



The story of an extraordinary year: Challenges and opportunities in responding to Covid-19

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ABSTRACT

Little more than a year after the first reports of a new coronavirus in Wuhan, China, the world is in the middle of a pandemic that has brought dramatic changes in societies all over the world. This is our story, as seen from the Department of Immunology and Transfusion at Oslo University Hospital (OUH).

During the last week of February, skiing tourists returning from winter holidays in the Alps sparked a major outbreak of this new corona virus in Norway. The first outbreak in a health care facility occurred at Oslo University Hospital (OUH), in the Department of Ophthalmology, during the following days in which six employees were infected [1]. For the hospital this represented a huge challenge, and containment measures had to be based on limited knowledge about this new disease. The Department of Ophthalmology was closed, hundreds of patients and employees were quarantined, and appointments were cancelled.

During the following weeks, hectic activity took place in a lot of areas to prepare for rough times ahead. A few examples are mentioned:

- Development of new PCR tests for the diagnosis of SARS-CoV-2 that were independent of commercial reagents already in short supply
- Acquisition of microbiology analysis equipment that could run thousands of tests night and day
- Acquisition of new plasmapheresis machines for production of convalescence plasma

In addition, several research projects were launched, some of which are described below.

Thursday, March 12th at 2 pm, the Norwegian government implemented a nationwide lockdown, at the very same time as the specialist course in Haemotherapy was coming to a close at Oslo University Hospital. This would also be the last specialist course to be organized with the physical presence of participants for many months to come.

1. Controlling the first wave and flattening the curve: measures in the hospital/blood center

In the blood center, several measures were taken to prevent transmission of covid-19, whilst avoiding reduction in donation activity. Before the virus was circulating in Norway, there were strict traveling quarantines for blood donors. Following the first outbreak in the hospital, a significant reduction in the number of donors showing up was noted, and we had reports that people were worried about their own safety. We realized the potential negative effect it would have on the blood center's reputation if a donor contracted covid-19 from another donor or an employee, and therefore focused on measures to avoid this and on making donors feel safe. Also, precautions were taken to reduce uncertainty and stress among staff. Social distancing led to cancellation of internal meetings, or these were rescheduled on a digital platform. Information was increasingly given by e-mail. Donation in our mobile unit was cancelled or moved to the blood center because of the limited space in the bus. All contact points, including lunch, were reduced to a minimum.

Today, personnel with possible symptoms of covid-19 are told to stay at home pending the result of testing. SMS/e-mails to remind blood donors about their appointments, now include a recommendation to self-defer in case of symptoms or recent exposure to virus, with a link to the website for more details. All information relevant to blood donation is readily available on our website, which can also be downloaded as a smartphone app. To prevent entry of potentially infected donors into the hospital, a screening system (pretriage) has been set up. Outside the building, donors are questioned about symptoms, history of travel abroad, and contact with covid-19 patients, and there is disinfectant

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available both in the entrance area and inside the blood center. Waiting areas have been marked to prevent donors from being close to each other. Both donors and personnel wear facemasks when distancing is impossible, and we have plexiglass screens for protection both in interview booths and at the donation chairs. We have also introduced video interviews to reduce the number of people present, and to prevent crowding. The concept is to keep a distance between personnel and donors at all times. Until now, this has been successful – no transmission of virus has been traced to the blood center, and during the autumn none of the employees has been quarantined.

It has indeed been a demanding balance between the need to keep a sufficient blood supply, while reducing the risk of transmission of covid-19 as much as possible. Fortunately, the need for blood products has been low during this period, whereas the blood donors have actually shown up to a greater extent than usual. In daily life with work from home and social distancing, the occasional visit to the blood center may actually represent a welcome moment of social contact for the blood donors!

