resulting in death (Amy Caryn Sherman, 2019). The development of a so-called universal flu vaccine or universal flu therapies, would greatly benefit the protection against a variety of influenza strains. A correct prediction of the most prevailing strain of influenza for the upcoming season will largely predict the efficacy of the flu vaccination campaign. In the Netherlands, the efficacy for the flu season 2017/2018 was 44%. In the flu season 2018/2019 approximately 400.000 people in the Netherlands got ill from influenza. An approximate 165.000 people contacted their general practitioner with flu-like symptoms. The cost of care for influenza in

2017 in the Netherlands alone was 82 million. Which is 0.5% of the total cost of healthcare in the Netherlands. (Volkgezondheidzorg.info , 2021).

A universal flu vaccine would better protect against all the influenza strains, increase the efficacy of the flu vaccines, limit the disease burden for the Dutch population and decrease the cost of healthcare. A universal flu vaccine would need to be at least 75% effective, maintain protection for at least 1 year, protect against group I (e.g., H1, H5) and II (e.g., H3, H7) influenza A virus strains, and be effective for all age groups (Amy Caryn Sherman, 2019).

It is not possible to test the efficacy of an influenza vaccine with universal aspirations against all influenza strains in a field study in one season. A human challenge model could provide essential information to the efficacy of suchlike vaccines. The benefit of a universal influenza vaccine would be large for the Dutch population, the Academia, which has a historic and strong background in influenza research, and the Dutch Industry. Furthermore, without question, the establishment of a CHIM influenza model with multiple viral strains, would lead to a lot of interest from international academic groups and Industry.

The example of the benefit of an influenza CHIM model, which would require the set-up of an early phase infection unit since there is no dedicated inpatient location in the Netherlands where suchlike studies can currently be executed, is indicative for the overall use and need for an early phase infection unit. A similar case, albeit with different arguments (not all detailed in this report) can be made for other disease indications such as RSV.

In (preliminary) conclusion, the answer to the question this report set out to answer, specifically on whether it would be of benefit and need for the Netherlands to establish an early phase infection unit, can be answered in the affirmative. Confirming the notion of ZonMw of such a need, which lies at the basis of this preliminary investigation.

An early phase infection unit can have benefits for the Dutch population, the Academia and the Industry in that CHIM studies can be performed, as well as fundamental and methodological investigator initiated studies on the pathogenesis and characteristics of a disease agent and the correlates of protection. Furthermore, an inpatient setting where studies can be performed, under controlled conditions with respect to sampling, PK analytics, GLP and GCP practice, would have merit for studies to a new treatment of patients with an infection that demands high containment such as MRSA. Next to an inpatient setting, suchlike an infection unit could also serve to perform outpatient studies, needed for the contribution to for instance Phase I-III vaccine studies for companies working on vaccines against (pandemic) diseases.

5. Structure of an early phase infection unit

An early phase infection unit, Key activities, Key resources, and Key partners

Having discussed the overall need and use of an early phase infection unit, it is now essential to outline the requisites to the set-up of such a unit. Without any exception, out of the numerous of experts interviewed from Academia and Industry, all agreed to the notion that in order to make an early phase infection unit a success, it would be essential to make it a combined effort, including partners, capabilities and expertise from both Industry and Academia.

Key activities.

As discussed there is a need for a highly specialized facility that can perform high-quality registration-grade early phase clinical trials in infectious diseases, both for drug and vaccine development, including controlled human infection studies.

Key resources.

When discussing the resources needed for the performance of the key activities as outlined above, it is essential to foremost look at the format of a new early phase infection unit. The options range from i) a virtual entity, using existing facilities in the context of a (new or established) legal entity, to ii) building a new floor on an existing unit, as part of a new or existing legal entity, or iii) building a new early phase infection unit, separate from any existing infrastructure and governed as a new or existing legal entity.

An early phase infection unit: Virtual, add on or new building.

As mentioned, clinical trial capacity during the pandemic was very limited, particularly for inpatient studies. During the pandemic several groups were faced with major logistical challenges in the performance of clinical trials. Due to travel restrictions and restriction with regards to hospital logistics (e.g. entrance screening) it became increasingly hard to perform clinical trials involving human subjects in a hospital setting simply because they could not be “mixed” with the potentially vulnerable patient population. At the same time, professional units performing early phase clinical studies were not equipped nor did they had the expertise to perform clinical trials with potentially infectious subjects (here it is essential to note that COVID-19 vaccine trials required follow-up of all, including symptomatic, individuals). With that, there is a need for a unit with expertise in infectious diseases capable of managing large number of potentially infectious individuals.

It is evident that the establishment of a virtual new early phase infection unit will not lead to much improvement to the needs in clinical trials.

A situation in which an early phase infection unit, would be built as a *fit-for-purpose* facility on an existing infrastructure (add on), has clear benefits over a virtual entity. The infection unit could well implement the quality system, GLP and GCP practices, IT infrastructure, legal and financial systems etc. On the downside, suchlike a unit might be faced with potential building restrictions from the existing infrastructure. Furthermore, insufficient independence could mean the unit may ultimately be occupied for other purposes because these are financially more attractive.

Lastly, a new early phase infection unit, to be established as a new building, has the advantage in the potential to build the infrastructure anew. Initial feedback from companies involved in the build of Vaccinopolis in Belgium, revealed that that infection unit contained a water tank below the unit, to collect extinguishing water used by the fire department in case of fire. Also the need for a so-called kill tank, and the need for all materials to be cleansed by fumigation, are unique requisites currently not available in an existing clinical trial unit.

These unique requisites highlight the need for a new, state-of-the-art early phase infection unit, which is highly efficient, flexible, yet usable in pandemics. There would be a possibility to create a novel quality control system which is fully state-of-the-art, meeting the most recent legislation (GDPR) and benefitting from the most recent technological developments with regards to digital data acquisition

(remote sensors), FAIR principles and data sharing. On the downside, suchlike a unit would require a relatively large investment. To mitigate the higher cost, the implementation of the necessary systems from an existing clinical trial unit could be pursued.

This report will further focus on the concept of an early phase infection unit, in the form of a new building and (physical) infrastructure. The governance of suchlike a unit will be discussed later.

The facility.

From the interviews with experts, it became evident that the facility should operate under a dedicated quality control system, including dedicated staff trained for such purpose. By creating a separate facility there will be no risks of accidental carry-over of infectious agents from trial population to vulnerable patient populations. Location in the close vicinity of an (academic) hospital will be essential to ensure that the highest level of care is available, should this be necessary.

When looking at the specifics of the new early phase infection unit, one of the worst outcomes is that a new unit is build that doesn't meet the standards and cannot serve the purpose for which it is build. In that sense, it is worth to build a unit which is suited to perform studies in which the requisites are most demanding. Specifically inpatient studies with a need for high containment of the infectious pathogen. Annex 3 lists a set of requisites from the WHO for a unit suitable for the performance of COVID-19 CHIM studies. (World Health Organisation, 2020). These can be seen as a stringent set of requisites to a high containment unit.

In short, the unit should have high-level isolation capacity. All beds should be in separate rooms with individual air circulation systems, preferably hepa-filtered. Optionally the chambers would be placed under negative pressure. If needed a one-way patient-in-out system should be designed.

The unit should have a minimum of 30-40 (inpatient) 1 person rooms with beds in order to contribute to the global capacity and be able to form a 100+ bed multicenter unit together with SGS or Vaccinopolis in Antwerp, Imperial College London and NIH should this be necessary. In comparison, SGS is known to have 45 inpatient rooms with beds in a total unit of 1000 beds. Imperial college is said to have 30-40 rooms with beds for inpatient studies. Next to the separate rooms, the new unit should have 10 polyclinical chambers, a pharmacy-like laboratory to prepare high quality drug and vaccine products, and office space. Some experts made a preliminary estimate on the size of the unit which could be an approximate 1800-2000 m² for beds, outpatient unit, offices and laboratory space all included.

Staff

In terms of staff, the unit is envisioned to start small working towards expansion into a larger team. In a period of 5 years from its build, the unit should be financially independent. This will require an estimated staff of approximately 22.5 FTE. In a period of 5 years time, the unit is envisioned to grow from 10 FTE to 22.5 FTE with a total cost of employment in year 1 of 1.2 mEUR and a cost of employment in year 5 of around 2.5-3 mEUR.

