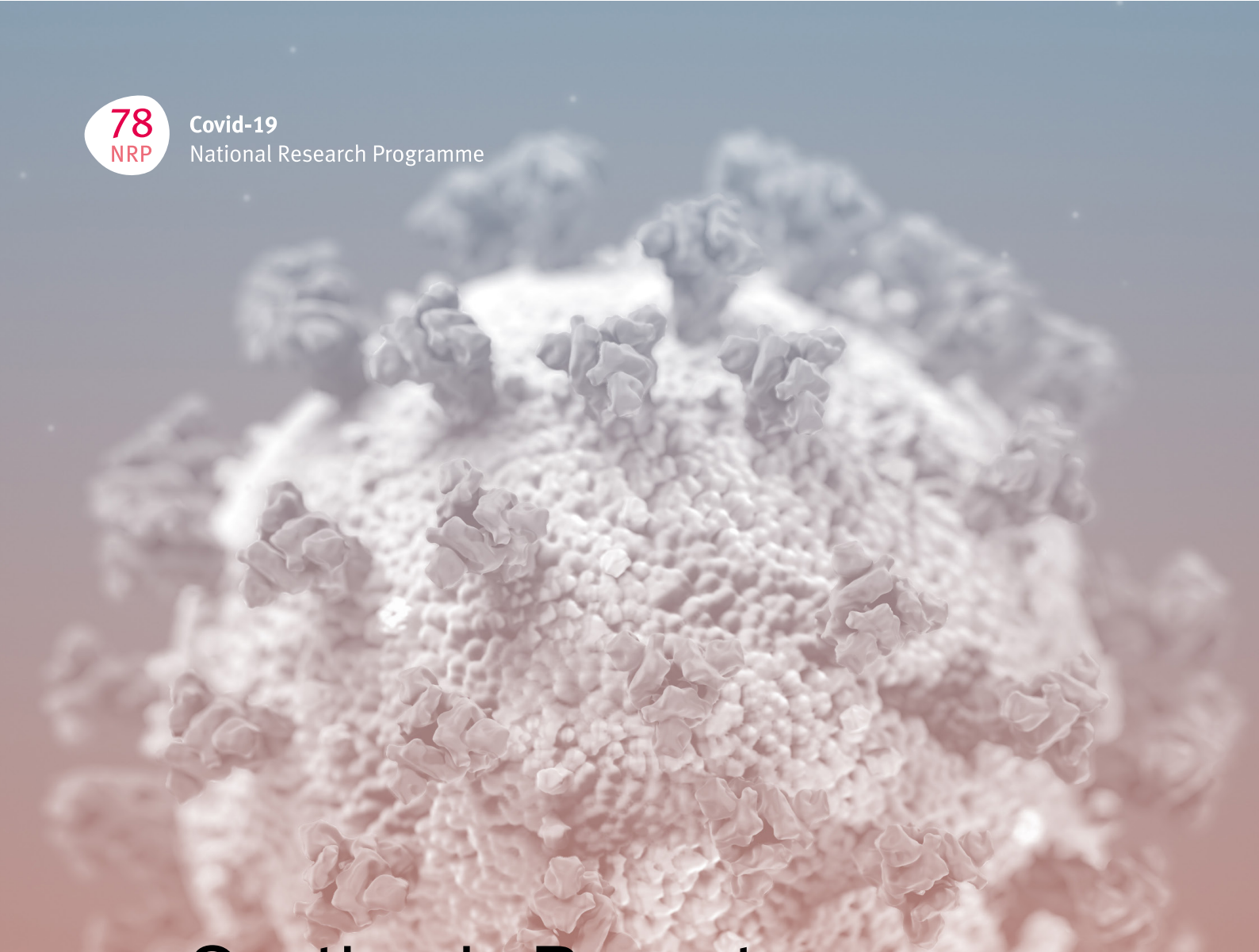
78 NRP

Covid-19
National Research Programme



Synthesis Report
National Research Programme «Covid-19» (NRP 78)

Results and Recommendations

Swiss National Science Foundation

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Part I
Programme Synthesis and Recommendations

Executive Summary

Initiated in the immediate aftermath of the Covid-19 pandemic outbreak, the Swiss National Research Programme "Covid-19" (NRP 78) had a comprehensive mandate. The programme was designed not only to advance our understanding of the novel coronavirus's biology, pathogenicity, and immunogenicity but also to innovate in the areas of epidemiology and disease prevention. Further, the programme sought to accelerate the development of vaccines, pharmaceutical treatments, and therapeutic interventions tailored for Covid-19.

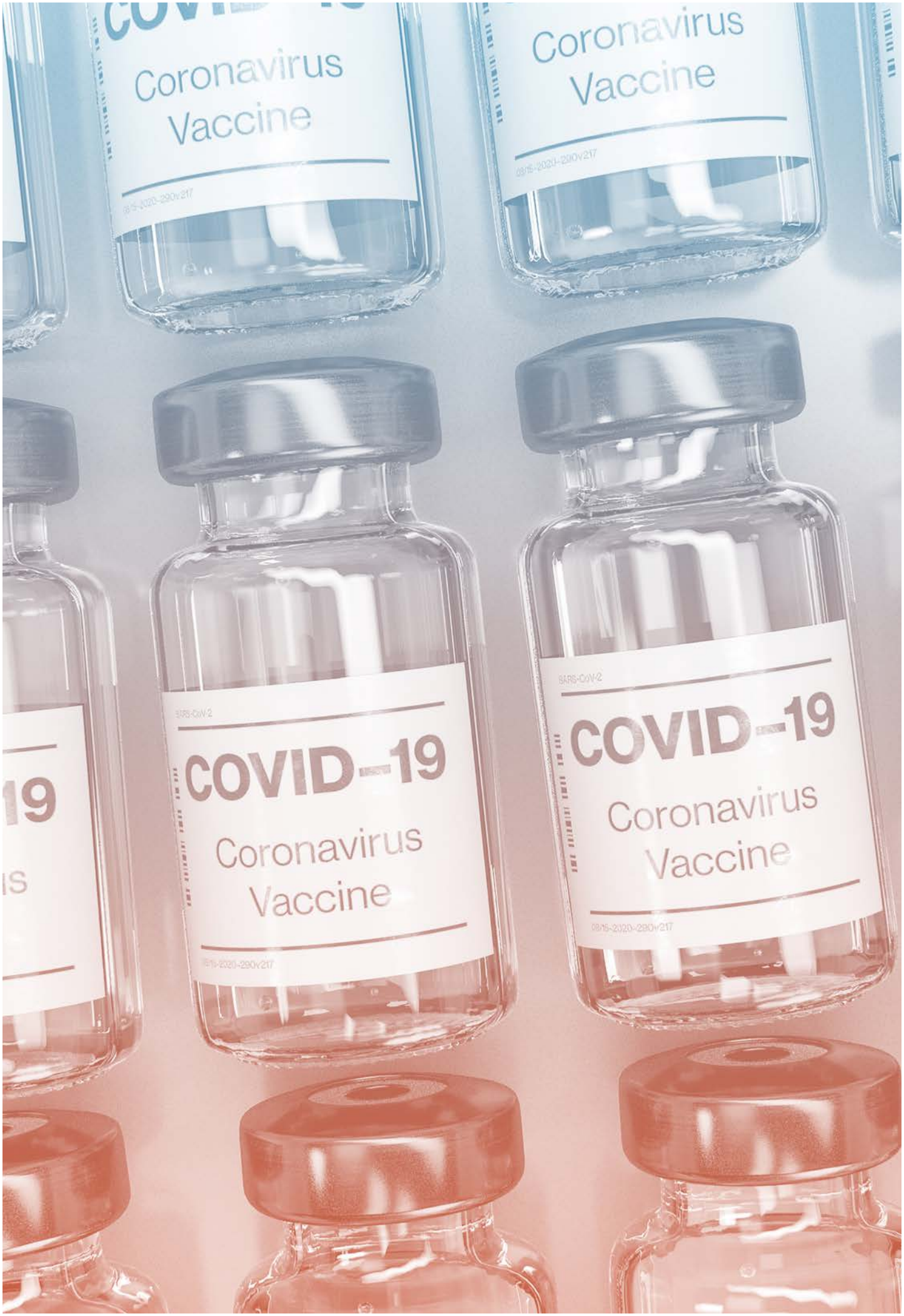
The scientific understanding of Covid-19 has evolved rapidly, and science has advanced at a speed never seen before. The success of NRP 78 is empirically evidenced by its prolific scholarly output. A multitude of high-impact publications were swiftly disseminated, initially appearing on preprint servers before being peer-reviewed and published in reputable scientific journals. The second part of this report is dedicated to detailing these accomplishments.

However, unlike other research programmes, NRP 78 was a programme in a historically unparalleled crisis. This unique context has provided invaluable insights into how to conduct research under such challenging conditions. As a result, we have suggested a few recommendations based on this lived experience. Although such recommendations may be highly relevant for the management of any crises, we have also highlighted key aspects about health crises in particular. We hope that they will be beneficial as Switzerland emerges from the pandemic.

The overall impact of NRP 78 has been amplified by numerous complementary initiatives, all of which are summarized and discussed in this document. Recognizing the critical role of effective communication in times of crisis, the programme gave particular attention to this aspect. Strategies for clear and transparent communication were developed and implemented, thereby facilitating better public understanding and engagement. The lessons learned from these communication endeavours are also outlined herein.

In summary, NRP 78 has been a landmark programme that has not only advanced scientific knowledge in the field of pandemic research but also served as a blueprint for research in crisis and relevant communication strategies.

Marcel Salathé
President of the NRP 78 Steering Committee


Coronavirus
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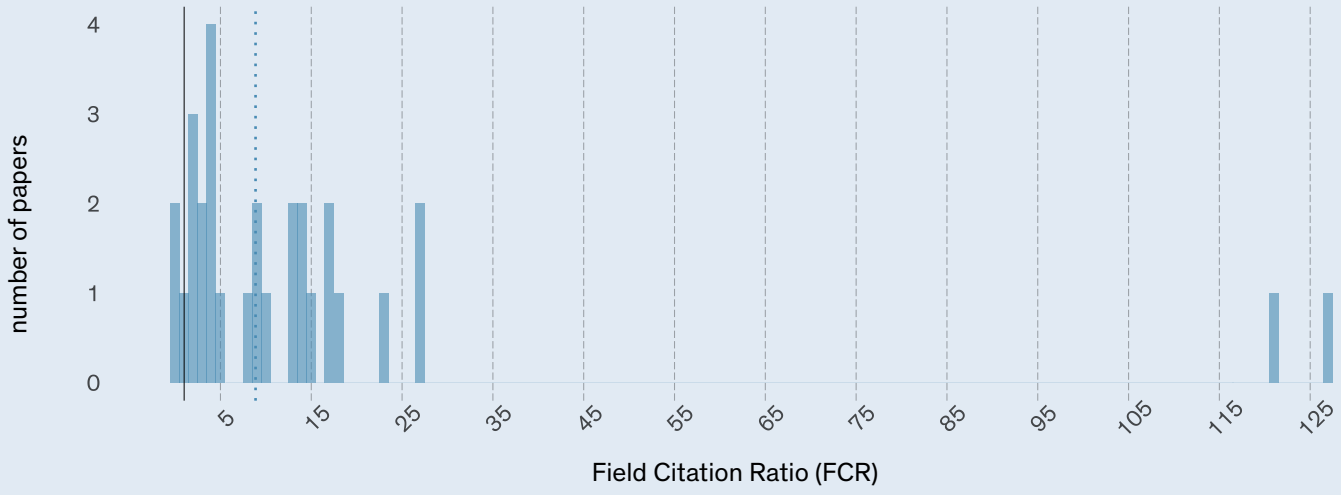
Research in Crisis Mode

The National Research Programme “Covid-19” (NRP 78) has played a constructive role in advancing Switzerland’s scientific understanding of the pandemic. Detailed in the second part of this report, the programme supported a diverse array of projects contributing important findings – ranging from basic aspects of SARS-CoV-2 biology, pathogenicity, and immunogenicity, to the development of vaccines, drugs, diagnostics, and communication strategies, among others.