Efforts to use this pandemic to speed up implementation of ongoing projects to modernize the blood center, have not been successful. The new situation has emphasized the need for improvements like web-booking of donor appointments (increases the probability that a donor will turn up for the appointment) and electronic health declaration forms (can be filled in at home before arrival in the blood center, thus reducing the number of people and the physical handling of paper forms). Electronic transfer of donation data (from blood mixers directly into the blood bank information system) could reduce time, work in narrow areas and physical contact with blood bags and samples; however, several dependencies remain before this is in place.

2. New research projects Norway/Oslo University Hospital

In the first weeks of the pandemic, several creative research projects were launched; almost every hospital department and many researchers submitted protocols. This included observational cohort studies, randomized clinical trials (RCT), biobanks, and quality assurance studies, covering a wide spectrum from basic science to medicine and psychology. A comprehensive list of projects can be found here (<https://www.norcrin.no/en/national-overview-of-covid-19-trials/>), and here (<https://www.ous-research.no/corona>) (for Norway and OUH respectively).

The Norwegian Research Council acted quickly and collected financial support from public and private sources to one large funding opportunity for every aspect of corona research with the aim to handle the covid-19 outbreak. Seventy-eight groups applied and 30 groups were rewarded with generous research funding starting in April. The list of financed projects can be found on (<https://www.forskningsradet.no/behandling-av-soknad/alle-soknadsresultater/SoknadsresuItat-COVID-19-hasteutlysning/>).

The most prestigious study was the *NOR-Solidarity RCT* (<http://nor-solidaritytrial.net/index.html>), initiated by the Deps. of Infectious diseases and Intensive Care Units at OUH and part of the international WHO-supported Solidarity trial. Remdesivir and hydroxychloroquine were tested against standard of care in covid-19 patients admitted to hospital. A total of 26 Norwegian hospitals from all health regions enrolled patients in the study until the interim conclusions were presented in October [2].

A second, ongoing project is the OUH initiated *Norwegian SARS-CoV-2 study* (<https://www.ous-research.no/home/ous/news/21311>), a globally anchored ISARIC (International Severe Acute Respiratory and emerging Infection Consortium, Oxford University, UK) / WHO (572 sites, 42 countries) national multicenter study involving 10 Norwegian hospitals from all 4 health care regions. The study investigates adult hospitalized covid-19 patients by serial clinical data and human and microbial biobank collection according to the ISARIC/WHO Clinical Characterization Protocol (isaric.tghn.org), in corroboration with several laboratories in Norway and abroad (Sweden, Finland, Germany,

Austria, Italy, England, China). In this global data sharing initiative, several fast track papers have been published and increasing numbers of hospitals and projects have been successively included, and in October a formal collaboration with the Norplasma MONITOR study (see later) was established. In collaborating hospitals, patients treated with covid-19 convalescent plasma (CCP) will therefore already have been included and data relevant to plasma treatment will be shared with the MONITOR study group.

Risk factors for community- and workplace transmission of COVID-19 (*Koronastudien*) is a large observational study of risk factors for transmission of covid-19. The study is a very large combined cross-sectional, case-control and prospective cohort study with participants including 2% with COVID-19. The main aim of the study is to explore risk factors for COVID-19 and the effects of the disease, in particular, in non-hospitalized patients. Preliminary results on spread among health-care workers, travelers and users of public transport have been released at MedArXiv [3]. Preliminary data indicated a potentially protective effect associated with dietary intake of vitamin D in the form of cod liver oil (“tran”), which is now tested in an RCT in collaboration with the manufacturer of the products.

3. Research projects where the Department of immunology and transfusion or Oslo Blood Center has been involved in different ways

3.1. Sampling and recruitment of convalescents

Through an early initiative between the blood center and the PI in *Koronastudien.no* (see above), active or previously active blood donors in the group of people who voluntarily had shared information about a positive SARS-CoV-2 PCR were contacted and invited to donate new blood samples. Based on fresh samples from these convalescents (of whom almost 25 % were found in the blood donor registry), we were able to develop and validate antibody tests and recruit plasma donors. Also, several research projects were initiated in groups that quickly changed their focus from previous research such as cancer to covid-19 immunology (Munthe, Olweus, Lund-Johansen, Andersen, Grødeland). Before additional testing facilities for sampling and biobanking were established, significant amounts of material were collected in the blood center.