Table 1: Tentative list of staff needed (specialty and FTE) from start of the early phase Infection unit (YR1) to its financial independence in 5 years (YR5).

Staff	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5
<i>Clinical specialist infectious disease</i>	0,50	0,60	0,75	0,85	1,00
<i>Microbiologist</i>	0,50	0,60	0,75	0,85	1,00
<i>clinical pharmacologist</i>	1,00	1,25	1,50	1,75	2,00
<i>methodologist/epidemiologist/modeller/big data</i>	0,50	0,60	0,75	0,85	1,00
<i>Nurses</i>	2,00	2,75	3,50	4,25	5,00
<i>lab staff</i>	2,00	2,75	3,50	4,25	5,00
<i>Pharmacy trial manager</i>	0,50	0,50	0,50	0,75	1,00
<i>data management</i>	0,50	0,50	0,50	0,75	1,00
<i>IT-support</i>	0,50	0,50	0,50	0,75	1,00
<i>CTA</i>	0,50	0,50	0,50	0,75	1,00
<i>QA</i>	0,25	0,25	0,30	0,30	0,35
<i>Project management</i>	0,50	0,50	0,50	0,75	1,00
<i>Secretary</i>	0,50	0,50	0,75	0,75	1,00
<i>BD/Legal/Collaboration manager</i>	0,50	0,50	0,50	0,75	1,00
<i>Biosafety officer</i>	0,10	0,10	0,10	0,10	0,10
Total:	10,35	12,40	14,90	18,45	22,45

Challenge material

As discussed, the challenge agents (viruses, bacteria, parasites) form an essential part of the challenge studies. Given the relative novelty of the CHIM studies, overarching guiding regulations to the production of challenge agents is currently not formalized. The need to agree and implement quality principles involved in the development, qualification and manufacture of challenge agents across the world has been highlighted by stakeholders (scientists, regulators, clinical staff, volunteers) involved in human infection studies (Isabelle Bekerredjian-Ding, 2020). Challenge agents should be produced according to GMP, be GMP-like or be GMP-compatible. The exact requisites to the production of challenge units is under debate. Within the EU regulations, challenge agents are mostly considered Auxiliary medicinal products (European Commission). For the production of challenge agents, the possibility to use Next Gen Sequencing for adventitious agent testing should be discussed with the 'Centrale Commissie Mensgebonden Onderzoek' (CCMO) and or the 'College ter Beoordeling van Geneesmiddelen' (CBG). A white paper with guidance for challenge agent production is close to finalization (funded by the Wellcome Trust).

Some challenge agents can only be effectively administered by a vector. For example, mosquitoes (*A. stephensi*) have been used for the administration of *Plasmodium falciparum* (malaria) sporozoites to healthy volunteers. The use of vectors for the administration of challenge agents brings with it some additional stringent requisites to the production of these challenge agents.

Although the production of a challenge unit comes with very stringent demands, the subsequent testing of the challenge agents and reporting into a certificate of analysis is extensive. Results of the following tests should be included (when possible) in the certificate of analysis.

- Identification – confirmation of identity
- Biological activity/potency/viability
- Purity/Impurity profile
- Quantity
- Microbiological Quality Testing including adventitious agent testing

These activities and services should be performed in a dedicated and expertised lab. Given the complexity of the production of challenge agents, it is argued that these activities should be performed by a specialized Contract Development and Manufacturing Organization (CDMO). Some testing, (e.g., adventitious agent testing or sequencing) could be outsourced to specialized service providers when needed.

Although the experts from industry, interviewed for the purpose of this report, all agreed that challenge stock production, analysis and testing could best be performed in an expertised facility, outside of the new infection unit, some experts from academia proposed that the production of challenge agents could be performed in house, certainly in case of a pandemic, which would require a (small) BSL-3 GMP production unit. Not all challenge agents might easily be produced in CDMO's as these lack the experience or capacity to produce certain challenge agents, such as *Shistosoma mansoni* cercariae. Also CDMO's might not always have a (financial) incentive to produce challenge agents. As such, one could argue that a small BSL-3 GMP facility should be part of the challenge unit, to facilitate the production of these agents there, when opportune. In addition, for some challenge agents one could possibly rely on the input from Universities. This might be the case for instance for CHIM studies performed with *Plasmodium falciparum*. The Netherlands is privileged with some renowned research groups working on CHIM studies whereby volunteers are infected with malaria parasites by the bite of an infected mosquito.

A quick decision process.

The success of an early phase infection unit is not only served by a strong infrastructure and access to challenge agents. The studies performed in an infection unit will be served by a quick decision process. Certainly in a pandemic, decision processes for the performance and execution of clinical trials have to be efficient and fast. This requires a strong relation between the infection unit, its (principal) investigators and entities such as the CBG, the CCMO and possibly even the 'European Medicines Agency' (EMA). In order to expedite the process of the testing of new vaccines and compounds, certainly in case of CHIM studies, a centralized process, by which (clinical) protocols can be submitted and reviewed by regulatory agencies is proposed to be essential.

Although sufficient regulating principles are in place, regulatory bodies should be made more aware and involved in the foreseen studies early stage. There are several initiatives worldwide to establish more practical guidelines following existing regulations. Research into ethical frameworks for infection trials is much needed which may be provided soon as a result of global efforts from amongst the WHO and Wellcome Trust.

Key partners

Building a new infection unit will, by itself, not serve its maximal potential. All experts interviewed expressed the opinion that the success of a new infection unit would be dependent on its partnership with a number of parties. For one, the development, qualification and manufacture of challenge agents could be performed by specialized service providers, when opportune and possible. Challenge agents could possibly be produced by parties such as Halix, Intravacc or Batavia in the Netherlands. A partnership with a Dutch CDMO can benefit the overall public private partnerships in the Netherlands and strengthen the position of the Netherlands in the fight against infectious disease. This might benefit the overall Dutch Biotech ecosystem and potentially attract more (NGO) funding and interest from (Big) Pharma worldwide.

The quality of challenge agents is of the foremost importance and as such, partnerships with CDMO's, there where opportune, would need to be sourced as if these were audited by a pharma company. Although not all challenge agents are currently available, several challenge agents including some influenza strains, SARS-CoV-2, RSV and Dengue might be available at infection units in the UK (Imperial) and the USA (NIH) or public private partnerships already established in the Netherlands. A partnership with international infection units and existing Public Private Partnerships is therefore of high importance. The partnership with the CDMO's and service organization providing services in producing or qualifying the challenge agents, as well as a partnership with international infection units, would have to be steered from the infection unit.

Besides a partnership with CDMO's and service providers serving the development, qualification, manufacturing and biobanking of challenge agents, the infection unit would need to partner with service providers, specialized in the analytics of for instance, biomarkers, virology and the humoral and cellular immune responses. Depending on the disease and pathogen studied, highly specialized assays could be performed at a University. Parties such as the Centre for Human Drug Research (CHDR), specialized in biomarker and microbiome analysis and Viroclinics-DDL, specialized in the cell-based virology, molecular diagnostics and the measurement of the immune response to a variety of pathogens, could potentially be strategic partners. It is not realistic that the analysis of all clinical studies, performed in the infection unit, could be performed by the (relatively) small staff of the infection unit.

The benefit of working with established Contract Research Organizations (CRO's) might lie in the fact that these service providers have established qualified and validated assays for determining the molecular diagnostics and (immune) response to a variety of disease indications. Partnering with these parties could benefit the validity of the data analyzed, and could allow a better translation of findings from early-stage clinical trials (e.g. CHIM) to later stage clinical development, where the use of validated assays is an absolute requisite. Furthermore, by partnering with commercial CRO's, allowing them to promote for instance the capabilities of the infection unit to their (international) sponsors, could promote an easy match to sponsor-initiated studies, which could benefit the financial independence of the infection unit as well as serve the overall offering of the service providers. Suchlike a partnership between the infection unit and the CRO's could create a win - win scenario.

Besides a partnership with CRO's, investigator initiated studies and sponsor initiated studies might benefit from the newest insights from assays with novel scientific tools (NGS, CyTOF, hyperion, Proteomics). Given the academic excellence needed to operate and interpret data, and the cost of maintenance, these services are best outsourced. Still, a strong partnership with (academic) centers capable of performing such analysis is essential.