The primary objectives of NRP 78 were to advance our understanding of Covid-19, develop recommendations for clinical management and public health response, and to drive the development of vaccines, therapeutics, and diagnostics. The main vehicle to achieve these objectives was scientific publications, which allow policymakers and other scientists to rapidly utilize the results in their work. Assessing the impact of these publications is inherently challenging, but one way of gauging it is through the Field Citation Ratio (FCR). This citation-based metric measures the scientific influence of one or more articles by dividing the number of citations a paper has received by the average number received by documents published in the same year and in the same research category. As Figure 1 illustrates, for papers published before 2023, the FCR is notably higher than 1, suggesting these papers have received substantially more citations than the mean in their respective fields.

Figure 1: Field Citation Ratio of NRP 78 publications

FCR is calculated only for publications before 2023.
An FCR > 1 means that a publication received more citations than the mean within its field of research.
The median FCR is indicated by the dotted line (8.87).



A key goal of NRP 78 was not only to produce impactful insights but also to disseminate them as swiftly as possible. The urgency of sharing research findings was a significant consideration for the programme, given the rapid developments of the pandemic. Figure 2 elaborates on the timelines involved in this dissemination, emphasizing the efficiency of our processes.

In addition to the rapid creation and dissemination of research findings, the NRP 78 has been proactive in communicating scientific knowledge to a broader public. Our outreach extended beyond traditional academic avenues, as elaborated in the 'Communication and Impact' chapter of this report. This chapter shows how the NRP 78 has successfully leveraged various platforms, from social media to community outreach, to effectively share the research findings.

Research Project: Covid Norms
Thomas Friemel – University of Zurich
Mark Eisenegger

The Covid-Norms project investigated the prevention behaviour of the population as well as the public discourse on the most important containment measures against Covid-19 in Switzerland. Weekly surveys and a continuous media analysis allowed to monitor the dynamic development of attitudes towards different prevention measures, the perception of compliance in the Swiss population, and its effect on individual behaviour. The project provided a detailed understanding of the barriers and motivations for prevention behaviour during the Corona pandemic.
The research results were made available to the responsible decision-makers at the FOPH and supported them in developing an effective communication strategy. In this way, the planning of the vaccination campaign as well as later measures could benefit from the studies.

From these perspectives, our conclusion is that the NRP 78 has successfully achieved its core mission. However, the programme has also offered lessons for research programmes in times

Figure 2: Preprints and Publications from NRP 78

Figure adapted from Stalder, T., Holtz, Y. (2021): Extended Dumbbe/1 Plot in R with ggplot2. R graph gallery. Access: r-graph-gallery.comlweb-extended-dumbbel/-plot-ggplot2.html. Date: 15-08-2023.

of crisis and beyond. Its two-year duration and initial allocation of resources proved insufficient for the evolving challenges posed by the pandemic – emerging phenomena like "Long Covid", new variants, and the need for accelerated research processes, for example. These limitations have underscored the necessity for a more flexible approach to programme duration and resource allocation, as well as the adoption of speedier, yet still rigorous, research processes.

Research Project: Immunoglobulin signature as a predictor of Long Covid
Onur Boyman – University Hospital of Zurich
Bernd Bodenmiller, Jakob Nilsson, Daniel Pinschewer

The causes of Long Covid are still largely unclear. A detailed investigation of immunological markers in the blood has provided clues about susceptibility to Long Covid. The research group generated a forecasting model that predicts the risk of Long Covid, based on the factors of age, number of symptoms during the primary infection, history of asthma, and the measured blood concentrations of IgM and IgG3. The forecasting model was tested in a second, independent cohort of 395 Covid-19 patients.
The finding that CoV2-specific antibodies could be found in mucosal fluids of individuals that tested negative for CoV2-specific antibodies in blood was the first of this kind and highlighted the importance of mucosal immunity against CoV2. Similarly, the data on individual clones of CoV2- specific B and T cells followed up after infection characterized for the first time the factors important for long-lived cells. This contributed to identifying the risk factors of Long Covid with the help of a Long Covid (LC) / post-acute Covid-19 syndrome (PACS) risk score calculator.

Furthermore, researchers' experiences have illuminated systemic issues affecting the interplay between science and policy. There is an urgent need for better, institutionalized, and resilient collaboration between the scientific community and governmental institutions, particularly health authorities. Current frameworks rely largely on ad-hoc relationships and lack the institutionalized, resilient networks and protocols capable of withstanding the pressures of a large-scale crisis. Addressing these issues will not only help to prepare us for future health crises but will also make the research ecosystem more robust, agile, and responsive to the complex challenges of our interconnected world.

In the subsequent sections, we will outline five areas where the NRP 78 research community has identified room for improvements. We have formulated a series of recommendations that we hope will be useful to the broader community beyond health research.

Crises evolve in unpredictable ways and last longer than assumed

The National Research Programme "Covid 19" (NRP 78) was initially designed as a two-year programme, reflecting early assumptions that the pandemic would be short-lived. These assumptions were rooted in the prevailing sentiment at the onset of the crisis, guided by limited data and understanding of the SARS-CoV-2 virus. This optimistic timeframe, while understandable, set the stage for a series of challenges that would manifest as the situation evolved.

The two-year framework restricted the programme's ability to adapt and allocate resources to new areas of concern that emerged later. For example, phenomena like "Long Covid", rapidly

emerging variants, and shifts in understanding of transmission routes (from droplet to aerosol-based), to name only a few, became prominent well after the programme had commenced. Further, given the two-year limit, many research projects already had to conclude as their themes were becoming highly relevant, creating a disconnect between research timelines and real-world needs. Overall, the short duration made it difficult to pivot or reallocate resources toward newly emerging challenges.

Research Project: Development of a real-time SARS-CoV-2 biosensing system to improve health-worker safety
Walter Zingg – University Hospital Zurich

Airborne transmission has been recognized as a critical issue. This project aimed to provide a tool to assess the level of SARS-CoV-2 exposure in hospitals and nursing homes. The research group developed a biosensor for virus detection and to monitor the virus concentration. The real-time detection system contributes evidence on the role of airborne SARS-CoV-2 transmission and to risk assessment for healthcare workers. The monitoring facilitates the tracking of the epidemiological situation, the warning of increasing infection risks, the identification of key drivers leading to virus spread in the Covid ward and the understanding of the transmission dynamics.

Recommendations

Longer Duration: To address the limitations of a fixed time frame, future research programmes designed to address a crisis should consider a longer duration. For instance, adopting a classical four-year programme could allow for mid-term adjustments. However, it's crucial to note that a longer time frame could risk locking in resources, potentially reducing the ability to address other crises. A solution could be to build in periodic pivot points, where the focus and resource allocation can be reassessed.

Phased Approach: Implementing a phased approach where the scope and duration are adjustable based on interim evaluations could be beneficial. While this adds administrative complexity, the benefits of adaptability within planned research phases may outweigh the disadvantages. Streamlined administrative processes can mitigate added overhead.

Crises are marked by problems that are not visible at the start

The NRP 78, like many research programmes, allocated the bulk of its resources at the outset based on initial selection of the 28 funded projects. This approach is typical for most research programmes where the research questions and challenges are well-defined. However, in the context of a rapidly evolving crisis like the Covid-19 pandemic, this method proved to be less than ideal. Initial assumptions did not account for the unpredictable nature of the crisis and the emergence of new, critical research areas over time.

The upfront allocation of resources made it challenging to adapt to new research questions that emerged as the pandemic unfolded, such as "Long Covid", new variants, and aerosol transmission, to name just a few. Without available resources later in the programme, potentially

transformative research areas could not be explored, leading to missed opportunities for impactful discoveries.

Research Project: Large-scale serological profiling of SARS-CoV-2 with high-throughput microfluidic nano-immunoassays
Sebastian Maerkl – EPFL Lausanne
Isabella Eckerle

The research group rapidly developed and validated new technologies enabling cost-effective large-scale sero surveillance and deployed these locally in Geneva and Lausanne to support sero-surveillance programmes in this region. They eliminated the need for serum and concomitant venous blood draws by developing approaches to collect ultra-low volume capillary blood samples obtainable by simple fingerpick. The use of this assay contributes to findings on seroconversion in the general population as well as in children and enable child-friendly outbreak-investigations. The system was also used to study mucosal antibody responses supporting the importance to develop SARS-CoV-2 vaccines that elicit mucosal immunity. The findings on infectious viral loads indicate that vaccines may lower the transmission risk for Delta and Omicron BA.1 variants of concern and, therefore, have a public health benefit beyond individual protection from severe disease. The innovative high-throughput microfluidic technology is now being used by the start-up Adaptyv Biosystems, that was founded within the framework of the NRP 78 project.

Recommendations

Staggered Allocation: A staggered allocation of resources could allow the programme to adapt to new challenges as they arise. While this approach may require more frequent evaluation and reallocation efforts, these 'pivot points' could be invaluable for adapting to unforeseen challenges. One added benefit is that it also allows for the integration of patient groups, which often only emerge as a crisis progresses. However, it is critically important to have the full resource commitment from the beginning. As a crisis unfolds, there is inevitably an effect of habituation that makes it much more difficult to obtain dedicated resources, even if the negative effects of the crisis are just as severe or more than at the beginning.

Dynamic Review Process: Implementing a dynamic, ongoing review process for resource allocation can ensure that funds are directed where they are most needed. While this adds a layer of complexity, the ability to pivot quickly could make the difference in addressing urgent research questions.

Research can be fast

The urgency of the Covid-19 pandemic necessitated a dramatic acceleration in all aspects of the research process. This crisis-mode operation was not merely an internal phenomenon within the NRP 78; it was reflective of a global urgency to understand and mitigate the impacts of the pandemic. Initial concerns that speed might compromise quality were quickly dispelled as the research community successfully adapted to the fast-paced environment. NRP 78 projects published rapidly and made extensive use of preprints in order to accelerate the rapid transfer of gained knowledge.

Bureaucratic processes such as ethical approvals and funding timelines can slow down research. However, these were handled expeditiously, showcasing the system's potential for speed without sacrificing integrity. The real challenge arises in considering whether this speed can be maintained post-crisis. A return to slower processes could be viewed as a step backward, especially when it has been demonstrated that faster operations are possible without quality or integrity loss.

Research Project: Combined epidemiological and molecular investigation of 3 nosocomial outbreaks of SARS-CoV-2 cross-infection
Stephan Harbarth – HUG Geneva
Samuel Cordey, Walter Zingg

After having conducted studies about nosocomial outbreaks of SARS-CoV-2 in 3 hospital sites in the Department of Rehabilitation and Geriatrics of HUG Geneva, involving both patients and Health Care Workers, the research group developed "Escape Covid-19", a playful learning course (serious game) for employees in nursing, care and support across all areas of health care. In four everyday situations at home, on the way to work, at work and in contact with patients, residents and clients, the correct preventive behaviour is discussed and illustrated. In their publication, the researchers demonstrate that the serious game "Escape Covid-19" increases the willingness of health care workers (HCW) to change their behaviour regarding infection prevention and control (IPC). In order to achieve the broadest possible distribution, the web platform was supported by the Federal Office of Public Health (FOPH) and various other actors in the health sector such as the Swiss Red Cross, Spitex Switzerland, Curaviva, H+, Insos, senesuisse, FMH, Public Health, KOGS (OdA) and other organisations.