3.2. General biobank for future research projects on covid-19

From the beginning, separate projects established specific collections of human biological material related to covid-19. OUH soon established a common general research covid-19 biobank with a steering committee comprising representatives from relevant clinical divisions. The project leaders for the separate projects are represented as advisory members to ensure access to materials for initiated projects. The general covid-19 biobank uses a broad consent form to enable use of collected material for future research on covid-19. An important objective for OUH is to establish a common general research biobank for covid-19 to provide overview of collected samples, electronic tracking of stored samples, and optimal use of available patient material. Donors include patients, healthy controls, blood donors, and previously covid-19-infected individuals. See information: <https://www.ous-research.no/covidbiobank>

3.3. CEPI/NIBSC antibody reference panel/standards

Contacts with the National Institute for Biological Standards and Control (NIBSC) established during the Ebola epidemic in West Africa in 2014 were revived. For the purpose of developing an antibody standard panel, early convalescents from covid-19 (not blood donors) were recruited in a separate project to collect antibody-containing plasma (<https://www.who.int/publications/m/item/WHO-BS-2020.2403>). The standards and reference panels were made available on January 5th,

2021 (https://www.nibsc.org/science_and_research/idd/cfar/covid-19_reagents.aspx).

3.4. The NORPLASMA project

In an initiative by the Norwegian blood banks in cooperation with the Norwegian Directorate of Health, an organization for collection and treatment with covid-19 convalescent plasma (CCP) was established (<https://www.ous-research.no/norplasma>). The project consists of three parts:

- 1) Production of CCP: All aspects of collection, storage and transfusion of CCP were controlled by a group where all major regional blood centers are represented, and based on EU/EBA principles.
 - The first units of CCP were collected by the end of April. In the following months, CCP was collected in 12 centers.
 - Convalescent blood donors (>28 days following resolution of symptoms) were primarily evaluated using local, commercial SARS-CoV-2-tests (e.g., Roche, Architect) with the cut-off values recommended by the manufacturers.
 - Plasma units were stored in accordance with regulations agreed with fractionation partners (Octapharma) to ensure later sale in case of not being used for patient therapy.
 - Together with plasma, serum samples are biobanked for future testing and evaluation in relation to patient samples, and results will be shared with the EU commission database (https://ec.europa.eu/health/blood_tissues_organs/covid-19_en).
- 2) Microbiology: Development/validation of antibody testing, recommendations for test strategy and product safety.
 - The department of microbiology at OUH validated a range of commercial antibody tests for diagnostic use. Other major hospitals performed their own validations, all guided by a national group of experts in microbiology and infectious medicine.
 - In parallel, in-house antibody tests (based on flow cytometry/microsphere affinity proteomics (MAP) and neutralization assays, see below) were developed at OUH, to serve the purpose of screening large population groups and plasma donors. Samples from convalescent plasma donors at OUH have since been analysed by all available techniques in an effort to allow conclusions to be made about which methods correspond best to antibody neutralization and compare well with results published internationally.
- 3) Clinical research: a multi-disciplinary group led the work to establish protocols for research projects to test (NORPLASMA CARE) and observe (NORPLASMA MONITOR) the treatment with CCP:

NORPLASMA MONITOR: In April 2020, The Directorate for Health recommended Norwegian blood banks to make CCP available for patients all over Norway, at their responsible doctor's discretion, but preferentially within the framework of clinical studies. From the end of March 2020, the NOR-Solidarity study actively recruited all consenting eligible covid-19 patients admitted to the Deps of Infectious Diseases and Intensive Care Units, and CCP could not be included in the RCT. In addition, CCP treatment was likely to confound results in NOR-Solidarity, and lead to exclusion of patients. When this was discussed in May, the number of patients had become very low. With this background, the MONITOR study was designed, not as an RCT but with the aim of collecting observational data from patients receiving CCP at the discretion of their treating physicians.