Although a large number of assays could best be outsourced, given the high level of expertise needed and the cost of the (proper) development of the assays as well as the cost of maintenance of essential equipment, the unit, according to some experts, should have capacity to do large-scale cell isolation and freezing as well as simple flowcytometry (Aurora), ELISAs and ELISPOTs. Most importantly, the unit should be able to process BSL-3 samples.

A partnership with the academic centers is considered of the utmost essence. Not only can these academic centers potentially provide essential expertise and infrastructure on the respective disease indication and/or pathogen. A strong partnership with the academic infrastructure could also benefit the access to potential patients.

Whereas a new infection unit could benefit the needs of the Dutch population, the Academia and the Industry, as well as provide an essential ecosystem for the understanding and combat against infectious disease, the unit is proposed not be isolated and could actively seek partnerships with other infection units like SGS and Vaccinopolis in Belgium, Imperial in the UK and the NIH and WTCC in the USA. The unit could furthermore seek partnerships and collaborations with essential agencies and NGO's such as CEPI, the Bill and Melinda Gates Foundation, the Wellcome Trust and the WHO.

6. Cost and Revenues of an early phase infection unit

Cost of an early phase infection unit

The cost of a, newly build, infection unit, depends amongst others on its location. The cost of the land to build a new unit on are out of scope for the current preliminary report. Given that the location needs to be in close proximity to a (University) Medical Center, to warrant proper patient care if needed, the number of options for the location of a new unit are limited.

The initial ball park estimates for the costs of a new unit range from 8 MEUR to 24 MEUR, depending on the size. A unit of 2000 m² might be in the range of 8 MEUR whereas Vaccinopolis, with 7000 m², will be built for 24 MEUR. The target price of a new unit is €2000 / m² for office space without Biosafety level, €3500 / m² for Biosafety level 2 space and €4500 / m² for Biosafety Level 3 space.

The cost for the maintenance of the infrastructure (building etc.) is estimated at 0.15-0.3 MEUR per year. The cost of personnel are an approximate 0.7 MEUR in year 1 (10.5 FTE) to 1.5 MEUR in year 5 (22.5 FTE), after the inception of the unit. After this 5 year period, the unit should be financially independent.

The cost for the GMP production of challenge agents is an approximate 1.5 MEUR per challenge agent, dependent on the pathogen. Cost could potentially be mitigated by working collaboratively with parties such as the infection unit (to be) Vaccinopolis in Belgium, and Imperial College in the United Kingdom.

The overall thinking of the academic and industry experts, interviewed for the purpose of this preliminary report, is that the benefit of an infection unit will mostly serve the overall Public Health. Whereas companies typically work with discounted cash flow methods to estimate the value of an investment based on expected future cash flow, Public Health is something which doesn't easily get captured in these types of financial calculations. To safeguard the independence of the infection unit, certainly given its contribution to Public Health, it is essential that the unit is funded from public sources. Public funding would allow for pre-competitive research, thereby working closely with industry and private partners that are essential to the success of the infection unit. Public funding can

either come from the Dutch Government, or from Parties such as CEPI or the Bill and Melinda Gates Foundation (BMGF).

Revenues from an early phase infection unit

The revenues of the infection unit would have to come from its activities. Specifically, the revenues would have to come from the performance and support of clinical studies.

In terms of the revenues a typical phase 1 vaccine or drug trial could range between 0.3-0.8 MEUR with an average of 0.6 MEUR. An inpatient challenge study reportedly typically costs 1.5-1.8 MEUR (± 25 individuals). Outpatient challenge studies cost roughly 30 000 euro per individual included. Here, it is essential to note that the cost of the studies can be, according to the experts performing these studies, significantly decreased based on the overall experience of the dedicated team. Whereas investigator-initiated studies could potentially be performed at cost, a 100% mark-up for sponsor-initiated studies is market practice and these sponsor initiated studies can be performed at a cost of 3.5-4 MEUR per study.

Depending on the type of study (e.g Phase I, CHIM, outpatient study) a minimum of 10 and a maximum of 20 studies could be performed in the infection unit on an annual basis. A quick calculation learns that the revenues from the work performed in the infection unit, could easily cover the cost of the unit. Therewith, an infection unit should be able to run financially independent, relatively shortly after its start. The experts interviewed confirm the reasoning that an infection unit should be able to operate financially independent after a few years from its inception. Although an exact calculation on the cost and revenues for the infection unit is difficult to provide at this moment in time, there are examples of clinical trial entities that operate financially independent. One example of a successful, self-sustainable entity is the CHDR in Leiden. This foundation with 280 FTE, runs both investigator-initiated clinical studies as well as sponsor-initiated studies and operates independent of external funding. An interview with representatives from clinical trial units revealed that there is an overall need for (new) clinical trial centers to perform regular clinical pharmacology studies. For this, in the unforeseen case the occupancy of the early phase infection unit does not cover its cost, it could potentially be used for non-infectious disease regular pharmacology research. While it is foreseen that the infection unit could operate financially independent within a (short) number of years following its start, maintaining a focus on its mission, opening the capacity for other clinical trial research (while maintaining an overall priority on infectious disease) could further de-risk the investment if essential for its (financial) survival.

The future infection unit is envisioned to combine investigator-initiated (at cost or below cost) studies from public entities as well as commercial industry-initiated studies to make it sustainable. It is envisioned to have the capacity to perform highly complex early phase clinical studies (phase I-II), including controlled infection studies for developing drugs as well as vaccines. According to most experts interviewed, the unit should have a not-for-profit basis so it could use potential revenues to invest in methodology development or support the development of products for “poor” markets using public (e.g NGO) funding. The primary focus of the unit is proposed to be on infectious disease with a pandemic potential or current pandemic effect, as well as disease indications for which there is a high need for a vaccine or therapy for the Dutch population, or Global Health.

By clustering infection trials in one unit, trials are envisioned to be performed more efficiently at lower cost. The establishment of a unit with high quality performance, with possible access to academic high-tech facilities such as high dimensional immunological analyses (CyTOF, RNAseq, Aurora, Proteomics)

or more complex samples (BAL, Bone marrow aspirates) on top of access to partnered (commercial) contract research organization, performing for instance viral neutralization with a set of variants in a validated assay, will attract private sponsors. By contributing to the development of vaccines and drugs, the population might benefit from an earlier access to these drugs and vaccines. Furthermore, the unit could create job opportunities and it might attract additional biotech companies to the Netherlands which might lead to further economic benefits.

Besides attracting additional biotech companies to the Netherlands, the unit could further the existing interest of important funding and advisory agencies such as CEPI, the BMGF and the WHO. Already all of these parties have engaged with experts from Academia in the Netherlands to request expertise and the potential input and performance on studies with COVID challenge models, pan-coronaviruses and universal vaccines for influenza.

Parties such as CEPI and the BMGF have substantial funding and are known to invest substantial amounts of money in the development of essential models to combat current and future diseases.

7. Governance legal form, partnerships and potential location of an early phase infection unit

The interviews with experts and best practices from other infection units outside of the Netherlands, clarified a number of important points, in terms of the governance and legal structure of an infection unit. Specifically,

- The unit is envisioned to be build and initiated with public funding (and possibly funding from NGO's like CEPI and the BMGF). The unit should - in the opinion of most of the experts interviewed - be not-for-profit, true to its mission, and as such, a legal structure as a foundation could be preferred.
- The high complexity of the clinical studies, the regulations and the various stakeholders, combined with the fact that clinical studies into infectious diseases are in general of less economic interest compared to for instance research into transplantation and oncology, give rise to the idea that the infection unit could be governed independently from any existing organization. Still, it could be advantageous if the unit could build on essential infrastructures such as quality systems, IT, finance, legal and GCP, there where opportune. The latter could de-risk the investment into the new infection unit.
- The unit can only thrive if the infrastructure, essential for its performance, is fully in place. This means that partnerships would likely have to be formed between the infection unit on the one end, and CDMO's and for instance CRO's on the other end to guarantee the production, analysis and certification of challenge agents and the access to validated analytical assays for patient samples on the other end.
- The unit is proposed to support both investigator-initiated studies as well as sponsor-initiated studies.
- When engaging in sponsor-initiated studies, the unit could focus on precompetitive research. Clinical studies from precompetitive public private partnerships could be one of the focus areas of the infection unit.
- Competitive sponsor-initiated studies could (only) be initiated if that doesn't interfere with the independence of the infection unit. Furthermore it could be essential to see if the performance of competitive sponsor-initiated studies might be conceived as a distortion of competition which would need to be avoided.