Recommendations

Review and Retain: A comprehensive review of the accelerated processes could identify which aspects can be permanently incorporated into the research ecosystem. While speed is an asset, it's important to consider that an always-on crisis mode may lead to even more stress within the research ecosystem, or potential oversight. Therefore, a balanced approach that retains speed where it adds value without compromising well-being should be considered.

Institutionalize Quick Approvals: Processes that were expedited during the crisis, like ethical approvals, could be institutionalized to maintain a faster pace in regular times.

Future-Proofing: Establish frameworks for rapid activation of accelerated research modes during future crises. This would enable a swift transition into high-speed operation without the initial period of adjustment and potential chaos. A specific emphasis should be placed on bottlenecks due to shutdown of travel and logistical challenges.

Leverage Preprints: The NRP 78 research community made significant use of preprint servers for disseminating findings quickly. Preprints offer a way to share data and insights in almost real-time, vastly accelerating the spread of knowledge. While critics often point to the lack of peer review as a downside, the rapid feedback loop from the global scientific community can generally act as an "informal" review mechanism. Furthermore, peer review can follow the initial preprint publication, ensuring quality control in the longer term. Concerns regarding preprint publications include, among other issues, the persistence of outdated or refuted data and hypotheses on preprint servers, and the premature dissemination of unverified claims in the media.

Promote Open Science: Open science initiatives, which include but are not limited to open access publications, open data, and open methodology, should be more strongly encouraged. The scientific response to the Covid-19 pandemic has significantly benefited from the sharing of data, methods, and results. These practices increase transparency, allow for more robust peer scrutiny, and accelerate the application of research findings, and are applicable in all scientific domains.

By implementing these recommendations, the research community can capture the benefits of accelerated processes without sacrificing quality, thereby setting a new standard for efficiency in scientific research.

Crises as the new normal

Traditionally, research programmes have been designed to function optimally under 'normal' conditions, with crisis scenarios viewed as exceptional states requiring extraordinary responses. This perspective is increasingly misaligned with the realities of our interconnected world, where crises are frequent, complex, and far-reaching. The assumption that we can simply "switch" to a crisis mode when needed is losing its validity.

The conventional model is inherently reactive, mobilizing resources and adapting processes only when a crisis has already occurred. This leaves little room for proactive measures that can mitigate the crisis's impact. Operating under the assumption that crises are rare leaves research programmes unprepared for the escalating frequency and complexity of modern crises, from pandemics to climate change. Further, the sudden need to shift into crisis mode can strain resources and create inefficiencies, as the system is not designed for sustained crisis management.

Research Project: Agent-based tracking of disease spread
Kay Axhausen – ETH Zurich
Alexander Erath, Melissa Penny, Thomas Van Boeckel

The research group expanded rapidly the MatSim (Multi-Agent Transport Simulation) software with the results of the mobility study MOBIS: Covid-19. While many previous models were based on a homogeneous population, the new platform was based on individual persons and their heterogeneous characteristics, e.g. previous illnesses and behaviour patterns. Through the additional inclusion of mobility habits, it was possible to calculate whether several people are in the same rooms and vehicles. As a result, more precise prediction of the spread of the virus, enables on the one hand forecasts for future developments, such as the occupancy of intensive care beds in hospitals, which gained massively in precision through the project compared to the first pandemic wave. Secondly, the effectiveness of planned strategies could be better predicted, which was useful in evaluating containment measures such as travel restrictions. Altogether, these tools can increase the efficiency of managing pandemics, as their use for example in the Swiss National COVID-19 Science Task Force demonstrated.

Recommendations

Continuous Preparedness: Adopt a new operational paradigm that assumes a constant state of mild crisis, ensuring that any research programme is always geared for quick mobilization. While this may seem like over-preparation, the increasing frequency and unpredictability of crises would justify this approach.

Build Resilience into Systems: Design research processes that are inherently flexible and can scale or adapt quickly. Instead of viewing crises as exceptions that require a complete overhaul of standard operations, integrate crisis-resilient features into the standard operating procedures. This could include regularly updated contingency plans, dedicated crisis-response teams, and real-time monitoring of global events that could precipitate a crisis.

By adopting these recommendations, research programmes can better align themselves with the reality of an increasingly interconnected and crisis-prone world, thereby ensuring they can respond more effectively when the next crisis hits.

SNSF Special Call on Corona Viruses Research Project: COWWID-19 | Surveillance of SRS-CoV-2 in Wastewater - an Early Warning System to Track the Spatio-temporal Development of Covid-19d
Christoph Ort – Eawag Aquatic Research Institute Dubendorf

This project, conducted in 2020, facilitated the development of methods to measure SARS-Cov-2 RNA in wastewater, which helped to track Covid-19 disease dynamics in the community as a complement to other epidemiological indicators. The pioneering work formed the basis for national wastewater surveillance. As of 2023, 14 wastewater treatment plants participate – covering approximately 25% of the Swiss population. The viral loads measured in wastewater are also used to estimate the effective reproductive number independent of reported cases and are only weakly affected by altered excretion rates. During times of intensive clinical testing, the relative trends of reported cases and wastewater agree well. With substantially reduced testing of people as of January 2023, wastewater analyses remain an objective source of information on the disease dynamics. Further, sequencing of SARS-CoV-2 in wastewater extracts also provides insight into the circulation of new variants of concern. Based on the outcomes from this project, the national surveillance was expanded to other respiratory viruses such as influenza and RSV.

Strengthening the collaboration between science and governmental institutions

The Covid-19 pandemic brought into sharp focus an underestimated and therefore overlooked issue: the partnership between the scientific community and the governmental institutions was not sufficiently developed to withhold the enormous pressure of a pandemic crisis. In Switzerland, this is particularly surprising, given that the country has robust mechanisms for translating scientific and technological advancements into the private sector. The initial assumption may have been that existing channels of communication and collaboration between science and health authorities would suffice in a crisis, but in the Covid-19 pandemic, this proved not to be true.

Especially in the early stages of the pandemic, there seemed to be a disconnect between the scientific community and governmental institutions, leading to confusing communication re-

garding interventions and their scientific justification. This confusion highlights the need to foster stronger relationships and communication channels between the scientific community and governmental institutions already well before a crisis occurs. Compared to the knowledge and technology transfer to the private sector, the transfer to governmental institutions is more complex due to the numerous constraints in policy making. This complexity further emphasizes the need for a resilient and institutionalized collaboration between the scientific community and governmental institutions.

Research Project: Daily life experiences of Covid-19 in the canton of Vaud
Patrick Bodenmann – University of Lausanne
Murielle Bochud

The medical anthropological study complemented the epidemiological quantitative methods used in SeroCovid, a serological study aiming to determine Covid-19 immunity at cantonal level. By building on solid interdisciplinary collaboration, the project has contributed to the development of public health strategies empirically grounded in people's living conditions and integrating the interplay of environmental, social and biological factors for the general population and specific groups.

Recommendations

Strengthen Academic-Public Partnerships: One of the key lessons from the successful collaboration of academic research with the private sector is the effectiveness of institutionalized mechanisms of knowledge transfer. Similar models could be developed for governmental institutions to ensure a more seamless translation of scientific knowledge from academic research into the political decision-making process, taking into account the different conditions for research and policy-making.

Invest in Collaborative Platforms: Build platforms and frameworks that facilitate ongoing dialogue and partnership between the scientific community and public health agencies. A particular focus should be put on collaborative research projects, joint educational trainings and institutionalization of the collaboration. While the more traditional consulting model remains important, true impact will only be achieved through a stronger, goal-oriented practical and resilient collaboration.

Policy Readiness: Strengthen resilient, institutionalized and transparent systems to ensure that the governmental institutions remain updated with the latest scientific and technological developments, thereby enabling quicker decision-making. The collaboration model will play a significant role in making us much better prepared for integrating scientific knowledge in future crises.

By tackling these challenges head-on, Switzerland can better position itself to respond effectively to future crises and ensure that public policy is informed by the current scientific knowledge.

Reflections on Future *Health* Crises

Pandemics and other *health* crises will unfortunately remain unavoidable in the future. It is therefore important that we can draw on the lessons learned from Covid-19. While the research performed in the context of NRP 78 and elsewhere has contributed significantly to the understanding of the Covid-19 pandemic, we have also seen that the collaboration between universities, responsible for academic knowledge generation, and the public health authorities, responsible for policy making, leaves room for improvement.

The current model of health research, including the division of roles and tasks, is well demonstrated in the document "Forschungskonzept Gesundheit 2021–2024" of the Federal Office of Public Health FOPH. According to this model, various stakeholders such as health institutions, political entities, authorities, and the public generate the demand for research and communicate this need to the FOPH. The FOPH then sets the research priorities: It performs part of the analysis on its own and outsources research projects to universities and other scientific and private institutions. Once the results are delivered, the FOPH disseminates the knowledge further to the stakeholders from where the demand was generated.

The Covid-19 pandemic has revealed that this model is not well adapted for a health crisis. First, it is much too slow when confronted with rapidly unfolding and evolving crises like a pandemic. Second, it does not adequately account for the reality of science and academia today. In this model, the collaboration between universities and public health authorities limits the role of the former to that of mere providers of research knowledge based on demand from stakeholders. However, it has become evident during the pandemic that research plays a critical role in early detection as well as in the overall pandemic response. University researchers, being at the cutting edge of their field, and highly connected internationally, are often able to rapidly identify developing situations and the corresponding research needs first, even before other stakeholders. At the same time, researchers are often not aware of the needs and constraints facing public health authorities. For all of these reasons, the scientific community should not merely act as knowledge providers but should be much more involved in active and practical research collaborations with the FOPH and other stakeholders to identify urgent needs for research and evidence generation. Furthermore, because this research often requires data and insights from the field, only a collaboration between research and stakeholders like the FOPH allows for a successful performance in this activity – neither actor can do it alone.

It is important that these collaborations become structural and institutional. Previous collaborations have largely rested on personal networks that have grown organically. While these are valuable, they are simply not robust enough to withstand the strains of a large-scale crisis. Emergencies pull people in multiple directions, and key individuals may become unavailable

for various reasons, including being affected themselves. It is therefore critical to develop continuous processes that enable research collaborations between the academic actors and the health authorities. Such continuous processes also allow the development of trust and familiarity with the respective people and culture, which is critical especially in a rapidly unfolding crisis.

The need for strengthening research collaboration

Stronger institutional research cooperation between academic institutions and FOPH as well as other stakeholders is thus highly desirable. While concrete models will have to be worked out by all involved stakeholders, we offer a few suggestions derived from the experiences during the pandemic, both in Switzerland and abroad.

Much of the focus of the ongoing debate about the interplay between science and policy focuses on scientific advisory bodies during times of crisis. Although this is understandable in its intent, such an approach risks fostering a narrow view of the role science can play. The episodic, 'on-demand' advisory model has shown certain limits during the Covid-19 crisis. A model of continuous collaboration between scientists and the health authorities would not only help to avoid duplication of efforts, but also improve the quality and timeliness of scientific insights that feed into policy decisions. A continuous collaboration model would also allow for better adaptability and faster response times in rapidly evolving crisis situations. In this light, it would be more effective to treat scientific expertise as an integral component of an institutionalized collaboration, which will ideally lead to evidence-based policy making.

A model for continuous research collaboration

To build a robust and effective partnership that withstands crises and meets evolving research demands, we propose a holistic model for continuous research collaboration between academic institutions and governmental institutions. This model, which will have to be worked out in detail, should incorporate three key components:

Collaborative Ph.D. Programmes: Universities and the FOPH should jointly design Ph.D. programmes to combine academic rigor with practical needs. Legal and ethical frameworks will need to be developed for accessing health data while complying with Swiss data protection laws.

