ZonMw

Knowledge agenda for biomedical research into post COVID syndrome

Publisher's details

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ZonMw's main clients are the Ministry of Health, Welfare and Sport (VWS), and the Dutch Research Council (NWO).

For more information about the Knowledge Agenda on Post-COVID Biomedical Research, please contact the administrative office via e-mail covid19@zonmw.nl or call +31 (0)70-515 03 13.

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1 Rationale

Post-COVID syndrome, also called long COVID or post-acute sequelae SARS-CoV-2 infection (PASC), refers to the continuing health problems that people might experience after recovering from a SARS-CoV-2 infection, the virus that causes COVID-19. These health problems can range from mild to severe and may include persistent symptoms, such as fatigue, shortness of breath and trouble concentrating, as well as long-term effects, such as damage to the heart, lungs or brain.
Recent studies show that one in eight people sustain long-term health problems after having COVID-19. In the Netherlands, an estimated 450,000 patients suffer from persistent symptoms. Many of these patients recover over time. However, for a small group of COVID-19 patients, recovery proceeds less propitiously. About half of this group of patients requires rehabilitation, either clinically, with a medical specialist or as an outpatient. The number of people in the Netherlands who suffer serious impairment due to post-COVID syndrome is estimated by the *Maatschappelijk Impact Team* (MIT) at 90,000, based on research conducted in the UK by the Office for National Statistics (ONS).

Much is still unclear about the clinical picture and there are currently no effective treatments available that can reduce or eliminate post-COVID symptoms and their causes. Significant contributing reasons are the lack of information about the underlying disease processes and health-recovery factors. Because the condition has not yet been clearly defined, due to the wide spectrum of reported symptoms, only limited insight has been gained into the nature and scope of post-COVID syndrome.

2 Aim

ZonMw has been instructed by the Ministry of Health, Welfare and Sport to facilitate an overarching knowledge agenda for post-COVID syndrome together with relevant parties.

The overarching knowledge agenda has a dual aim to produce:

- A review of the research into post-COVID syndrome that is currently being conducted at the national and international levels.
- An advisory report about promising treatments and where more research is needed; in addition, to identify the most significant knowledge gaps brought together in the overarching knowledge agenda.

The knowledge agenda is divided into two research fields that ZonMw believes require additional studies of post-COVID syndrome: i) biomedical research, and ii) clinical or care-related research.

This report concerns the biomedical part of the knowledge agenda. The research questions drawn from the overarching post-COVID knowledge agenda will guide research projects funded under the ZonMw grant programme *Post-COVID Syndrome: Research programme, knowledge infrastructure and expertise network.*

3 Method

ZonMw asked the post-COVID knowledge agenda committee to advise on a selection of specific research questions for biomedical research on post-COVID syndrome. A review report of the current knowledge about the disease and ongoing research projects created by the Institute for Responsible Use of Medicine (IVM) and C-support served as the basis, supplemented by the post-COVID core committee.

The committee met on 3 August 2023 to discuss the research questions and topics in the field of biomedical research on post-COVID syndrome, and thereafter to prioritise their findings, based on their own experience and expertise. The committee's deliberations included but were not restricted to the review report of ongoing research into the post-COVID syndrome at the national and international levels. The committee subsequently issued recommendations about urgent research questions which should be included in the post-COVID programme.

During prioritisation, the focus was on the knowledge required to unravel the underlying mechanisms driving post-COVID syndrome, which may consequently lead to new insights and/or starting points for diagnosis and treatment.

In order to identify the top five knowledge gaps, the committee was asked to prioritise these gaps based on a number of criteria.

Criteria:

1. The research leads to new biomedical insights and/or starting points for diagnosis and treatment of post-COVID syndrome, preferably in the short term.
2. The Netherlands is in a good position to perform this research, i.e. research where the Netherlands can add value to research that is already being carried out internationally;
3. The research is not already being conducted elsewhere, or adds value to ongoing (international) research.
4. Availability of competent research groups who can take this up in the short term (feasibility).
5. There is a good balance between the necessary costs and the expected gains.