- The unit could serve the interest of the Public Health for the Dutch population and Global Health and be built on the broad expertise of Academia. To safeguard independence, the unit is proposed not to be governed by one specific academic center. Furthermore, the unit should be governed and run with the efficiency and mindset of a commercial entity. As such, the unit is proposed not to be governed (predominantly) by Academics. According to some Key Opinion Leaders interviewed for the purpose of this report, there are ample historic examples of public funded initiatives/ institutes, governed by leadership with an academic mindset, which have not been able to meet the goals they set out to achieve. To avoid a recurrence of public funding not spend well, it is therewith proposed that the foundation is governed by knowledgeable (infectious disease) and business savvy leadership.

In terms of its exact governance, the initial thought was that the new infection unit, in the form of a new physical building, could be formed as a foundation. It could operate on a non-for-profit basis and support both investigator-initiated studies and (precompetitive) sponsor-initiated studies. Alternatively, some experts from Industry have stressed that an early phase infection unit, could be initiated with initial seed funding from public sources (against for instance a minority stake), and subsequently be run as a commercial entity. In case of a pandemic the unit could work for instance with a first priority scheme. The upside for Industry to this alternative scenario might be that clinical studies are really run in accordance with their stringent requisites and in a timely manner. Sponsor-initiated studies are aimed to evaluate the safety and efficacy of products developed by Industry. The sponsor is responsible for the Investigational New Drug (IND) application to the study and as such also carries the liability (risk) of the study. For this, there is a desire from Industry to have studies executed in a CRO – like model. Examples of units offering support to sponsor initiated studies include SGS (in Belgium) and hVIVO (in the UK) and the NIH (in the USA). The downside of having a full commercial entity (seed funded with public funds) could be that such a unit might not prioritize studies into indications which are of importance to Global or National Health for which there is no current commercial market (e.g. Schistosomiasis, AMR).

Whether the unit is to be governed as a foundation, with a CRO mindset, or as a (commercial) CRO, with a priority on diseases including those with a primary burden in Low and Middle Income countries, fundamental studies and clinical studies for which there is no immediate commercial market, remains to be investigated in more depth. Either way, the new unit, could partner with essential partners to benefit its performance including parties which can manufacture challenge agents and parties which can analyze the patient samples in validated assays there, when opportune. Partners are proposed to be selected by thorough due diligence on their capabilities. Commercial CDMO's and CRO's serve a broad number of sponsors which might have an interest in the performance of clinical studies on top of the services rendered by the specific commercial parties. Strategic partnerships might be opportune, with service organizations that bring in new (sponsor-initiated) studies. A strong relation with international bodies such as the BMGF, CEPI and the WHO could be of (the utmost) essence. Furthermore, collaboration with international infection units such as Vaccinopolis, SGS, Imperial College and the NIH should be pursued. A strong international collaboration with other international institutes could benefit the performance of the infection unit in the Netherlands by learning from the 'best practices'. Furthermore, a potential sharing of essential material such as challenge agents could increase the comparison between studies and save time and money. The (leadership of the) new infection unit is envisioned to keep in close contact with Key Opinion Leaders worldwide and specifically in Europe. By collaborating with international infection units and Key Opinion Leaders with

expertise, knowhow and capacity, the global threat of existing and new infectious diseases could potentially be tackled more effectively.

The proposed governance structure of an infection unit could comprise a small, Executive Board. Ideally this Executive Board is to include subject matter experts and key opinion leaders, such as former ‘captains of industry’ with a clear vision, a track record in public institutes or academia and private companies. To avoid a conflict of interest, these Board members are envisioned not be employed by private parties. In order to make a new infection unit into a success, business-savvy and expertised leadership is of the utmost importance.

A small Management Team of Subject Matter experts could govern the day to day operations and be responsible for alliances and partnerships with parties such as CEPI, the BMGF, the NIH, other infection units such as Vaccinopolis, Imperial College, CDMO’s and CRO’s and the Dutch and International Universities and Key Opinion Leaders. In order for the infection unit to focus on its mission, run and operate at its best potential, it is essential that its governance structure is mean and lean, operating independently, while actively collaborating with public and private parties there where opportune. Examples (for reference) of institutes which run effectively and independent in the Netherlands include the Prinses Maxima Centrum in Utrecht and the CHDR in Leiden.

In terms of its location, the new facility should be built in the vicinity of a (University) Medical Center to safeguard essential point of care (ICU) when needed. Also access to sufficient volunteers (e.g. public transportation and parking space) is considered essential.

The interaction of the public and private parties is essential for the success of the infection unit. The availability of a GMP facility for production of challenge products at BSL-3 level is key. Some experts have argued that the unit should ideally be based in a biotech hub or on a bioscience park and could for instance function under an existing clinical trial organization, piggy bagging on its expertise.

The new infection unit would have to be governed independently by key experts. Furthermore, much like Vaccinopolis, the requisites to the new unit require it to be formed in a new building. To de-risk the development of the new unit and leverage, as much as possible, on an existing infrastructure, one could envision that the new unit is to be formed as a Foundation (or alternatively a Commercial CRO), with an independent governance structure, under an existing infrastructure (like for instance the CHDR which is in itself a Foundation). This would allow maximal use of the existing infrastructure while still maintaining independence and governance by key experts. In time, if needed, the Unit should be able to become a fully independent and separate entity.

Within various Academic centra, expertise in the performance of vaccine and infection studies is clearly present. Existing collaborations and networks between some Academic centra with other infection units (e.g the NIH, Imperial college) important international funding agencies such as CEPI and the BMGF, advisory bodies such as the WHO, leading initiatives such as the Wellcome trust and public private partnerships with CDMO’s and CRO’s are already established in so. Very recently, Inno4vac, an innovative public private partnership aimed at accelerating vaccine R&D timelines, was granted 33 million euro’s. In this public private partnership, parties will amongst receive a total of 4 million euros to help controlled human infection models for influenza RSV and clostridium difficile. The 41 consortium partners to the Inno4vac consortium include various Dutch and international Universities and Dutch commercial entities such as Enpicom and Viroclinics.

Other initiatives and needs in the Netherlands

Following the SARS-CoV-2 pandemic, various initiatives for building and developing new expertise have been proposed. The Pandemic & Disaster Preparedness Center (an initiative from the ErasmusMC and the TU Delft) focusses on amongst research into influenza and coronaviruses. A 'Groeifonds' aanvraag is currently being established.

From the interviews with experts from both Academia and Industry, it became clear that a collaboration with both public and private partners would be essential to the success of the infection unit. The unit could be governed by subject matter experts and remain true to its mission. The unit could partner with other (academic) initiatives in the Netherlands as much as possible.

In the interviews with specific key experts it was explicitly mentioned that, besides the need for an early phase infection unit, there is a need for a BSL-4 facility in the Netherlands, a better link between preclinical (e.g BPRC, Viroclinics, WBVR) and clinical facilities and more focus and funding for either AMR or antiviral therapies. As these topics are out of scope to the current report these will not be further discussed.

One key suggestion from one of the experts interviewed is furthermore noteworthy. Specifically, during the pandemic, there has been an overall shortage of GMP facilities capable of producing (therapeutic) compounds and vaccines against infectious disease. If the new unit would include a small GMP manufacturing laboratory, for the production of challenge stocks, such a (costly) facility could possibly also produce biologicals in case of a pandemic, further supporting the (lack of) GMP capacity in case of a pandemic, benefitting its overall mission to contribute to combatting the pandemic, whilst de-risking the financial investment of such a GMP lab in an early phase infection unit.

8. Conclusion and recommendations

This preliminary report set out with the aim to investigate whether there is a benefit and a need for the establishment of an early phase infection unit in the Netherlands. Information gathered from public sources, documents shared under embargo and specifically through interviewing a broad panel of Academic and Industry experts, it is evident that there is a (strong) case for the establishment of an early phase infection unit.