Regular Exchange Programmes: Enabling scientific staff including visiting professors of health authorities to spend extended periods of time working at universities, and vice versa, could be a valuable and productive opportunity for both parties. Such professional exchanges would not only enhance mutual understanding and facilitate the sharing of the latest methodologies but also foster a collaborative culture necessary to rapidly solve problems in an unfolding crisis.

Regular Symposia: Meetings involving academic researchers, health authority experts, and government representatives should be organized regularly to discuss ongoing projects, share

findings, and identify research gaps. Such regular exchange reinforces the ability of all parties to stay up to date in a rapidly changing landscape. This includes the execution of common workshops, side-events, presentations and publications on established conferences and symposia.

The effective implementation of such a collaborative, practice-oriented model requires institutional support. It should not rely on individual initiatives but needs structural backing to be resilient enough to handle crises. By building a comprehensive model, we can improve not only the quality and timeliness of research relevant for the governmental institutions, but also the readiness and responsiveness of the health sector to future crises.

Impact of the Research Programme

The National Research Programme NRP 78 was swiftly initiated following the Federal Council's proclamation of an "extraordinary situation" on March 16, 2020. A call for proposals was disseminated on April 30, 2020, setting an ambitious deadline for submissions by May 25, 2020. Researchers faced the formidable challenge of crafting high-quality, feasible proposals within a compressed 25-day window. Despite these time constraints and heightened expectations for scientific rigor, the program received an overwhelming response with more than 190 submissions.

Project selection in NRP 78 involved a meticulous evaluation process conducted by a panel of approximately 30 experts in the field, who relied on external peer reviews for their assessments. While the call for proposals underscored the importance of practical applicability, the objectives concerning actual implementation remained somewhat vague. The majority of the approved projects leaned towards basic research. This orientation was largely a product of the timing; in May 2020, the full scale and implications of the pandemic were still uncertain. Consequently, there was limited scope to tailor the projects for immediate implementation or practical utility.

In hindsight, it is clear that the conditions caused by the pandemic were not conducive to straightforward implementation and knowledge transfer as would occur in normal times. Given a backdrop of overwhelmed healthcare systems, heightened mortality rates, and restrictive measures like shutdowns and quarantines, the focus naturally gravitated towards immediate crisis management. It's important to acknowledge that the evaluators themselves were grappling with the day-to-day demands of the pandemic. Their engagement in shaping the research agenda was an addendum to already burdensome responsibilities.

The unique circumstances of launching an NRP at the inception of a crisis, compounded by immense time pressures, raise a critically important question: To what extent can research programs yield rapid implementations and early, validated results under such conditions? Insights garnered from the NRP 78 experience are instrumental for shaping future research endeavours, particularly those occurring in times of crisis.

Individual instruments for implementation and KTT in NRP 78

The initial call for proposals in the NRP 78 was principally geared towards acquiring knowledge about the pandemic. Consequently, no comprehensive framework for impact measurement was defined for the program. The diverse instruments for implementation were developed in a responsive manner, adjusted to meet situational needs, given the time-sensitive nature of the crisis.

Project Analysis for Implementation Potential (2020)

Conducted by Markus Ehrat, EK Biosciences and Innosuisse Innovation Mentor, the project analysis aimed to discern those projects with the highest potential for effective implementation. Initiated shortly after the projects received approval, EK Bioscience significantly contributed to generating timely and actionable evaluations for subsequent actions.

Among the 28 funded projects, four were assessed as having a high potential for implementation, while an

additional seven were perceived to offer immediate impact capabilities in terms of the targeted Knowledge and Technology Transfer (KTT). The evaluative framework primarily focused on industry-related indicators like Technology Readiness Levels (TRL), patent prospects, and market analysis. The identification of projects with high short-term impact could potentially have been broadened if the program call had explicitly set forth KTT expectations and incorporated these as selection criteria. However, the timeframe prevented such meticulous parameter setting.

Express Implementation Support for Three Projects (2021)

Emerging from the project analysis were three projects with particularly strong potential for swift implementation. These were rapidly advanced from January to March 2021, even though they were in their nascent stages and now had to juggle research and implementation simultaneously. EK Biosciences played an effective role in facilitating this dual focus.

The anticipated outcomes of these three initiatives held direct relevance for pandemic management. These included the "Escape Covid-19" serious game for healthcare workers, developed by the Harbarth research group at HUG Geneva, and the sero-prevalence surveillance platform spearheaded by the Maerkl research group at EPFL. Additionally, the Ohnmacht research group at Lucerne University, which devised non-pharmaceutical interventions for travellers, was also projected to offer tangible benefits for early containment strategies based on the project analysis.

Constraints in NRP 78's resource allocation precluded any further support for the implementation of these high-impact projects. Subsequent discussions regarding the feasibility of accelerated implementation were conducted with the targeted technology and application recipients. In accordance with its legal mandate, Innosuisse was only able to support the projects within the scope of its existing funding. The FOPH built up an internal task force at this time and focussed on managing the public health sector. By doing so they were unable to promptly assess and finance these projects for immediate execution.

This experience underscored a structural issue in Switzerland concerning knowledge and technology transfer towards governmental institutions. To tackle this, a dedicated framework that fosters stronger, more systematic, and institutional collaborations between the scientific community and governmental institutions are urgently needed. Our corresponding recommendations are outlined in the sections "Research in Crisis Mode" and "Reflections of future *health* crises".

Implementation Programme NRP 78 (2021)

To better leverage the quick application of research findings, a targeted implementation programme was rolled out in 2021 under the umbrella of NRP 78. This programme extended its support to project proposals aimed at both current and future crisis management. The call for proposals was diverse, encompassing implementation projects, innovation mentorship, collaborative research initiatives, and science-practice exchanges.

The programme stood out for its speedy rollout, adaptability, and a bottom-up design that empowered researchers to develop and submit their unique project ideas. Final reports from the seven projects that were carried out mostly indicated success. However, the programme witnessed limited participation, likely because a large chunk of NRP 78's projects were centred around basic research. Enhancing the programme's appeal might require more tangible offerings beyond mentorship - like access to patent research, freedom-to-operate assessments, regulatory guidance, or direct connections with industry partners.

Implementation Programme SNSF Special Call on Coronaviruses (2022)

The NRP 78 was requested by the SNSF to include projects from the SNSF Special Call on Coronaviruses. Given that no extra budget was specifically allocated for this, the private foundation Les Mûrons stepped in to finance a selection of these special call projects. The extra funds were directed towards communication support for these special call projects as well as for an implementation programme.

The implementation scheme for the SNSF Special Call on Coronaviruses mirrored that of the NRP 78, offering four distinct types of projects. While the programme aimed for accessibility with a bottom-up approach, it garnered only a handful of project submissions. A contributing factor to this muted response was the timing of the programme's launch, which coincided with the tail end of the special call's research period. By then, several research groups had already wrapped up their projects.

SNSF Corona Research Conference in Thun (2023)

During the SNSF Corona Research Conference held in Thun in March 2023, which focused on scholarly dialogues and updates on Covid-19 research, the subject of implementation along with knowledge and technology transfer (KTT) was proactively addressed in a concurrent session. This breakaway session featured participation from industry representatives and Innosuisse, and it showcased select projects from the NRP 78 that have a practical application focus. Project leads took the stage to share their KTT experiences and hurdles, while a mentor outlined additional funding avenues available through Innosuisse for translating research findings into real-world applications..

Requirements for implementation and KTT in the NRP 78

The NRP 78's call for proposals highlighted that beyond top-notch research, public communication, stakeholder engagement, and knowledge transfer were also central tasks. The directive was that this knowledge transfer should align closely with key entities such as the Federal Office of Public Health (FOPH) and Innosuisse. Implementing these guidelines turned out to be challenging within the constraints of a crisis focused NRP. Although collaboration with FOPH and Innosuisse demonstrated their fundamental commitment, tangible outcomes were limited. FOPH's resources were stretched thin by pressing responsibilities, while the short duration of NRP 78 hindered careful planning and execution of implementation and KTT strategies.

The fast-paced nature of the Covid-19 crisis greatly impacted planning and execution within the NRP 78. Given the immense time pressures, efforts to assess potential projects commenced early on, always with the objective of fast-tracking certain initiatives beyond the SNSF's usual frameworks. Later projects also prioritized swift action, as speed was a critical factor during the pandemic.

Communication

The strategic and the management principles in the Knowledge and Technology Transfer (KTT) concept of the NRP 78 put a strong focus on communication throughout the program's duration. A dynamic and agile communications strategy was implemented, featuring a streamlined decision-making process, and initial communication measures were quickly activated. The communications tasks for the SNSF Special Call on Coronaviruses were also integrated into NRP 78's overall communication activities.

A major area of focus, given the fundamental nature of NRP 78's research, was fostering dialogue and knowledge exchange with stakeholders. Additionally, considerable attention was directed towards communication via social media. However, the planned focus on media relations was at times challenging to execute, as mainstream media coverage was often absorbed by the unfolding events of the global pandemic, rather than background information on basic research projects in Switzerland.

The NRP 78's communication strategy was thus geared towards engaging stakeholders to ensure the incorporation of scientific evidence into decision-making processes. Given the fast-paced development of the pandemic, establishing a dialogue between research, politics, and society was ambitious, especially since no prior structures for such exchanges existed before the coronavirus outbreak.

The public's expectation for quick research outcomes created a paradox: When public interest converged on a specific research topic, NRP 78 could only state that research was underway, with results pending. This made it challenging to convey the importance of Swiss research within the international community to the media. Conversely, when concrete results from NRP 78 projects became available, public attention had frequently already shifted to the next pressing issue related to the pandemic. In the following sections, we outline six key communication activities employed throughout the NRP 78.

Basic information about the programme and its projects

At an early stage of the program, the website was designed to focus on news contributions from the 28 research projects, as well as to promote upcoming research and dialogue events. Additionally, to better explain the scope and objectives of the research program, a brief overview was created in the form of a leaflet and distributed to both the media and interested stakeholders.

Regular project news updates

While media attention was predominantly focused on breaking news related to the pandemic's latest developments, a significant task for the NRP 78 was to explain the various research areas and content of the projects. To accomplish this, several web news articles and numerous newsletters were compiled to provide background information about both the Swiss Corona research community in the NRP 78 and the SNSF Special Call on Coronaviruses. Throughout the three-year duration of the programme, around 50 project news articles were edited in multiple languages, and various newsletters offered in-depth insights into the research conducted under both the NRP 78 and the SNSF Special Call on Coronaviruses.

Due to the rapidly evolving nature of the pandemic, quick and agile communication channels were crucial not only for researcher interaction but also for informing the general public and specifically journalists. In the early stages

of the pandemic, the social media platform X (formerly known as Twitter) served as the primary platform for both scientific exchange and dissemination of information to the wider public. Over 300 tweets were sent out about program activities, and the dissemination of messages from the research projects was notable, particularly as some NRP 78 researchers quickly gained status as scientific opinion leaders or influencers.

A striking example of this social media dynamic was a "Twitter Space" event organized at extremely short notice in late November 2021, following the emergence of the Omicron variant. Marcel Salathé, president of the NRP 78 Steering Committee, invited researchers Volker Thiel, Isabella Eckerle, Emma Hodcroft, and Christian Althaus for an informative exchange and discussion. The event attracted more than 1,600 participants, who frequently cited the researchers.

However, the social media platform X lost some of its credibility after implementing major changes to its account verification and content policies in 2022. As a result, NRP 78 initiated a scientific channel on the emerging decentralized social media platform Mastodon. To date, Mastodon has not fully replaced X, and many researchers found themselves without a rapid and agile communication channel when they left the original platform.