NORPLASMA CARE: A randomized, controlled treatment study of patients with covid-19 in nursing homes. Institutionalized elderly were chosen because of the high mortality in this particular group, and 28-day mortality was chosen as a primary endpoint.

By the time the protocol for this trial was completed and had received ethical approval, the first wave of infection was over, and there were not enough patients for the planned trial. Also, contacts with the authorities responsible for health care in nursing homes revealed

skepticism to committing to a clinical study before adequate funding had been provided.

Because antibody testing had to be established before the clinical studies employing NORPLASMA CCP could be started, the deadline to apply for funding within the covid-19 financial support initiative was not met. Several attempts to release financial support have been unsuccessful, even during the rise of the second autumn wave despite considerable numbers of covid-19 deaths in the group of institutionalized elderly. The CARE study will therefore not be conducted. However, this study is similar to the RCT recently published by the INFANT-COVID-19 group (4), where a positive effect of CCP to prevent development into serious covid-19 disease in elderly patients is found.

3.5. Use of CCP

In contrast to most countries, the use of CCP therapy has been very limited in Norway. Even after the conclusion that none of the so far studied interventions in the NOR-Solidarity trial showed any efficacy, Norwegian physicians have been hesitant to prescribe plasma in an investigational setting, and have preferred to wait for conclusions from the RECOVERY Trial (<https://www.recoverytrial.net/>). By the end of 2020, some 25 patients had received plasma therapy in Norway, and observational data has been included in the NORPLASMA MONITOR or the Norwegian SARS-CoV-2 study for most of them.

An interesting subgroup is the group of immunosuppressed patients with protracted covid-19 disease not able to mobilize a normal immune response due to immunodeficiency. This includes patients with malignant disease, immunosuppressive treatment, and primary immunodeficiency [5]. A small number of such patients have received CCP therapy, and towards the end of the year, the Norwegian Society for Infectious Diseases issued guidelines for use of plasma in these particular patients (www.legeforeningen.no/contentassets/685dcaa4d3b744c8a9d3f110b59f3892/covid-19behandlingv7_181220.pdf) [6].

3.6. Developing large-scale testing for SARS-CoV-2 antibody screening

A multiplexed bead-based flow cytometric assay, referred to as microsphere affinity proteomics (MAP), was adapted for detection of SARS-CoV-2 antibodies [7]. A single microliter of serum or plasma can be investigated for antibodies to Spike/Receptor Binding Protein (RBD), nucleocapsid protein, and a range of human coronaviruses causing the "common cold". Furthermore, an assay measuring antibody-dependent inhibition of binding between viral proteins and the ACE2-receptor has been adapted to the MAP format. The results are in good agreement with those obtained using tests for the ability of serum to neutralize virus (Grødeland), and the proxy assay is now being chosen as the national platform for evaluation of CCP for patient therapy (Lund-Johansen/Andersen).

3.7. T-cell immunology in covid-19 patients

We have performed a broad characterization of CTL and Th cell immunity towards 115 peptides in over 100 donors and compared anti-SARS-CoV-2 T cell immunity to antibody responses. Results may help explain why most individuals are protected from developing severe covid-19. We have also assessed immunity as a function of age including young adults and the elderly. T cell immunity has also been assessed as time progresses after recovery (8-9 months). The first manuscript has been submitted (Myklebust, CV et al).

T-cell immunity in recovered patients, convalescent blood donors and healthy controls is also being investigated by use of T-cell characterization methods developed for mechanistic studies of cancer immune responses (Olweus et al., unpublished).