An early phase infection unit, to be built as a new building, will benefit the Dutch population, Academia and Private parties. By combining investigator-initiated (at cost) studies performed for public entities in addition to the performance of commercial industry-initiated studies the unit is envisioned to be financially independent. The infection unit is proposed to have the capacity to perform highly complex early phase clinical studies (phase I-II), including controlled infection studies for developing drugs as well as vaccines. The unit should ideally have a not-for-profit basis so it could use potential revenues to invest in methodology development or support the development of products for "poor" markets using public (e.g NGO) funding. The primary focus of the unit is suggested to be on infectious disease with a pandemic potential or current pandemic effect. Furthermore, clinical studies assessing disease indications for which there is a high need for a vaccine or therapy for Public Health, or Global Health could be performed. The eventual focus of the infection unit in terms of pathogen or disease indication studied would follow the needs of Academia, Industry and the Public/Global health, which might shift over time.

Of course, in case CHIM studies are more easily performed in another (outpatient) setting and/ or the goal of the study is to look at transmission outside the medical setting, studies should be performed

where most opportune. Although the infection unit should be open for collaborations with the various University Medical Centers, it is not envisioned to have the monopoly on the performance of CHIM studies in the Netherlands.

The new early phase infection unit is envisioned to be governed as a foundation (or other legal form that meets its mission and the interest of its stakeholders), by a small management team and a small executive Board consisting of business-savvy, subject matter experts. Collaboration with private partners should be encouraged and is considered to be a crucial factor to the success of the new unit. In addition, further collaborations with international infection units and Key Opinion Leaders, Non-Governmental-Organizations like CEPI, the BMGF and for instance the Wellcome trust could be pursued. Whereas the new unit needs to be build in the proximity of a (University) medical center, to warrant the access to best patient care when needed, and possibly outsource some of the analytics, it is considered very important to safeguard independence.

As a follow up from the initial conclusions from this preliminary report on the need and benefit of an early phase infection unit, a list of next steps that could be pursued include

- An in-depth investigation into the exact needs (e.g square m², Biosafety level, number of inpatient rooms) of the new infection unit and the cost of suchlike a new unit. The eventual role out of a unit could potentially be done by a DBM procedure (Design Build Maintain).
- An investigation into the regulations of public funding to a new infection unit (e.g state aid)
- An investigation into the tentative formation of a foundation or other legal entity governing the activities of a new unit, including a tentative look-out for key subject matter experts to be involved in the executive board and management of such a unit
- An investigation into the operational practice and governance of a foundation or other legal entity, serving both the public and the private interest.
- The set-up of a discussion group between the foreseen management of the early Phase infection Unit and key regulatory bodies to expedite the process for the review of clinical protocols for infection studies (e.g in case of pandemics).
- A preliminary investigation on the option of finding co-funding of the initiative through for instance NGO's.
- An exploration of the public and private partnerships (e.g strategic partnerships with CDMO's and CRO's) to further create the ecosystem, essential for the success of the early phase infection unit.

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Annex 1: Questionary for Experts from Academia (A) and Industry (B)

General info

1. Please state your name, Profession and affiliation
2. (A) Main focus and expertise (e.g. virology, AMR, parasitology, human challenge trials, pediatrics)
2. (B) What is the core focus of the company in terms of products and services (e.g. antivirals, anti-bacterials, vaccines, therapeutics, repurposed drugs, CRO, CDMO)?

Understanding the pains and gains of a potential early phase infection unit

1. Are you active in the field of infectious disease and specifically in infection trials?
2. (A) Is there a need for a unit dedicated to performing (EMA/FDA acceptable) early clinical development studies and methodology development (e.g. controlled human challenge models) in infectious diseases in your specific focus area (e.g. Malaria, COVID-19, RSV, Influenza) or any other area outside your specific focus ?
- 2 (B) Would a unit dedicated to performing (EMA/FDA acceptable) early clinical development studies and methodology development (e.g. controlled human challenge models) in infectious diseases in your specific focus area (e.g. Malaria, COVID-19, RSV, Influenza) or any other area of your expertise outside your current focus, benefit the development of your products or services ?

If so, could you specify which benefit an early phase infection unit might have (e.g. in terms of time to market, development time, costs, emergency use of the compound, gaining meaningful results etc.) would bring?

3. (A) Have you, or any of your colleagues, encountered hurdles in the performance of an early clinical development study in the infectious disease area in the past years and if so, could you please describe these hurdles?
3. (B) Has your company or have any of your collaborators, encountered hurdles in the performance of an early clinical development study in the infectious disease area in the past years and if so, could you please describe these hurdles?
4. During the SARS-CoV-2 pandemic where you forced to move clinical studies abroad or in suboptimal environments and if so, could you please provide an example?
5. (A) Would it be of benefit if the community of expert physicians, would have access to an early phase unit dedicated to performing (EMA/FDA acceptable) early clinical development studies and methodology development (e.g. controlled human challenge models) in infectious diseases in the Netherlands?

If so, could you please elaborate on the benefit for i) the scientific and medical community (e.g. University medical centers, investigator driven studies), ii) the clients you serve (e.g. including private sponsors) and iii) the Dutch population as well as the Dutch Government?

- 5 (B) Would it be of benefit if your company, would have access to an early phase unit dedicated to performing (EMA/FDA acceptable) early clinical development studies and methodology development (e.g. controlled human challenge models) in infectious diseases in the Netherlands?

If so, could you please elaborate on the benefit for i) your company and collaborators, the scientific and medical community (e.g. University medical centers, investigator driven studies) iii) the Dutch population and the Dutch Government?

Aside from the benefit an early phase infection unit might have for the above segments, is there an overall benefit of the establishment of an early phase clinical unit for the '*B.V The Netherlands*' ((e.g. investment climate of Pharma, new research, establishment of a Biotech hub)?

Infection Unit

1. Assuming an infection unit would be established in order to address the issues and hurdles outlined in the section above, what would be the pro's and cons of having
 - i) a virtual entity, (actual work to be performed in existing sites), governed and orchestrated by a new (or existing) legal entity,
 - ii) a new infection unit, to be build as an extension to an existing building/ clinical unit, governed by a new (or existing) legal entity
 - iii) a new infection unit, to be established as a new building, to be governed as a new (or existing) legal entity
2. Which types of studies should be supported in the infection unit (e.g. PK studies, only studies with infectious material, only studies supporting pandemic preparedness, neglected diseases, all pathogens, methodology development and validation studies, investigator initiated, Sponsor initiated)?
3. What should be the ideal size of the infection unit (e.g. square meters, number of beds (inpatient and outpatient))?
4. Are there any special requisites to the infection unit in terms of the facilities (e.g. BSL3+, how to deal with aerosols, GMP unit needed, patients in - patients out, containment, air treatment)?
5. Is there a need for supporting capabilities to an eventual infection unit (e.g. serology, virology, cellular immunity, NGS)? If so, should these be offered inside the infection unit or can these best be outsourced?

6. In case of the use of infectious material, how will the access and quality of the infectious material (e.g. SARS-CoV-2 stocks) ideally be covered? Are there specific regulations that need to be taken into consideration when using these pathogens (e.g. CCMO, IGJ, CBG) in clinical trials?
7. Is there a need for regulating principles from the EMA or the CBG to govern infection trials or are these in place?

Partnerships and collaboration (B)

1. What can your company or your collaborators contribute to the set-up of a early phase infection unit (e.g. knowledge, stock production, sample analysis, regulatory support, best practices)?
2. To what extent can your company benefit from the establishment of an early phase infection unit and how can the infection unit contribute to the companies goals?
3. Do you have an idea on how your company might, if opportune, collaborate or partner with an early phase infection unit. What would be the format of an ideal partnership?