Facing conspiracy theories

X, while serving as an agile platform for scientific exchange and an important resource for journalists, also became a primary tool for individuals to create and disseminate misinformation and conspiracy theories. Although conspiracy theories have always existed, the scope and scale reached new heights during the Covid-19 pandemic. Many researchers who spoke out publicly faced insults and, in some instances, even threats. Unprepared for the intensity of these dynamics, they had to develop coping strategies, such as taking a hiatus from X or ceasing the distribution of public statements altogether. The NRP 78 programme conferences provided a forum for discussing these phenomena and potential countermeasures.

Another social media platform prone to the spread of conspiracy theories is YouTube. Recognizing this, the NRP 78 decided to establish its own YouTube channel to disseminate credible scientific information about the pandemic. In addition to short videos about individual research projects and footage from programme conferences, the NRP 78 produced a video series that presents the results of various projects under both the NRP 78 and the SNSF Special Call on Coronaviruses.

Scientific exchanges – virtual and face-to-face

The first NRP 78 programme conference took place virtually in April 2021, drawing nearly 200 participants. In virtual poster and break-out sessions, researchers explored new avenues for scientific dialogue. The panel discussions focused on rapid scientific results, Knowledge and Technology Transfer (KTT), and broader conversations with political and societal stakeholders. Participants from both the research and political sectors emphasized the importance of regular dialogue between scientists and decision-makers.

As 2021 drew to a close and it became apparent that the coronavirus pandemic would last longer than initially anticipated, the NRP 78 convened a "Reality Check" scientific online conference. Attended by 100 participants, this meeting provided an opportunity for researchers to update their study designs and discuss the latest pandemic dynamics.

By May 2022, the NRP 78 research community was able to convene in person for the first time, gathering for the second programme conference in Interlaken. Highlighted presentations included a scientific analysis of Switzerland's Covid-19 situation by Tanja Stadler, the former president of the Swiss National Covid-19 Science Task Force, and insights into WHO's future pandemic scenarios by Annelies Wilder-Smith, a member of the NRP 78 Steering Committee.

In March 2023, the SNSF Corona Research Conference in Thun marked both the conclusion of the NRP 78 programme and the launch of the new research initiative, "Covid-19 in Society" (NRP 80). The conference gathered researchers from the NRP 78, NRP 80, the SNSF Special Call for Proposals on Coronaviruses, as well as from Innosuisse and EU-associated coronavirus research projects.

Fostering the dialogue

One of the primary communication goals was to facilitate dialogue among researchers, politicians, and the general public. This initiative began in 2021 through a collaboration with the Swiss Public Health Conference, where various NRP 78 projects showcased their research or participated in panel discussions.

In September 2021, the NRP 78's communication and crisis management approach was featured at ScienceComm, Switzerland's largest science communication conference.

Efforts to engage with the medical and clinical communities were evident on multiple occasions. In February 2022, the NRP 78 took part in a webinar hosted by Solothurn hospitals, fostering interactions between researchers, clinicians, and general practitioners. The programme was also presented at the SAFE ID Conference on infectious diseases in Engelberg, where it was the subject of panel discussions. Additionally, during the 2022 annual meeting of the Swiss Society for Microbiology, some of the programme's most promising projects were presented and debated.

In line with its dialogue-centric objectives, the NRP 78 developed a strategy to enhance communication between the research community and the business and trade sectors. In partnership with the Schweizerischer Gewerbeverband SGV, a national dialogue event was organized in Bern in August 2022. Nearly 100 participants from the Corona research community and representatives from the economic and trade sectors attended. A World Café-style discussion facilitated meaningful exchanges among participants. One of the event's highlights was a debate between Marcel Salathé, the president of the NRP 78 Steering Committee, and Casimir Platzer, the president of GastroSuisse. The event demonstrated the importance of open dialogue as a foundation for future collaborations.

Reaching out to the media

Throughout the entire pandemic, Covid-19 consistently dominated media coverage. For the NRP 78, this presented a challenge in securing media attention, as its 28 research projects were primarily focused on basic research, rather than offering the breaking news that daily pandemic updates demanded. Journalistic inquiries mostly concentrated on topics like vaccinations, Long Covid, or Gain of Function research. Despite this, the NRP 78 issued seven media releases highlighting specific research projects and the general state of Swiss Corona research. In September 2022, a national press conference was held at the Media Center of the Federal Palace in Bern, offering preliminary findings. A final press conference in November 2023 marked the conclusion of the entire research programme.

Acknowledgements

The success of the NRP 78 programme is a cumulative result of the dedicated efforts of numerous individuals and organizations, to whom we extend our deepest gratitude. We wish to acknowledge the researchers who have devoted their time, expertise, and intellectual capital to advance the field of study. Your commitment to rigorous scientific inquiry forms the backbone of this programme.

Special recognition is due to the members of the Steering Committee, whose strategic vision and managerial oversight have been invaluable. We are also indebted to our partners in academia, government, and the private sector for their collaboration and financial support, which have enabled us to reach new heights of scientific excellence.
We are grateful to everyone involved in communication for their dynamic and agile strategies in promoting our research and engaging with the broader community. Your work has been crucial in ensuring the impact of our scientific findings beyond the academic sphere.

Further, we extend our thanks to the Swiss Public Health Conference, the Swiss Society for Microbiology, and other scientific organizations and conferences that have provided platforms for our researchers to present their work and engage in vital interdisciplinary dialogues.

Our appreciation extends to the media who have taken interest in our work and helped disseminate it to a broader audience, despite the challenges of communicating complex scientific research during an ongoing global crisis.

Lastly, we thank the general public and stakeholders for your interest and engagement with our research. Your involvement is essential for translating scientific achievements into meaningful impact.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PART II
Overview Research Projects and Scientific Module Summaries

Summary Module 1

Basic aspects of SARS-CoV-2 biology, pathogenicity, and immunogenicity

Olivier Terrier, International Centre for Research in Infectious Diseases, Lyon (France)

With the emergence of a new human pathogenic virus, it is critical to understand the fundamental aspects of its biology and associated mechanisms related to immunogenicity and pathogenesis. The challenge for researchers is to "start "from scratch" and answer fundamental questions by leveraging their expertise and previous know-how acquired in the study of other viruses and pathologies. From this perspective, the six projects selected in this research module have met this challenge by each contributing to a better understanding of the biology of SARS-CoV-2 and paving the way for diagnostic, prophylactic and therapeutic applications.

Better understanding of the immune response facets

The first key question addressed was to better understand the two facets of the immune response to Covid-19, with a beneficial antiviral response and the establishment of long-term immunological memory on the one hand, and a deleterious response on the other. By establishing a prospective, multicentric and controlled Covid-19 cohort, Onur Boyman's group characterized specific differences in innate immune and antibody responses between mild and severe Covid-19 patients. This project also highlighted the importance of mucosal immunity to SARS-CoV-2, as specific antibodies were found in the mucosal fluids of individuals who tested negative for SARS-CoV-2 specific antibodies in their blood. The group also found that Long Covid (LC) was associated with risk factors (older age, asthma, severity) and distinct changes in the immunoglobulin repertoire, with low total IgM and/or IgG3 levels measured in the blood of individuals with LC. Based on these findings, a prediction model was created and validated in an independent cohort, and a LC risk score calculator was developed and made publicly available.

Michel Gillet's group investigated the harmful side of the interferon (IFN) response, with particular interest in the Covid-19 skin manifestations associated with moderate and severe forms of the disease. This project highlighted a STING-dependent type I IFN signature mediated primarily by macrophages in the vicinity of endothelial cell damage. This project not only provided a mechanistic basis for the pathological responses to type I IFN in Covid-19, but also an interesting proof of concept for the development of host-specific therapies.

Mechanisms underlying the vascular damage caused by Covid-19

Another important question studied in this research module concerns the mechanisms underlying the vascular damage caused by Covid-19, which is an aspect of the pathology that is still poorly understood. The collaborative project led by Yvonne Doering has established new in vitro and in vivo models to explore the productive infection of SARS-CoV-2 in vascular cells, including the endothelium, smooth muscle cells, pericytes and cells of the blood-cerebrospinal fluid barrier. While human endothelial cells do not appear permissive to SARS-CoV-2 infection, infection induces increased and sustained expression of cell surface molecules linked to endothelial cell activation. The vascular inflammatory effect of SARS-CoV-2 can therefore be reproduced in vitro. Using in vitro models of the human blood-brain barrier and the blood-cerebrospinal barrier, the team was able to demonstrate that iPSC-derived cerebral microvascular endothelial cells and cerebral pericyte-like cells are refractory to infection by SARS-CoV-2, probably due to the absence of angiotensin-converting enzyme (ACE2) expression. In

contrast, choroid plexus epithelial cells, which form the barrier between blood and cerebrospinal fluid, were productively infected by SARS-CoV-2 in an ACE2-dependent manner. The project lead by Matthias Hediger highlighted the role of ACE2-associated amino acid transporters in blocking viral entry during infection. Interestingly, mutations in the genes encoding these transporters, observed in specific metabolic pathologies, are associated with losing this blocking role. Additionally, drug discovery efforts led to the identification of novel peptides that mimic the viral receptor ACE2. Interestingly, these ACE2-mimicking peptides significantly block the SARS-COV-2 entry into human cells, opening another interesting avenue for the development of host-targeting therapy.

Translating new knowledge into antiviral molecules or vaccines

A large part of the research was also directly devoted to strengthening our arsenal against SARS-CoV-2 by translating new knowledge into antiviral molecules or vaccines. Structure-based rational design holds promise for accelerating the process of identifying antiviral drug candidates but still needs to be optimized to meet the need for rapid high-throughput screening under biologically relevant conditions. The project led by Meitian Wang has developed a framework for structure-based antiviral development employing cutting-edge X-ray macromolecular crystallography, including fast structure screening to uncover novel and existing antivirals and exploring viral protein/antiviral interactions at physiological temperature, and has applied these methods to several SARS-CoV-2-encoded proteins. Using these tools, the team has been able to combine high-throughput synthesis and high-throughput crystallography to target the main protease of SARS-CoV-2 (3CLpro), as well as carrying out drug repositioning approaches for other components of the SARS-CoV-2 replication machinery (nsp3/PLpro), highlighting compounds, some of which are potentially effective across a broad spectrum against all coronaviruses. The collaborative project led by Volker Thiel, combining expertise in RNA biology, cellular translation, molecular virology, and in vivo models, consisted in identifying the vulnerabilities of the virus as it uses the cellular machinery for its own replication. More specifically, the project focused on the hijacking of host translation by the virus, with the aim of producing live attenuated vaccines against SARS-CoV-2, by exploring different strategies affecting the translation of viral mRNAs. Two approaches, codon-pair deoptimization (CPD) or increasing the number of codons likely to become a stop codon with a single mutation (one-to-Stop codon, OTS) have led to two fully attenuated SARS-CoV-2 vaccine candidates that induce protective immune responses after infection/vaccination. These two vaccine candidates have successfully passed pre-clinical studies and have now entered the GMP production phase to generate vaccine doses for phase I/II human clinical trials - in collaboration with a company. Other approaches have also been explored, using translation kinetics or viral RNA modifications, and are likely to lead to other live attenuated vaccine candidates. This original approach could ideally complement the existing vaccine arsenal, mainly based on mRNA technology and adenovirus vectors.