In addition, the ZonMw committee advised on possible follow-up programmes for the selected research questions. The advisory report provides recommendations on how to fill the knowledge gaps with regards to the following subjects:
- Mobilising funding instruments
- Available data and ongoing research
- Availability of competent research groups in the Netherlands
- Connecting in the national and international context
- Opportunities for and strengths of the Dutch research field
- Required funding

4 The committee

The following members were appointed to the post-COVID knowledge agenda committee:

- *Chairperson*
  - Professor Frits Rosendaal (NFU, LUMC)
- *Committee members*
  - Professor Mihai Netea (RadboudUMC)
  - Professor emeritus Hemmo Drexhage (ErasmusMC)
  - Dr Anne Wensing (UMCU)
  - Dr Femke Mollema (HMC)
  - Professor emeritus Ria Nijhuis-van der Sanden (RadboudUMC)
  - Dr Peter Kunst (OLVG)
- *Observers*
  - Marloes Dankers (IVM)
  - Dr Sara Biere-Rafi (C-Support)
  - Margreet Schreurs (VWS)
  - Joanna Udo de Haas (VWS)

5 Results

5.1 Theme 1: Diagnosis

A reliable diagnosis is, in the eyes of the committee, essential for carrying out any type of post-COVID syndrome research going forward. It is therefore crucial that we acquire a solid definition of post-

COVID syndrome, or at least of the various subtypes, in order to be able to classify patients according to subtype, severity and prognosis.

The committee agrees that a major impediment to a reliable diagnosis of post-COVID syndrome – and thereby all other forms of research into post-COVID – is the paucity of objectifiable criteria for such a diagnosis. This holds for the pathological/biological criteria and the clinical criteria. Identification of these criteria is impeded by the heterogeneity of the group of patients with post-COVID syndrome.

Both in the early phase of the pandemic and in the current period, medical professionals face huge challenges in objectively diagnosing an infection of SARS-CoV-2 due to limited access to diagnostics with a documented test result. This means that it is often difficult to even identify the hard determinant of post-COVID syndrome, namely a recent period of illness with the disease.

The committee also proposes that clinical-scientific research is impeded because diagnostic criteria are not clear. This makes it difficult to assign patients to the right subgroup. By including a heterogeneous group of patients in, for example, therapeutic research, a positive effect of a treatment in a subgroup can be missed.

Much research is being conducted on biomarkers in post-COVID syndrome, but the clinical relevance of such biomarkers is as yet largely unclear. It is also still unclear whether such biomarkers will be able to differentiate post-COVID syndrome from other conditions.

With regard to the identification of biomarkers, the committee deems it important to distinguish two distinct types:
- Biomarkers that predict whether someone has a higher chance of developing post-COVID syndrome:
  - These markers may, in theory, be used for the preventive treatment of patients in order to reduce the chances of them getting post-COVID syndrome. The committee would like to add, however, that preventive treatment is not relevant yet, because it has often not been determined whether someone has COVID-19.
- Biomarkers in people who have developed post-COVID syndrome, with the aim of sorting patients into subgroups.

The committee deems it important to map the actual clinical evidence (with routine data). Classifying symptoms may lead to a better, more differentiated collection of symptoms, plus an understanding of how they coalesce in syndromes. Just as important, in the eyes of the committee, is mapping the biological parameters of the condition, using a wide range of diagnostic methods and new technologies, such as Artificial Intelligence and machine learning.

To sum up, the committee deems the following research of primary importance:

The identification of post-COVID syndrome subtypes by means of clinical phenotyping and biomarkers, combined with the latest modern diagnostic methodologies (including an omics-based approach).