Finance, Organizational format and Governance

1. Is there a need to establish an infection unit with public funding and if so, what would be the benefits of public funding for Investigator studies, the sponsor studies and the Dutch population?
2. How much money/funding would be needed for the establishment, and yearly maintenance of an early phase infection unit?
3. (B) Are you planning to perform early phase clinical studies in need for performance in an infection unit in the future and if so, can you make an estimate of the number of trials (e.g per year)?
4. How many trials can realistically be run in an infection unit on a yearly basis?
5. (A) What's the average cost (please distinguish between Investigator Initiated study and sponsor initiated study) of 'a typical' clinical trial, to be performed in an early phase infection unit?
5. (B) What would be your estimate of the average cost of 'a typical' clinical trial, to be performed in an early phase infection unit? What would your company be willing to pay for suchlike a study?

6. In terms of its location, is there any preference for the establishment of an infection unit and if so, why (e.g. containment, access to volunteers, patient population, presence to infrastructure etc.)?
7. (A) In terms of governance, what would be an ideal model from the view of you as expert physicians, (e.g foundation, co-investment of private entities, partnerships and alliances between UMC(s), industries and CRO's CDMO's)?
- 7 (B) In terms of governance, what would be an ideal model from the view of your company, (e.g foundation, co-investment of private entities, partnerships and alliances between UMC(s), industries and CRO's CDMO's)?
- 8 Are there any key resources, that are not part of the infection unit itself, which would need to be secured in order for the infection unit to run?
- 9 If a partnership is foreseen, whom would be ideal partners (e.g CRO's in Serology and virology, IMPD writing, PK analytics, regulatory support etc.)?
- 10 Any other information that is essential to the possible installation of an early phase infection unit you would like to share?

Annex 2: Alphabetical list of Key Opinion Leaders from Academia and Industry, interviewed for input to the current preliminary report.

The list below represents the list of key experts and opinion leaders, interviewed for the purpose of this preliminary report. This preliminary report aims to provide insights into the viewpoints of the experts and the support for a (newly build) early phase infection unit. Various experts were interviewed (e.g. experts from Academia and experts from Industry) with often different viewpoints and different interest. The findings and recommendations in this preliminary report reflect the combined input from the experts consulted, not necessarily indicating that each of the experts consulted supports every suggestion and recommendation made.

Academia

Dr.	Else	Bijker
Prof. Dr.	Louis	Bont
Dr. Ir.	Dimitri	Diavatopolous
Dr.	Bart	Haagmans
Prof. Dr.	Meta	Roestenberg
Prof. Dr.	Rogier	Sanders
Prof. Dr.	Robert	Sauerwein
Prof. Dr.	Leo	Visser

Industry

Dr.	Jaap	Goudsmit	Leyden labs
Dr.	Dinja	Oosterhoff	Intravacc
Dr.	Ab	Osterhaus	Various
Dr.	Victor	Schut	Agilebiotics
Dr.	Saskia	Smits	Viroclinics-DDL
Dr.	Bernd	Van Buuren	Prothini Therapeutics
Dr.	Anne	van Loon	Leyden Labs
Dr.	Elly	van Riet	Intravacc

Clinical Trial Service Provider

Dr.	Koos	Burggraaff	CHDR
Dr.	Wim	Tamminga	QPS
Undisclosed			Leading global commercial Clinical Research Organization

Annex 3: Capabilities, medical expertise / support care that should be available on a SARS-CoV-2 Challenge unit, as described by the World Health Organization Advisory Group tasked to consider the feasibility, potential value and limitations of establishing a closely monitored challenge model of experimental COVID-19 infection and illness in healthy young adult volunteers.

Units chosen for SARS-CoV-2 challenge studies should be high-level containment units that can house subjects in single rooms. Nursing stations should have full telemetry monitors to view vital signs, heart rhythm, and pulse oximetry. They should have the equipment and monitoring capability of an intensive care unit or step-down unit. Ideally, the challenge inoculum could be stored in a secure, locked, high security freezer in a pharmacy on the unit. If possible, the unit should have an on-site specimen processing area and point-of-care assays for some basic clinical laboratory tests. Clinical specimens will have to be sent to the central hospital laboratory for many of the tests. It is likely that some sample processing will need to be done elsewhere (such as PBMC processing).

Because airborne precautions will be required and will limit what can be brought on and off the unit, careful consideration should be given to what diagnostic equipment is available on the unit to minimize subject transport to and from different testing suites (radiology for example).

- Dedicated portable ultrasound with staff trained in performing the ultrasound and interpreting the results should be available on the unit.
- Oxygen and ventilatory support should be available on the unit. In addition, the site should have the clinical staff and capability to evaluate and manage other complications of SARS-CoV-2 infection such as vascular complications.
- Experienced clinicians should staff the unit at all times. The unit should have available critical care facilities and staff either as part of the unit, or transport to an ICU should be readily available.
- The clinical staff and protocols must be in place for initiating advanced care such as intubation or emergency surgery and for transfer to the ICU or other specialty service. Team members should include, in addition to the protocol PI and study team members:
 - o Pulmonary / ICU specialist
 - o Critical care nursing staff
 - o 24-hour physician coverage on the unit (in addition to 24-hour nursing staff)
- Other support services to consider
 - o Oxygen in the rooms
 - o Continuous pulse oximetry, telemetry
 - o Pulmonary U/S on the unit with an experience team member to perform U/S
 - o EKG machine
 - o IV pumps and fluids
 - o Full crash cart including Intubation kits
 - o Dietary support. Meals can be prepared outside the unit and brought in daily
 - o Entertainment on the unit (subjects may have to remain on the unit for weeks)
 - o Housing: can more than 1 subject be in a room?

Addendum

**Preliminary report and investigation into the benefit and necessity of
an early phase infection unit.**

Ploemen Life Science Consultancy BV

Dr. Ivo Ploemen, MBA

Note: This Addendum is written and delivered by Ploemen Life Science Consultancy B.V as commissioned by ZonMw. The findings and recommendations of this report follow from in-depth interviews with private parties and academic experts, public sources, and academic literature, as well as information received under embargo from subject matter experts.

Contact information:

Dr. Ivo Ploemen, MBA www.plsc.nl Ivo.ploemen@plsc.nl

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Executive summary

ZonMw has the potential means for an impulse investment into the initiation of an early phase infection unit. This Addendum to the 'Preliminary report and investigation into the benefit and necessity of an early phase infection unit', provides advice on the legal entity and team that would be best equipped to receive a potential impulse investment in support of the initiation of an early phase infection unit. Furthermore, this addendum advises on a stage-gated approach in such case the impulse investment is insufficient for the build of the complete (new) infrastructure of an early phase infection unit.

A new early phase infection unit should start as a Foundation ('Stichting'). A representation from University Medical Centers, expertised in the performance of clinical infection and CHIM studies, could be at the basis of the Foundation. The Foundation could be led by a small Management Team and be governed by a Supervisory Board consisting of representatives from the University Medical Centers as well as experts from Industry. The Management Team of an early phase infection unit to be should start with the set-up of a center of excellence for the performance of future studies. Also, the Management Team is advised to start working on a solid business case, taking into account the potential scenario of an 'add on' unit to an existing infrastructure or a scenario of a completely new infrastructure. The business case should describe the set-up of a self-supportive unit, which (in time) would be running independently from external funding. The option of sourcing certain tasks (e.g. GMP production of challenge agents, sample analyses for sponsor-initiated studies) to partners should be explored in-depth.

Management Samenvatting

ZonMw heeft mogelijk de beschikking over gelden voor een impulsinvestering ten behoeve van de initiatie van een vroege-fase-infectie-unit. Dit Addendum bij het eerder opgeleverde rapport naar het nut en noodzaak van een vroege-fase-infectie-unit geeft concreet advies over de rechtsvorm en het team welke het best gevormd kunnen worden voor ontvangst van een dergelijke potentiële impulsinvestering. Daarnaast adviseert dit addendum over een stapsgewijze aanpak in het geval dat de impulsinvestering niet voldoende is voor de financiering van de initiatie van een volledige (nieuwe) infrastructuur van een vroege-fase-infectie-unit.