Importance for future research on emerging new pandemics

This research module encompasses a spectrum of accomplishments across 6 projects, reflecting the collective efforts of 19 dedicated research teams comprising over 60 researchers. This collaborative endeavor has yielded 23 publications to date, alongside patents, diagnostic and drug testing applications, and a large number of both national and international collaborations. While a comprehensive evaluation of the projects' full impact is premature, their undeniable contribution lies in bridging crucial knowledge gaps within SARS-CoV-2 biology and the underlying immuno-pathogenic mechanisms. This burgeoning knowledge has been translated into novel therapeutic strategies targeting both the host and the virus, as well as pioneering vaccine innovations. Furthermore, these projects have yielded an array of tools and methodologies with potential applications that extend beyond their immediate scope. These advancements hold promise in addressing forthcoming challenges posed by new emerging zoonotic viruses on the horizon.

Research Project

Immunological risk prediction of post-Covid-19 syndrome or «Long Covid»

Onur Boyman, University Hospital Zurich
Bernd Bodenmiller, Jakob Nilsson, Daniel Pinschewer

With the emergence of the current severe Covid-19 pandemic, we wanted to contribute to the understanding of beneficial and harmful immune responses following SARS-CoV-2 infection. Thus, we characterized the immune response at different times after SARS-CoV-2 infection.

Background

With the emergence of the current Covid-19 pandemic, it became paramount to understand the beneficial and harmful immune responses following SARS-CoV-2 infection. Whereas beneficial immune responses comprise the elimination of SARS-CoV-2 and long-term immunological memory, harmful responses could relate to SARS-CoV-2-mediated immune-mediated disorders.

Aim

We established a prospective, multicentric and controlled Covid-19 cohort to study two main aims. In Aim 1, we assessed the immune response to primary infection by SARS-CoV-2 infection. In Aim 2, we determined several immunological markers of immunity, including SARS-CoV-2 -specific B and T cells at six and 12 months after primary SARS-CoV-2 infection. These results were compared to the clinical data of our study participants.

Results

Using our Covid-19 cohort, we characterized the innate and adaptive immune response during the acute and memory phases following a SARS-CoV-2 infection. We observed differences in innate immune and antibody responses between individuals that got mild versus severe Covid-19. We also reported that CoV2-specific antibodies could be found in nasal secretions, tears, and the saliva of a subset of individuals that tested negative for SARS-CoV-2-specific antibodies in the blood. Moreover, we were able to follow – for the first time – individual clones of SARS-CoV-2-specific B and T cells at 6–12 months after infection, which allowed us to characterize the factors important for long-lived memory B and T cells.

At the end of 2020, when it became evident that a considerable fraction of individuals affected by Covid-19 developed prolonged symptoms lasting for one to several months, we started to work on this condition that became known as Long Covid, post-Covid-19 syndrome, post-acute Covid-19 syndrome, or post-acute sequelae of Covid-19. We found that Long Covid occurred more frequently in individuals with lower-than-normal concentrations of two antibody subclasses, namely immunoglobulin M (IgM) and G3 (IgG3), which are important in early scavenging of pathogens and anti-viral responses, respectively. This reduction in titers of IgM and IgG3 was validated in an external cohort. Moreover, we observed that older age, a history of allergic bronchial asthma, and clinical severity during acute Covid-19 significantly increased the risk of Long Covid.

Specific contribution to tackle the current pandemic

Our finding that SARS-CoV-2-specific antibodies could be found in mucosal fluids of individuals that tested negative for SARS-CoV-2-specific antibodies in blood were the first of this kind and highlighted the importance of mucosal immunity against SARS-CoV-2. Similarly, our data on individual clones of SARS-CoV-2- specific B and T cells followed up after infection characterized for the first time the factors important for long-lived cells. Moreover, we contributed to identifying the risk factors of Long Covid.

Research Project

Consequences of SARS-CoV-2 infection in cardiovascular disease

Yvonne Döring, University of Bern
Britta Engelhardt, Nadia Mercader, Robert Rieben

Shortness of breath and lung damage are key symptoms of severe Covid-19 disease. Many patients also simultaneously experience cardiovascular disease, kidney failure and central nervous system disorders. However, too little is known about the mechanisms underlying the (long-term) vascular damage caused by Covid-19.

Background

Damage to the cardiovascular system is a significant determining factor of mortality rates among Covid-19 patients. To understand the connections between cardiovascular disease and Covid-19, it is important to elucidate the mechanisms underlying SARS-CoV-2 infection in the cells of the vascular wall. SARS-CoV-2's key point of entry is a molecule called ACE2, which is found in vascular wall cells in all organs. Knowing how SARS-CoV-2 infection particularly impacts the vasculature is key to characterizing various clinical symptoms and developing new treatments.

Aim

Our aim was to investigate the effects of SARS-CoV-2 infection in vascular wall cells, including cells of the blood-brain barrier and heart muscles. Once these cells have been infected, we would use gene expression profiling to investigate the immune system's inflammatory response and virus-induced changes. The more complex effects of SARS-CoV-2 infection that affect the entire body would be researched in zebra fish and mice. Animal experiments would enable us to investigate the entire cardiovascular system and gain a better understanding of Covid-19.

Results

We used human endothelial cells grown in vitro under physiological flow to evaluate the interaction of SARS-CoV-2 with the vascular wall. When exposed to SARS-CoV-2, human endothelial cells did not show productive viral replication. Yet, treating human endothelial cells with SARS-CoV-2 spike protein induced increased and sustained expression of cell-surface molecules related to endothelial cell activation. The vascular inflammatory effect of SARS-CoV-2 can thus be replicated in vitro. Using in vitro models of the human blood-brain barrier and blood-cerebrospinal fluid barrier we found that iPSC-derived brain microvascular endothelial cells and brain pericyte-like cells are refractory to SARS-CoV-2 infection possibly due to the absence of ACE2 expression. In contrast, choroid plexus epithelial cells, forming the blood-cerebrospinal fluid barrier, were productively infected with SARS-CoV-2 in an ACE2-dependent way. Zebrafish were used to perform toxicological assessment of over 150 compounds repurposed or suggested for repurposing in Covid-19 treatment. Most compounds, with the exception of Baricitinib, led to mild developmental defects in zebrafish larvae at clinically relevant concentrations. Aiming to generate models to investigate cardiovascular consequences of Sars-CoV-2 infection, we generated a zebrafish transgenic line overexpressing human ACE2 in a tissue specific manner to study what happens if infection occurs in heart muscle cells or blood vessels. In addition, we generated two different mouse models prone to develop cardiovascular disease and fed them a Western-type diet for 4 or 12 weeks. Some mice were challenged with spike protein binding to ACE2 while others were directly exposed to SARS-CoV-2. Spike-treated female, but not male mice, revealed persisting inflammation characterized by an increased frequency of leukocytes and inflammatory cytokines in blood. In addition, SARS-CoV-2 infected females displayed enhanced alveolar macrophage counts in the lungs. While the extent of atherosclerotic lesions was not affected in any of the groups, SARS-CoV-2 infected females also displayed enhanced inflammation of the arterial endothelium.

Specific contribution to tackle the current pandemic

We have established novel in vitro and in vivo models to explore productive infection of SARS-CoV-2 in vascular cells including endothelium, smooth muscle cells, pericytes and cells of the blood-cerebrospinal fluid barrier. These models allow to follow up on cell-specific and systemic effects of SARS-CoV-2 infection to better understand its detrimental function on the vasculature and subsequent events like thrombotic complications.

Research Project
STING inhibitors for SARS-CoV2 immunopathology

Michel Gilliet, CHUV Lausanne
Andrea Ablasser

SARS-CoV2 infection can lead to pulmonary and systemic viral spread with delayed detrimental hyperinflammatory responses of unknown origin. This project investigated these responses and tested the efficacy of STING inhibitors to treat detrimental outcomes of SARS-CoV2 infections in pre-clinical models.

Background

Covid-19, induced by SARS-Cov2 infection, can manifest with detrimental lung pathology and extra-pulmonary complications. Type I interferons (IFNs) have been recognized to play a central role in the immune-pathogenesis of Covid-19. Rapid induction of type I IFNs in the early phase of the infection can limit virus propagation, whereas sustained increase of type I IFN levels in the late phase of the infection is associated with hyperinflammation and poor disease outcomes. However, the mechanism that drive late type I IFNs and detrimental hyperinflammation were not understood.

Aim

We first focused our attention to Covid-19 skin manifestations associated with moderate to severe disease. The profiling uncovered a type I IFN signature, which was primarily mediated by macrophages adjacent to areas of endothelial cell damage. There is another common skin manifestation: the chilblains, also called Covid-toes. Chilblains were observed mostly in patients who were asymptomatic and showed negative results from SARS-CoV-2 tests. We therefore hypothesized that Covid-toes patients are predisposed to mount a robust innate immunity against the virus.

Results

Macrophages were found to engulf dying endothelial cells and to sense the self-DNA in the cytosolic compartment cyclic GMP- AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway, which controls immunity to cytosolic DNA. Activation of the cGAS-STING pathway led to the production of type I IFNs by macrophages. Thus, the cGAS-STING pathway is a critical driver of the late pathogenic type I IFN response in Covid-19 skin lesions associated with moderate to severe disease.

A lung-on-chip model revealed that infection with SARS-CoV-2 activated cGAS–STING signaling in endothelial cells by inducing mitochondrial damage and DNA release and the subsequent endothelial cells death triggered type I IFN responses in macrophages also through cGAS-STING activation. In mice, pharmacological inhibition of STING reduced lung inflammation induced by SARS-CoV-2 and improved disease outcome. Collectively, our study established a mechanistic basis of pathological type I IFN responses in Covid-19 via an intrinsic and extrinsic activation of cGAS-STING.

By profiling skin lesions in the early stage following chilblain onset, we uncover a transient IRF7-dependent type I interferon (IFN) signature that is driven by the acral infiltration of systemically activated plasmacytoid dendritic cells (pDCs).

Patients' peripheral blood mononuclear cells (PBMCs) demonstrate increased production of IFNα when exposed to SARS-CoV-2 and influenza A, but not herpes simplex virus 1, indicating a heightened ability to detect RNA - but not DNA - viruses. Further investigations revealed enhanced responsiveness of pDCs in chilblain patients to the RNA sensor TLR7, but not the DNA sensor TLR9.

Our study established a two-step model for the immunopathology of SARS-CoV-2-related chilblains: enhanced TLR7 immunity in pDCs, likely triggered by SARS-CoV-2 exposure at the mucosal site, leads to prompt viral clearance, which explains the lack of infection markers in most cases. Subsequently, systemic spread of activated pDCs and infiltration of the toes, probably caused by acral coldness, results in IFN-mediated tissue damage, clinically manifesting as chilblains.

Specific contribution to tackle the current pandemic

There is still a lack of fundamental knowledge of the mechanisms driving detrimental inflammatory responses in SARS-CoV2 infections. By combining clinical and fundamental research, this project could define the role of innate DNA immunity in SARS-CoV2 pathology and provide innovative new therapeutic targets. The clinical development of STING inhibitors is pursued by several world-leading pharmaceutical companies for the treatment of STING associated vasculopathy with onset in infancy. The proposed studies therefore have the potential to rapidly move from bench to clinical use and potentially change the outcomes of patients with severe SARS-CoV2 pathology.

Research Project
SARS-CoV-2 and therapeutic approaches

Matthias Hediger, University of Bern
Bruno Vogt

We have identified host gene variants associated with SARS-CoV-2 infectivity and disease severity in patients with metabolic disorders. Our findings form the basis for the development of patient-tailored therapeutic approaches. In addition, we are searching for blockers of viral susceptibility as hit/lead substances for the development of new treatment strategies.