5.2 Theme 2: Etiology, mechanism and prognosis

Etiology

The committee defines the risk factors as those that determine whether someone will get post-COVID syndrome with a certain degree of severity and combination of health problems. The review of current research put together by IVM and C-support outlines a number of possible risk factors, including being a woman and being admitted to hospital for COVID-19. Most published studies focus on people who were admitted to hospital, but post-COVID syndrome also occurs in those who go through a period of illness with relatively mild symptoms. This differentiation may be important because those who were admitted often had other risk factors and comorbidities, which may point to differences in the original pathophysiological mechanism. The most important risk factors for post-COVID syndrome are the severity of the disease, the variant of the virus, treatment, period of illness, comorbidities, plus individual factors, such as age, sex, BMI, lifestyle and socio-economic factors, but also genetic, immunological and haemostatic factors.

The committee agrees that other possible risk factors and the interaction between these risk factors has been insufficiently investigated. For example, in many immune-related diseases, the human leukocyte antigen (HLA) type plays a determining role. In order to investigate whether this plays a role in the etiology of post-COVID syndrome, larger groups of patients are necessary. The committee therefore deems it highly important to first identify well-defined subtypes of the condition before conducting any research.

Based on studies conducted in Italy, anxiety and depression are potential risk factors for post-COVID syndrome, but also seem to function as manifestations of post-COVID syndrome. This clinical picture is less clearly observed in the Netherlands. It is possible that this group can be differentiated as a subgroup of post-COVID syndrome patients.

To sum up, the committee finds that in order to identify risk factors, it is of the utmost importance to divide patients into subgroups, which makes proper diagnosis crucial. In the committee's opinion, research into risk factors must primarily look at risk factors that either offer starting points for therapy or are important for people with a higher risk of developing COVID-19, with the emphasis placed firmly on modifiable risk factors.

Prognosis
The committee believes that it is important to investigate the natural course of the disease in order to learn from people who recover from post-COVID syndrome and from people who have certain symptoms that disappear on their own. This would give greater insight into the factors that determine which people have a higher chance of recovering. Essential aspects that must be included, in the eyes of the committee, are socio-economic factors. The committee also sees the considerable importance of including the course of the illness when identifying patient subtypes.

Disease mechanism
The exact pathophysiology of post-COVID syndrome is unknown. There are different hypotheses about the underlying pathophysiology. The research review compiled by IVM and C-support lists the most commonly cited hypotheses, i.e.:

- Viral persistence
- Immune dysregulation (including reactivation of pathogens, insufficient SARS-CoV-2 antibodies and auto-antibodies)
- Dysbiosis
- Endothelial dysfunction
- Haemostatic dysregulation
- Autonomic dysfunction
- Mitochondrial dysfunction

Hypotheses cannot be seen in isolation, and the difference between cause and effect is as yet unclear. The committee believes further investigation of these hypotheses is important. The committee deems it important that research on these hypotheses should also be connected with therapeutic potential; additionally, possible interrelationships between the different hypotheses should be investigated by groups containing experts in the different areas of the hypotheses. In this light, it is also important to include postural orthostatic tachycardia syndrome (POTS) and post-exertional malaise (PEM) and take this along in research.

To sum up, the committee deems the following research question important:

Research into the pathophysiological mechanisms in order to identify subtypes, with the aim of finding new starting points for treatment.

5.3 Theme 3: Non-medicinal methods of treatment

The committee defines 'non-medicinal methods of treatment' as any kind of therapy that does not involve doctors administering or patients taking drugs or medicines. For example, exercise, lifestyle

interventions, psychotherapy. Non-medicinal treatments according to this definition fit better in the clinical section of the knowledge agenda.

The committee indicated that many interventions are tested at the present time. The committee believes it is important to find out which interventions work and which ones don't. When doing so, it is important to connect interventions with pathogenic mechanisms.

The committee furthermore observed that we must first reach greater clarity about the pathophysiology and etiology of the condition, before it makes sense to test such things as exercise interventions as possible treatments that might have an effect on the pathophysiology. It is quite conceivable that certain interventions could have a positive effect on some groups of patients with specific symptoms and not on others, or even have a negative effect on some; one might think of patients with post-exertional malaise (PEM). Clearly defined subtypes are crucial, as is insight into the pathogenic mechanisms.