Een nieuwe infectie unit kan het beste in de rechtsvorm van een Stichting worden gestart. Een vertegenwoordiging van Universitair Medisch Centra, gespecialiseerd in het uitvoeren van klinische infectie- en CHIM- studies, zou aan de basis kunnen staan van de oprichting van de Stichting. De Stichting zou geleid kunnen worden door een klein Management Team en overzien door een Raad van Toezicht bestaande uit vertegenwoordigers van de Universitair Medische Centra en deskundigen uit het bedrijfsleven. Het managementteam van een toekomstige vroege-fase-infectie-unit kan beginnen met het opzetten van een expertisecentrum voor de uitvoer van toekomstige klinische studies. Ook zou het Management Team kunnen beginnen met het werken aan een solide business case, rekening houdend met het mogelijke scenario van een 'add on' unit op een bestaande infrastructuur of een scenario waarbij wordt uitgegaan van een volledig nieuwe infrastructuur. De businesscase dient de opzet van een zelfvoorzienende eenheid te beschrijven, die (op termijn) onafhankelijk van externe financiering kan bestaan. De optie om bepaalde taken (bijv. GMP-productie van 'challenge agents' en, monsteranalyses voor door sponsors geïnitieerde studies) uit te besteden aan partners, zal gedegen moeten worden onderzocht.

March, 2023

Background

The 'Preliminary report and Investigation into the benefit and necessity of an early phase infection unit' was delivered in 2021 following the request and commission by ZonMw. At that time, SARS-CoV-2 was pandemic. At present, in March 2023, SARS-CoV-2 has become endemic, and every day business has mostly returned to its pre-pandemic state. Still, the needs and benefits of an early phase infection unit have not waned. The so-called rebound effect of infections such as RSV, influenza, and Strep A infections, has put pressure on capacity of child ICs in the Netherlands. Highlighting the need for more research, therapeutics and vaccines that combat infections.

Recently, in support of its mission to reduce or even eliminate the risk of future pandemics, CEPI has launched an ambitious five-year plan which includes a 'moonshot' objective to help compress vaccine development timelines to 100 days, which is about a third of the time that it took the world to develop a COVID-19 vaccine. An early phase infection unit could well contribute to unraveling the mechanisms of action to the induction of immune responses to a variety of pathogens. Also, Controlled Human Infection Models (CHIM) could potentially contribute to decreasing the clinical development time of new vaccines and therapeutics against infectious disease. For example, CHIM studies could potentially provide information on the correlate of protection in vaccine studies and the efficacy of vaccines early stage thereby reducing the size and potentially obviating the need for (large) clinical efficacy studies.

Research into the development of new therapeutics and vaccines as well as research focused on the discovery and workings of (new) biomarkers is essential in the context of pandemic preparedness. This type of research requires a high level of expertise in, for instance, the processing and detection of pathogens in biospecimens and the measurement of (complex) immune responses. Working with infectious pathogens adds to the operational complexity for studies into the effect of therapeutics and vaccines. The operational complexity becomes even more of an issue in case of a current pandemic whereby working with pathogens in a clinical trial setting would ideally require a dedicated (high containment) infrastructure. The set-up of such a (new) infrastructure requires a large investment.

ZonMw has the potential means for an impulse investment in support of the initiation of an early phase infection unit. The foreseen impulse investment is likely not sufficient for the funding of a complete and new infrastructure. The 'Preliminary report and Investigation into the benefit and necessity of an early phase infection unit' concluded that there is a need and benefit for a new highly specialized facility that can perform high quality registration-grade early phase clinical trials in infectious disease, both for drug and vaccine development, including controlled human infection studies. The preliminary report concluded with a number of suggestions and recommendations to further propel the business case and provide guidance on the inception of an early phase infection unit in the Netherlands. The preliminary report did however not provide explicit advice on the legal entity (and team) that would be best equipped to receive a potential impulse investment in support of the initiation of an early phase infection unit. Nor did the preliminary report clearly define the conditions and considerations that would structure the business case of an early phase infection unit and hence support its success. Lastly, the report did not provide advice on a stage gated approach whereby the eventual early phase infection unit would be initiated with seed funds that would not cover the cost for the full (new) infrastructure.

This addendum aims to address these topics by looking at and advising on the legal entity, the team and the governance of an envisioned early phase infection unit. Furthermore, this addendum aims to provide guidance to the conditions that need to be taken into consideration in such case the impulse investment is insufficient for the build of the complete (new) infrastructure of an early phase infection unit.

Advice on Legal entity, Team and Governance of a (future) early phase infection unit.

Legal entity

Since the impulse investment into the unit is envisioned to be (at least in part) made from public funds, the overall consensus is that the unit should be not-for-profit. The unit is envisioned to contribute to amongst a better understanding and faster development of therapeutics and vaccines directed against infectious disease. This will ultimately benefit (amongst others) the Dutch population. To safeguard that the unit is true to its mission and the revenues of the eventual unit are benefiting that mission (and not for instance its shareholders) the advice would be to provide an impulse investment to a legal entity that has the form of a Foundation (“Stichting”).

Stakeholders at the initiation of an early phase infection unit

In terms of stakeholders the preliminary report has identified various stakeholders which would have a benefit from and interest in the set-up of an early phase infection unit. Parties developing a proprietary product like a vaccine or drug targeting an infectious disease would have a benefit to use the services, knowledge base and infrastructure of an early phase infection unit. Service providers such as CRO’s and CDMO’s would likely support the set-up of an early phase infection unit to leverage their respective capabilities and services. All these parties have a (often in part commercial) interest in line with their own proprietary product development or services. To safeguard that the new Foundation is true to its mission, commercial CRO’s, CDMOs and developers of proprietary products (e.g Biotech or Big Pharma) would ideally not be founding/governing parties in the initiation of an early phase infection unit. Rather, these parties would be partners and supporters (for instance as a potential sponsor of a clinical study) for the early phase infection unit.

NGO’s such as CEPI and the BMGF might be important stakeholders but are less likely to initiate, guide and lead the establishment of an early phase infection unit in the Netherlands.

The findings and conclusion of the ‘Preliminary report and Investigation into the benefit and necessity of an early phase infection unit’ made use of the input from various leading academics from the Leiden University Medical Centre, the Radboud University Medical Center, the Amsterdam University Medical Center, the University Medical Center Utrecht and the Erasmus University Medical Center. The combined knowledge from (part of) these institutes could very well provide a solid foundation for the knowledge base and future services of an early phase infection unit. A partnership of (a representation from part) of the above-mentioned University Medical Centers supporting a Foundation could well be at the very basis of the initiation of an early phase infection unit. Some of the above-mentioned Universities have ample experience in the performance of CHIM studies and as such have the required expertise and (in part) the network to lay the groundwork for the new Foundation. To guarantee a broad support and knowledge

base it is advised to have a number of University Medical Centers join the effort in the initiation of the Foundation. To keep momentum and expedite the initiation of the unit, a number of University Medical Centers can potentially be at the initiation of the Foundation and other University Medical Centers can join the Foundation later, in further support of a national infrastructure.

Although Academic partners are proposed to take a leading role in the initiation of the Foundation which is proposed to further build an early phase infection unit, this doesn't mean that the governance of the unit should only be covered by a consortium of University Medical Centers.

Management and Governance of early phase infection unit

When it comes to the eventual management, the oversight and the governance of an early phase infection unit, the stakeholder analysis and expert interviews with members of Academia and members of Industry, has shown a somewhat different point of view. Academic experts are (most often) enthusiastic about the prospect, needs and necessity of an early phase infection unit aligned with their respective research interest and the expertise of their respective institutions. The experts from Industry (e.g. Biotech and Big Pharma) were eventually mostly interested in the benefits the unit could have for the proprietary product development of their company. Importantly, experts from Industry have expressed a clear view on the governance of a future early phase infection unit. According to the experts from industry, it is essential that an early phase infection unit is to be run as if it were a CRO, assuring the high quality of the research and studies performed and securing operational excellence for these (often) pivotal clinical studies.

The early phase infection unit is meant to support and facilitate both Investigator-initiated studies as well as Sponsor-initiated studies. Sponsor-initiated studies can be both pre-competitive as well as competitive. Sponsor-initiated studies will need to represent a substantial part of the total of studies performed to support an early phase infection unit independent of recurrent financial (e.g. Governmental) funding. Also, Sponsor-initiated studies require a CRO-like execution for their clinical studies. This means that, although the afore-mentioned University Medical Centers would likely be well suited to partner at the initiation of the early phase infection unit, a purely academic governance would not be desirable. An oversight by only Academia will have the risk in that the needs of Industry and commercial partners are not sufficiently voiced and addressed. This will potentially lead to a loss of income from Sponsor-initiated studies and therewith affect the revenues and business model of the unit. The Board of the Foundation (i.e. its Management Team) and potentially its Supervisory Board should therewith ideally reflect and secure the interest of the eventual users of the early phase infection unit (i.e. Investigator-initiated studies and Sponsor-initiated studies).