Background

SARS-CoV-2 infects a number of different cell types in the lung, heart, intestine and kidney via viral receptor ACE2. But the exact tissue-specific mechanisms that assist the viral entry, including the role of specific host cell targets, are still largely unknown, although they are crucial determinants of viral infectivity and pathogenesis. For example, the involvement of ACE2- associated amino acid transporters in viral entry, including the role of their genetic variants, has been largely neglected.

Aim

Using a range of biochemical assays such as micro-scale thermophoresis (MST) to determine SARS-CoV-2 receptor binding domain (RBD) binding affinity to its receptor, our goal is to clarify the roles of specific genetic variants of viral host genes in conferring Covid-19 severity. Another goal is to validate the association of the SLC6 amino acid transporter family members with ACE2 in lung airway epithelial cells, GI tract and kidney proximal tubule epithelial cells and to determine how SLC6-ACE2 interactions affects the SARS-CoV-2 binding and entry into different host cell types.

Results

Our results show that ACE2-associated amino acid transporters in the lung, kidney and intestinal cells prevent the viral entry into host cells. In addition, our studies show that the mutations in selected amino acid transporters failed to prevent the viral entry. It should be noted that a large number of patients with metabolic diseases such as type II diabetes mellitus, iminoglycinuria and acute kidney diseases have these mutations. Additionally, drug discovery efforts led to the identification of novel peptides that mimic the viral receptor ACE2. Interestingly, these ACE2 mimicking peptides significantly block the SARS-COV-2 entry into human cells. These peptides will be used for developing new antiviral therapy.

Specific contribution to tackle the current pandemic

Our finding highlights that patients with mutations in selected amino acid transporters are at significantly increased risk of developing severe Covid-19. The results can help develop patient-tailored therapeutic approaches. In addition, further understanding of these mechanisms will provide new insights into the management of lung, intestine and kidney damage. We also identified three novel ACE2 mimicking peptides , which will be useful for the development of new therapeutics against Covid 19, for example in the form of a nasal spray, as an alternative to vaccination.

Research Project

Generation of coronavirus live-attenuated vaccines

Volker Thiel, University of Bern
Martin Beer, Sebastian Leidel, Klaus Osterrieder, Ramesh S. Pillai

Live-attenuated virus vaccines (LAV) hold promise to provide protective immunity while not causing disease. By recoding the SARS-CoV-2 genome we developed LAV candidates that are fully attenuated in pre-clinical studies, induce protective B- and T-cell immune responses, and are now being produced for clinical trials in humans.

Background

SARS-CoV-2 caused the recent pandemic of upper respiratory disease and pneumonia that threatened countless lives across the globe. The virus critically relies on reprogramming of the cellular metabolism, in particular on hijacking and utilizing the translation machinery of its host. The goal of this project was to identify vulnerabilities of the virus during its usurpation of the host cell. Specifically, we have focused on comprehensively test multiple aspects that SARS-CoV-2 may use to hijack host translation with the aim to generate live-attenuated SARS-CoV-2 vaccines.

Aim

To attenuate SARS-CoV-2, we focused on strategies that affect translation of viral mRNAs, namely codon-pair deoptimization, increasement of one-to-stop codons in the SARS-CoV-2 genome, modifying translation kinetics of viral mRNAs, and exploring the impact of modification of viral RNA. To do this, we have assembled five research groups that unite expertise and experimental systems that cover the range from basic RNA biology, cellular translation, molecular virology, and animal systems to assess viral attenuation and host immune responses.

Results

During this project we focused on four approaches to generate attenuated SARS-CoV-2 viruses as vaccine candidates. All four approaches are based on the rationale to affect translation of viral mRNA in infected cells, but each approach is based on another principle. With all four approaches we have made significant progress. The codon-pair-deoptimization (CPD) approach and the one-to-stop (OTS) approach have led to fully attenuated SARS-CoV-2 vaccine candidates that induce protective immune responses after infection/vaccination. Two candidate vaccines (sCPD9 and OTS228) have successfully completed pre-clinical studies and have now entered the good manufacturing practices (GMP) production stage to generate vaccine doses for phase I/II clinical trials in humans. During the pre-clinical development and for the preparation of clinical trials in humans, we have established a Collaborative Research and Development Agreement with RocketVax AG, Basel. With Rocketvax we are now closely collaborating to guide the GMP vaccine production and to plan the settings of the clinical trials that are planned for end 2023 and early 2024.

We have also employed an approach to slow-down or speed-up translation of viral RNAs. This has been accomplished by identifying slow- and fast- translating codons and by recoding the SARS-CoV-2 genome to encode either an increased number of slow or fast codons. Both versions did severely affect viral replication and first pre-clinical studies in vivo demonstrate that these viruses are attenuated.

Finally, we have assessed and partially mapped RNA modification (methylation) of SARS-CoV- 2 RNAs and identified m6A methylation within the SARS-CoV-2 genome and at the first nucleotide at the 5'-terminus. Although this work has not (yet) led to the generation of an attenuated SARS-CoV-2, the identification of m6A methylation at the 5'-end and the identification of a cellular enzyme that is modifying the viral RNA is novel and holds promise to develop strategies for antiviral intervention.

In summary, we were able to attenuate SARS-CoV-2 by using several approaches and to rationally design re-coded coronavirus genomes to develop novel live-attenuated coronavirus vaccines. The strategies we have explored are not only applicable for SARS-CoV-2 but also for newly emerging zoonotic viruses in the future.

Specific contribution to tackle the current pandemic

Our work has led to promising live-attenuated SARS-CoV-2 vaccine candidates that are currently being produced for clinical trials in humans. We expect that this type of vaccine will complement the currently available vaccines that are mainly based on mRNA technology or adenoviral vectors. We expect that a live-attenuated SARS-CoV-2 vaccine will have advantages compared to current vaccines since they contain all viral antigens, induce immunity at the site of infection (mucosal immunity) and can be applied via nasal sprays.

Research Project

Structure based development of new agents against Covid-19

Meitian Wang, Paul Scherrer Institut, Villigen
Cui Sheng

Most Covid-19 therapeutics target the main protease. Combination therapy, however, may work better and reduce drug resistance. Using cutting-edge X-ray crystallography, we are implementing a screening pipeline to speed up the development of novel antivirals targeting different coronavirus proteins.

Background

In academia and industry, most Covid-19 pharmacological research is focused on developing a vaccine or evaluating the effectiveness of presently available medications against SARS-CoV-2. The comparatively lengthy development cycle has made efforts to create new antiviral agents of lower priority. We seek to fill this gap by collaborating with leading virologists at the Chinese Academy of Medical Sciences and pharmaceutical industry to design novel small molecule antivirals.

Aim

We elucidated the molecular structure of various coronavirus proteins and their interactions with druglike molecules using methods of X-ray crystallography. In parallel, we developed biophysical tests to assess the transferability of established antivirals as potential Covid-19 therapeutics. The knowledge gained from these two approaches has been combined in a third step to develop novel Covid-19 antivirals and to augment the efficacy of established antivirals.

Results

We aimed to provide a window into the molecular structure of coronavirus proteins and the structural basis for its potential interactions with antivirals. We first created a framework for structure-based antiviral development employing cutting-edge X-ray macromolecular crystallography, including fast structure screening to uncover novel and existing antivirals and exploring viral-protein/antiviral interactions at physiological temperature. The structure-based methods are augmented with biophysical assays for pre-screening potential antivirals.

We then applied these methods to SARS-CoV-2 encoded proteins. High-resolution X-ray structures may assist in finding small molecules to modify viral protein activity and inhibit viral replication. High-throughput X-ray technologies allowed us to determine five SARS-CoV-2 viral protein structures at atomic resolution and identify ~40 binders after screening over 1'000 compounds. This structural insight has served as the basis for current and future drug discovery efforts against SARS-CoV-2 with the potential to be utilized against related, prospective coronaviruses.

Finally, we investigated the structural dynamics of proteins by monitoring potential changes in structure as a function of temperature. This method can disclose intricate molecular interactions and help guide the design of antivirals.

Our X-ray structure pipeline at the Swiss Light Source is available to both academics and industry for their research and development to target the current and other disease relevant protein targets.

Specific contribution to tackle the current pandemic

This project aimed to aid the global fight against SARS-CoV-2 by revealing the atomic-level structure and function of viral proteins and identifying small molecules that interact with coronavirus proteins to help develop new antiviral drugs with novel mechanisms of action. Our academic environment allowed us to provide Swiss pharmaceutical companies and academic organizations with the tools they need to develop new antivirals using the synchrotron Swiss Light Source (SLS) at the Paul Scherrer Institute.

Summary Module 2

New approaches in Covid-19 epidemiology and disease prevention

Annelies Wilder-Smith, London School of Hygiene and Tropical Medicine

This research Module encompasses a spectrum of accomplishments across 8 projects that fill knowledge gaps with regards to the epidemiology and impact of the Covid-19 pandemic whilst aiming at addressing how best to mitigate such a pandemic (and the collateral damage of pandemic measures) through rapid data collection, modelling, nation-wide surveys, qualitative research, ethnographic studies, crowd sourcing and studies on preventative strategies. Of these 8 projects, two had a whole-country approach, two were focused on hospital settings, two on selected communities, one had a particular focus on tourism and travel, and one had a clinical focus on the neuro-psychological consequences of a SARS-CoV-2 infection. Three projects not only advanced our understanding of Covid-19 but also immediately shaped policy making and control measures and were therefore highly influential: the projects by the teams of Axhausen, Friemel and Harbarth. Three projects investigated the pandemic response (e.g. social distancing and other lockdown measures), of which one focused on the mental health impact (Salanti), one on the impact on vulnerable populations (Bodenmann), and one on special sub-populations such as travelers (Ohnmacht).

The Axhausen project developed forecasting models to support time-sensitive decision-making in terms of pandemic measures. These models helped to optimize the allocation of resources for Intensive Care Unit (ICU) beds, and supported model-informed scenario analyses to fine-tune non-pharmaceutical measures (eg when to start and ease lockdown measures), and therefore had real-life application in real time. This project influenced the pandemic response by the Federal Office of Public Health, the Swiss Task Force, the Sanitätsdienst of the Swiss Armed Forces, and policy-makers at-large. The OpenCovid Platform and icumonitoring.com became heavily used resources. Models were evaluated for their relative usefulness and also for new pandemics. Their research has highlighted the importance of a practical and legal framework to ensure data pipelines, rapid access and efficient communication to policy-makers.

Thomas Friemel's group conducted a prospective weekly survey throughout the earlier phase of the pandemic to track, monitor and describe how social norms of preventive behaviour evolved over time and how the media shaped social norms. By shaping normative perceptions through communication, compliance with preventive measures can be supported. The website www.covid-norms.ch was heavily visited in particular by the Swiss Federal Office of Public Health and resulted in a collaboration with health authorities thereby ensuring rapid translation of scientific insights gained from the continuous data collection into evidence-informed guidance for control and mitigation measures.

Timo Ohnmacht's research group applied theoretical models and qualitative research to validate travel intentions and acceptance of pandemic measures during travel with the ultimate goal to enable travel.

Walter Zingg's group investigated transmission of SARS-CoV via aerosols. To enable on-site virus detection and facilitate early-stage infection risk evaluation, the team developed novel plasmonic biosensor and aerosol collection methods. The developed tools were used for virus surveillance in the air in hospital settings in order to identify high risk areas of virus presence and hence transmission. Although original clinical study design to study the effect of different mask types was not implementable, the more focused and very technical research has enabled an improved biosensor, and applied modelling to assess infection risk based on number of inhaled infection viruses. Their methods were then used to identify transmission hot spots in different settings ranging from isolation wards to nursing homes.

Furthermore, their findings were applied to better describe mask filtration efficiency.