5.4 Theme 4: Medicinal methods of treatment

The committee made a distinction between preventive and curative medication.

Given the currently low incidence of acute COVID-19 leading to hospital admissions and the low testing frequency for COVID-19, research into preventive drugs is less relevant at present time. However, research into the effectiveness of preventive substances may offer potentially important insights into the pathophysiological mechanisms and risk factors.

The committee observed that there are currently no clear indications of a candidate drug for curative treatment. However, patients do receive various treatments that have not been tested, sometimes in other countries. Such treatments may carry risks. Moreover, healthcare providers need to have scientific backup for such treatments. For those reasons, the committee deems it important to register which treatments patients have undergone, to find out whether these treatments are effective and to identify what risks are associated with them. Such a method will allow patients to be better informed about the risks and effectiveness of such treatments.

The discontinuation of the COVID-19 testing policy is hampering diagnoses of new post-COVID syndrome patients, because these patients' symptoms can no longer be linked with any certainty to COVID-19. This in turn impedes research into treatments for post-COVID syndrome. One way of getting around this is to focus research primarily on people who can prove they were infected with the SARS-CoV-2 virus. Another option is to use one of the three subgroups in the inclusion of patients: proven, probable and possible infection. This method would require clear definitions of these three terms, but it would prevent certain groups from being excluded.

The committee likewise believes that the course of the disease – re-infections, new symptoms, symptoms that worsen or get better – is an important aspect to incorporate into the inclusion/exclusion criteria of clinical trials, which could better target strictly defined subgroups rather than a wide range of patients with a diverse symptomatology.

6 Conclusion and research questions

The committee is of the opinion that in order to conduct effective clinical investigations, it is important to first gain more insight into the pathophysiology of post-COVID syndrome. Secondly, good diagnostics must be made available in order to sort patients into the right subgroup. By dividing patients into subgroups, it will be possible to demonstrate the positive effect of a particular treatment within a certain subgroup. The committee therefore recommends that efforts should first be concentrated on diagnostics and pathophysiology before initiating research into medicinal treatments; their findings result in the following prioritisation:

1. **Identify methods that can be used to obtain an objectifiable diagnosis, which might include the use of biomarkers, imaging techniques or physiological tests.**

2. **Identify patient subtypes by means of clinical phenotyping of symptoms and syndromes, combined with the results of question 1.**

3. **Relate the diagnostic testing of question 1 and the subtyping of question 2 to severity and prognosis.**

The committee thus recommends the following important elements:
- Use clinical phenotyping, a wide range of diagnostics (from blood to imaging), and where useful new analysis technologies, such as AI and machine learning
- Classification according to severity and (variable) time dependence
- Use available routine data
- Engage in multidisciplinary research, with key roles for disciplines in the following non-limitative list of clinical specialties:
  - Internal medicine, infectious diseases, pulmonology, vascular medicine, neurology/neuroimmunology, pathology, radiology
  - Pathophysiological specialists in the fields of major bodily systems, such as immune system, haemostasis, inflammation, nervous system and endocrine system
  - Methodologies and data scientists
- It is important to seek connections with international initiatives in this area, where possible
- It is crucial to conduct studies in people who fully or partially recover (whether or not through natural course), or who exhibit a variable course of illness

4. **Research into the pathophysiological mechanisms of the post-COVID syndrome in order to identify subtypes, with the aim of finding new starting points for treatment.**

The committee thus recommends the following important elements:
- The committee recommends that these questions will be sent out in competition for funding
- It is important to consider potential treatment at the start of a research project. In order to encourage this, the committee recommends to investigate the possibility of follow-up funding for proof-of-principle studies or small-scale clinical trials
- The possibility of linking research into post-COVID syndrome with research into other post-infectious diseases should be explored
- The committee recommends a multidisciplinary approach
- Connecting with ongoing research is important
- When safe substances are available for trial, direct interventions using an experimental human study are preferred to those using a laboratory animal model

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