There are various ways to work towards this goal. It is advised to start a Foundation with a small Management team (i.e. Board of the Foundation) to initiate its start and oversee its set-up. Such a Management team might for example consist of a CEO (i.e. Managing Director), overseeing the initiation and day to day business, a Chief Medical and/or Scientific Officer, overseeing the scientific research and (future) clinical studies as well as the communication with the initiating University Medical Centers and a Chief Alliance and/or Business Development Officer overseeing/building the partnerships (rationale on partnerships in sections below) from the initiation of the unit onwards.

Representatives from each University Medical Center at the initiation of the early phase infection unit could potentially serve on a Supervisory Board. Complemented with members from University Medical Centers joining the Foundation later, if applicable. To safeguard the interest of eventual commercial

sponsors (Sponsor-initiated studies) the Supervisory Board should be complemented with members from Industry (or members with a strong background of working in Industry, e.g. so-called (former) Captains of Industry). Transfer of knowledge between the University Medical Centers and the early phase infection unit could be formalized in Consortia Agreements.

During interviews with experts from both Academia and Industry, it became evident that it would be essential for the success of the early phase infection unit to have a Management Team and a (potential) Supervisory Board consisting of subject matter experts. Ideally the team would have an in-depth knowledge, track record and expertise of working in the infectious disease space. The Chief Medical / Scientific Officer would ideally function as the Key Opinion Leader and should ideally have a broad network in infectious disease and CHIM studies, both with academia as well as with partners from industry, both nationally and internationally. To further support the partnerships and connections on an international level, some experts have, during their interviews, supported the notion of representatives in the Supervisory Board from abroad.

Gradual build of Management and Supervisory Board post initiation of the early phase infection unit

The Foundation will likely not be fully staffed with both a Management Team and a Supervisory Board at its initiation. External coordinators could potentially be key at the start of the early phase infection unit to establish and set-up the unit, and work towards the assignment of the complete Management Team and the Supervisory Board.

A stage-gated approach to an early phase infection unit.

From the interviews with experts, it became clear that the establishment of a virtual new early phase infection unit would not lead to much improvement to the performance of clinical studies, certainly not in case of a pandemic. Instead, a new early phase infection unit was proposed to build on one of two scenarios. The first scenario envisioned a unit as a fit-for-purpose facility on an existing infrastructure (add on). The second scenario foresaw a unit built as a completely new infrastructure. Given that the envisioned impulse investment by ZonMw would likely not be sufficient for the set-up of an 'add on' /new infrastructure, one of the first tasks for the Management Team would be to initiate and lay the foundation of the future unit in the absence of the real, physical (add on or new) infrastructure. In parallel, the Management Team could build a business case for a stage gated approach around the two scenarios (add on or new Infrastructure), taking into account the cost, benefits and risks associated with each of the scenarios.

With respect to laying the foundation of the unit in the absence of a real, physical (add on or new) infrastructure the Management Team could, upon a seed investment, start with the set-up of a 'center of excellence'. In such a 'center of excellence' the combined knowledge of participating Universities could be clustered into an 'infection hub'. The existing knowledge and expertise of running infection studies and specifically CHIM studies, from the Universities, will be key. The center of excellence could for instance focus on method development of clinical studies (also in the context of pandemic preparedness). A center of excellence would benefit the strength of the early phase infection unit and hopefully the set-up of

partnerships. The set-up of a center of excellence would be essential to support (future) Investigator-initiated studies and Sponsor-initiated studies and as such be at the basis of a solid business case. Investigator- and/or Sponsor-initiated studies that would be run as a pilot (at an existing infrastructure) could further build to the track record and notability of the Foundation. Having an established Institute with some track record would also de-risk any future investments.

While a pilot study in an existing infrastructure might contribute to the notability of the Foundation, an existing infrastructure cannot meet all the future needs of an early phase infection unit. Certainly not in case of a future pandemic. As outlined in the 'Preliminary report and Investigation into the benefit and necessity of an early phase infection unit' such a unit would rely on a new infrastructure in the form of an 'add on' to an existing infrastructure or a completely new building. The Management Team is envisioned to further develop and investigate these two scenarios which will lead to a solid business case for a future early phase infection unit. A solid business case based on scenario planning might further justify additional funding.

In the scenario planning, the Management Team should investigate in detail and elaborate on at least i) the program of requirements for the early phase infection unit ii) the business case (e.g. in terms of studies to be performed) in the early phase infection unit and iii) the (potential) partnerships needed to secure the business and financial independence of the eventual unit.

The scenario planning of the program of requirements should at least look at the material and immaterial assets and needs. Specifically,

- The clinical infrastructure, both for inpatient and outpatient studies, and its cost needed in the scenario of a fit-for-purpose 'add on' infrastructure and the scenario of a completely new infrastructure.
- The office space and its cost in each of the scenarios.
- The needs and costs of immaterial assets such as IT infrastructure, quality systems, HR and legal support in each of the scenarios.
- The envisioned size in terms of number of volunteers for inpatient and outpatient studies for its purpose (i.e. support of Investigator-initiated studies and Sponsor-initiated studies) and therewith, the proposed location for the unit taking into account ease of access.

The business case should clearly define,

- The number of studies (Investigator-initiated and Sponsor-initiated) that can be performed in the new unit, in each of the scenarios. These should be offset to the cost of the unit.
- The likelihood of performing a number of clinical studies (both Investigator-initiated and Sponsor-initiated) taking into account the Total Addressable Market and the Serviceable Addressable Market (e.g. by type of study and by pathogen studied). A clear business case that justifies the set-up and costs of the new unit (in each of the scenarios) should ideally also take into account the potentially competitive, current and future activities of parties offering similar services such as SGS, Vaccinopolis and hVIVO.

In the set-up of an early phase infection unit in the various scenarios the benefits and risks of engaging with partners should be explored in terms of what can be done in-house and what is to be outsourced.

For example, it was proposed that, for the production of challenge agents, a new BSL-3 (GMP) lab might need to be built. This would come at a considerable cost. In the various scenarios, the Management Team should investigate the costs, risks, and benefits of having a BSL-3 (GMP) lab to produce challenge agents versus the option to partner with existing third parties that can produce (GMP) challenge agents. Likewise, in the scenario planning the Management Team is proposed to explore the costs, risks, and benefits of establishing a lab for the analysis of biomarkers and for instance immune markers versus partnering with third parties taking into account the needs for both Investigator-initiated studies and Sponsor-initiated studies. Clinical studies from commercial sponsors in pursuit of a fast track to market authorization could potentially best leverage on (if available) validated assays for sample analysis. Commercial CRO's might have suchlike validated assays readily available.

Besides investigating the option of partnerships with CRO's and CDMO's, potentially limiting the need for investments into the infrastructure of an early phase infection unit, the Management Team could investigate partnerships with other parties that could further support and potentially fund its business. Potential partners include CEPI, the BMGF, the WHO, HERA, Big Pharma, Biotech and EU grant initiatives.

A broad and well-established early phase infection unit, leveraging its expertise and infrastructure to benefit both Investigator and Sponsor Initiated studies, will benefit the development of new vaccines and therapeutics. This can lead to substantial health benefits for the Dutch population and furthermore increase the recognition of the Netherlands as a serious partner in the combat against infectious disease. This in turn could have a positive effect and attract more (bio)business to the Netherlands.

Vooruitgang vraagt om onderzoek en ontwikkeling. ZonMw financiert gezondheidsonderzoek én stimuleert het gebruik van de ontwikkelde kennis – om daarmee de zorg en gezondheid te verbeteren.

ZonMw heeft als hoofdpdrachtgevers het ministerie van VWS en NWO.

ZonMw stimuleert
gezondheidsonderzoek en
zorginnovatie

Laan van Nieuw Oost-Indië 334
2593 CE Den Haag
Postbus 93245
2509 AE Den Haag
Telefoon 070 349 51 11
info@zonmw.nl
www.zonmw.nl