3.8. Inflammation markers in covid-19 infection

Samples from covid-19 patients and convalescent blood donors have been used to evaluate a test for the inflammatory marker protein, Neopterin, which is increased in covid-19 infection [8]. Further studies of inflammatory marker proteins calprotectin, Syndecan-1 and NETs are ongoing [9], as well as one in which possible antiviral effect of an extract (Andosan™) of the medicinal mushroom *Agaricus blazei* with antimicrobial property, is examined in corona-infected host cells [9]. From the Norwegian SARS-CoV-2 cohort study, several interesting results have been published [10–13].

3.9. Antibody screening in cooperation with the Norwegian Institute of Public Health

OUH collaborates with the Norwegian Institute of Public Health in performing weekly surveillance of SARS-CoV-2 antibody prevalence in randomly selected individuals from other, ongoing research projects. This is a valuable tool to assess the spread of SARS-CoV-2 in the community, to support the health authorities in their decision making. Results have demonstrated that the proportion of tests positive for SARS-CoV-2 antibody in Oslo varies from week to week (<0.5 % to >3.5 % with an average of 1.4 % (<https://www.fhi.no/studier/prevalensundersokelser-korona/resultat—moba/>)).

3.10. Antibody screening in blood donors

Since January 12th, 2021, all blood donors scheduled for donation have been asked for consent to analyse an extra sample for SARS-CoV-2 antibody. The project will provide up-to-date information about the prevalence in the donor population during the second wave of infection, and also allow calculations of the number of asymptomatic infections within this group. The frequency of asymptomatic infections may inform infection prevention policy in the blood center (see above). Also, donors have requested such testing to be performed.

The analysis will be performed using the MAP-testing for anti-RBD/AE2-inhibition as mentioned above, and antibody-positive donors will be contacted and recruited for follow-up with new tests in conjunction with future blood donations to provide insight into the duration of antibody production. Participants will also be invited to donate blood samples for T-cell studies to extend ongoing projects within T-cell immunology, and for the general covid-19 biobank at OUH (see above). In addition to the generation of important knowledge about immunity, the project will allow donors with high antibody levels to be recruited to donate CCP within the Norplasma project. Lastly, when these same donors become vaccinated, important information about how they respond to the vaccine can be collected, in comparison with vaccinated non-exposed individuals.

4. Is Norway different?

As of January 2021, Norway has had a lower incidence and mortality rate of covid-19 compared to most other European countries, thereby avoiding the most extreme measures to contain the epidemic. At the end of 2020 we had only around 440 deaths, and the hospitals have not been overloaded at any time. But this is not to say that contact reducing measures have not affected society. They certainly have. The reasons for the relatively favorable situation in Norway are not known, and this may change any time. But possible reasons include the timely introduction of contact reducing measures and high compliance by the population.

5. Vaccination strategy and looking ahead

Now, in early January, case numbers are increasing and there is concern that family gatherings over Christmas and mutated and more transmissible variants of the virus may threaten our success in fighting

the disease. Several new variants of concern have been found in Norway. Therefore, the government has imposed even stronger contact-reducing measures. The higher number of cases generates an increased number of available CCP donors, but the motivation to produce CCP is falling both due to lack of demand from clinicians and large-scale vaccination within reach. Vaccination against covid-19 has started with vaccination of elderly individuals in long-term care and a limited number of health care personnel. Other individuals in the highest age group will follow. However, until a protective effect of the vaccine in the older age groups has been achieved, CCP is a treatment option available for local outbreaks, as supported by the results from the INFANT.COVID-19 group [4].

Many tools needed to respond to this pandemic are now at hand, and we are ready for 2021. Vaccination will hopefully be the much-needed game changer. We know that vaccination can protect against disease, but need to learn more about the duration of protection, effect against mutant variants and effect on transmission of SARS-CoV-2. Until we know, we will not be able to resume our ordinary pre-pandemic life.

Links

<https://www.norcrin.no/en/national-overview-of-covid-19-trials/>.
<https://www.ous-research.no/corona>.

Publications with coauthors from OUS

<https://www.ous-research.no/home/corona/Right/21097>.

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