The Harbarth project did a combined epidemiological and molecular investigation of 3 nosocomial outbreaks at the University Hospital of Geneva. They found that a high proportion of transmission was attributable to health care workers (HCWs). Despite multiple importation events, HCWs were primarily responsible for transmission within the health care profession, as well as transmission to patients. These findings led to the development of enhanced measures to prevent nosocomial infections which includes educational materials to HCW on transmission paths, as well as the use and enforcement of personal protective equipment.

Julie Péron's group assessed the possible short-and long-term neurocognitive and neuropsychological consequences of the pandemic at 6 and 12 months after the infection. Frequent and resource-intensive investigations including neuroimaging processing enabled some in-depth and novel findings not described before: Cognitive disorders can persist for more than 12 months, independent of the severity of the Covid-19 illness. Furthermore, in addition to known clinical phenotypes objective memory deficits with lack of awareness of such were identified. These findings are important for the prognostication of SARS-CoV-2 infection and neuro-rehabilitative needs. The detailed investigations needed did not allow for a large sample size, hence incidence of long-term neurocognitive deficits could not be derived from this study.

The research team, led by Georgia Salanti, did a meta-ecological study of the effects of the pandemic on mental health, alcohol/substance abuse and violence over time in the general Swiss population, by conducting a combination of a living systematic review and crowdsourcing. The highest impact on depression and anxiety were observed in the first two to three months of the epidemic, after which coping mechanisms set in in varying degrees between studies, over time, and between populations. Because of the documented high heterogeneity of studies, it is difficult to quantify the effect on mental health and identify population-based risk factors. The firm conclusion from their study, though, was that mental health needs to be addressed from the very beginning of any pandemic, and should not be ignored due to the pressing medical needs. This team should be praised for their innovative approach in using crowdsourcing to enhance real-time data collection, an approach which should be more used in the future.

Bodenmann research group conducted an ethnographic exploration of daily life experiences during the Covid-19 in the Canton Vaud. They describe vulnerabilities of different social groups including asylum seekers.

Application for future pandemics

Research findings of several of these projects are applicable or transferable to other viral pandemics. Tools, models, websites, educational materials and methodologies were developed with promising applications that extend beyond their immediate scope. For example, Zingg`s biosensor can be used for detection of other viruses including multiple viruses simultaneously. Axhausen`s agent-based models were evaluated for their projection accuracy, parameterization and computational cost relevant to future pandemics. Harbarth`s educational materials to prevent in-hospital transmission can be adapted to future outbreaks. Crowdsourcing for qualitative research on a population level rather than just individual basis can be further refined to monitor the mental health impact of pandemics. Lessons from Friemel`s continuous monitoring of social norms and normative behaviour and the role of media should be applied for the next pandemic.

Research Project

Agent-based tracking of disease spread

Kay Axhausen, ETH Zurich
Alexander Erath, Melissa Penny, Thomas Van Boeckel

We developed short- and long-term forecasting models to support decision-making during the Covid-19 pandemic using aggregated and individual-based approaches focusing on ICU occupancies and pandemic spread. We also highlight challenges faced and made recommendations that should support faster reactions in the future.

Background

Historically, the spread of infectious diseases is simulated with compartmental models based on differential equations that can accurately reproduce epidemic trajectories. However, a central assumption in equation models is that of a well-mixed and homogeneous population. Agent-based models can overcome these limitations by operationalizing the heterogeneity in individual attributes, for example, demographic attributes and pre-existing diseases, and behaviors in the simulation of epidemics.

Aim

This project aimed to optimize the response to Covid-19 by exploring complex and spatially heterogeneous policies (cantons and tri-national regions with border effects and disease import from outside). Moreover, our results should also be relevant for preparedness against other pathogens with pandemic potential. Finally, this project aimed to address a fundamental question in disease modeling: what are the merits and limitations of the 'traditional' equation-based models vs. 'new' agent-based models regarding projection accuracy, parametrization and computational cost?

Results

The Covid-19 intensive care unit (ICU) occupancy forecasting model was developed to provide near-real-time forecasts of ICU occupancy from April 2020 to March 2022 in Switzerland. The outcomes were updated daily on icumonitoring.ch. The short-term (3- or 7-day) model output was requested by the Swiss Armed Forces (SAF) for allocating medical resources in the country's ICUs. The Covid-19 ICU capacity model combined a Susceptible-Exposed-Infected-Recovered model and a neural network model. Forecasts were based on hospital-level data on ICU occupancy from the "Koordinierter Sanitätsdienst" of the SAF and potential covariates (weather, cases, medical personnel data, etc.).

We developed a stochastic individual-based transmission model of SARS-CoV-2 dynamics and Covid-19 disease, OpenCovid, to support model-informed scenario analysis. All data necessary to calibrate and inform the model were publicly available. Per request of the Federal Office of Public Health (FOPH) via the Swiss National Covid-19 Science Task Force, Swiss TPH, University of Basel, addressed a wide range of national-level questions in early 2021, including 'When and by how much can Non-pharmaceutical interventions (NPIs) be lifted when vaccine roll-out starts?', using OpenCovid.

To look at the long-term impacts of the pandemic and NPIs, we developed a methodology to pair the agent-based transport model MATSim with an externally developed agent-based epidemiological model, EpiSim. We worked on improving the representativeness of the synthetic population and their weekly mobility behavior, which is fed to the developed model. Using the MOBIS-Covid long-term tracking data, we estimated econometric models showing the reduction of activity participation based on the state of the pandemic. The last stage concerns the pairing of EpiSim, MATSim, and the newly developed econometric models forming a feedback loop. Similarly, an agent-based transport model of the tri-national region of Basel was paired with EpiSim. This model was applied to analyze the impact on SARS-CoV-2 incidence of changed activity locations and activity participation rates over time, e.g., due to various contact reduction measures, including school and border closures.

Specific contribution to tackle the current pandemic

The Covid-19 intensive care unit (ICU) occupancy forecasting model was developed to provide near-real-time forecasts from April 2020 to March 2022 in Switzerland. The outcomes were updated daily on icumonitoring.ch. The short-term (3- or 7-day) model output was requested by the Swiss Armed Forces (SAF) for allocating medical resources in the country's ICUs. Per request of the Federal Office of Public Health (FOPH), Swiss TPH, University of Basel, addressed a wide range of national-level questions in early 2021 using the developed OpenCovid platform.

Research Project

Daily life experiences of Covid-19 in the canton of Vaud

Patrick Bodenmann, University of Lausanne
Murielle Bochud

Even though biological factors are important to understand differences in exposure to viral transmission, the spread of the disease and the adoption of protection measures cannot be properly grasped and assessed without considering the social conditions of life in specific local contexts.

Background

The Covid-19 pandemic made clear that individuals and communities are all affected differently, whether biologically, personally, socially or economically. The everyday environment, like housing and working conditions, or family and other social relations, has been shown to play a crucial role regarding the risk of exposure, viral transmission and protection measures. In our project we studied qualitatively how living conditions modulate experiences or viral exposures and protection measures in specific contexts.

Aim

In this medical anthropology project, we explored how living conditions – like the everyday environment at work, at home and while carrying out daily activities, social and economic circumstances and the physical environment – influence the risk of exposure and viral transmission as well as the adoption of protective measures, in three groups of the population: general population; workers in essential services; and asylum seekers.

Results

Drawing on interviews with members of the general population, we describe the "flexible lockdown" adopted in Switzerland as a governance regime based primarily on the principle of individual responsibility. Our findings confirmed the crucial importance of space availability when negotiating risk and protection.

The redistribution of gender roles and the responsibility for care provides an example of the reconfigurations that took place during the pandemic. The results from the study confirm not only that most care activities continued to be delegated to female family members, but also that men's roles evolved, as they endorsed greater moral responsibility for safeguarding family members. During a period when the essential importance of care for family well-being was so starkly revealed, our paper draws to the attention to the urgent need for concrete measures to address the moral responsibility of care and the burden of work it entails in daily life. At a practical level, the findings from this study confirm the need for women and other providers of care services to receive appropriate material and emotional support designed to mitigate gender inequalities, especially during crises.

In regard to asylum seekers, we showed that sharing living spaces was an important source of worries for those and that protective measures were perceived to increase social isolation, obscuring and disrupting future perspectives. Our study highlighted the impact of the Covid-19 pandemic for asylum seekers and the importance of tailoring public health measures to their needs and living conditions.

For essential sectors workers, we shed light on the various meanings of risk and on the negotiations of viral exposure taking place between the professional and the private spheres. This confirms that risk needs to be understood as a relational and situated category. Our study shows as well that risk of viral exposure is weighted by the risk of losing financial income. We also studied how "essential work" was understood and experienced during the pandemic and shed light on the ambivalent relation to work, as both having a protective role, and as increasing stress and pressure due to the worsening of working conditions generated by the changes brought by the pandemic and the protection measures.

Specific contribution to tackle the current pandemic

With the actors involved we co-constructed recommendations stemming from their experiences and the challenges they encountered on the ground. The management of risk in shared space and stress were identified as significant problems. Among those was Communication. The Promotion of direct contacts between health experts and people on the ground remains a key lesson. The impact of stress on health on the long term should also be acknowledged. A key recommendation is that stress and psychological support should be put in place at the beginning of crises.

Research Project

Covid-Norms: monitoring and analysing preventive behaviour

Thomas Friemel, University of Zurich
Mark Eisenegger

This project investigated how social norms of preventive behaviours have developed during the Covid-19 pandemic in Switzerland and which role the media played in this regard. We therefore combined weekly surveys of the Swiss population and a continuous content analysis of the Swiss media.

Background

Social norms are promising means in health crisis management and communication. First, they are a key mechanism to coordinate collective action, which is required to combat collective threats. Second, social norms provide guidance in times of crisis and uncertainty, as they convey information about others' behavior and attitudes. Third, they regulate compliance with preventive measures socially instead of forcing them by means of legal rules. Hence, they represent a legitimate long-term measure of risk control in democratic societies.

Aim

The project's aim was to gain a profound understanding of how social norms of preventive behaviour have developed in Switzerland during the Covid-19 pandemic and which role the media (i.e., news media, social media) played in this process. In this way, the project aimed to provide evidence-based guidance for monitoring and influencing norms of prevention behaviour in the Swiss population.

Results

Our weekly survey of prevention behaviour in the Swiss population revealed that the majority of the population complied with the Covid-19 measures, such as social distancing, mask wearing and getting vaccinated. We thus can speak of high prevention norms in the Swiss population. At the same time, the continuous content analysis of the Swiss news media showed that the Covid-19 measures were important topics in the media – especially the Covid-19 vaccination campaign dominated the media discourse for a long time after its introduction at the end of 2020. Correlational analyses between survey and content analysis data revealed that news media turned out to play a particular role in the process of norm formation during the Covid-19 pandemic. Based on the weekly survey data and the continuous content analysis of the media reporting, we found causal effects of news media reporting on the Covid-19 vaccination campaign on perceived vaccination norms in the population using a time series analysis. Results from further cross-sectional surveys on media effects on normative perceptions and prevention behaviours (e.g., social distancing, using the contact-tracing app) also show that attention to media was correlated with perceptions of prevention norms, which in turn were associated with individual prevention behaviour.

The findings point to the communicative strategic potential of social norms in risk interventions: By shaping normative perceptions through communication, compliance with preventive measures can be supported. Therefore, we tested this idea in an online experiment, in which we compared different norms-based campaign messages and their effects on the intention to get vaccinated. However, we found no effects of exposure to these campaign messages on vaccination intention. This points to the challenge to affect established normative perceptions that are, among others, the result of continuous and cumulative exposure to news media reporting.

Specific contribution to tackle the current pandemic

We published the monitoring data on the project website

https://covid-norms.ch/ on a weekly basis. This website was heavily visited by health authorities, like the Swiss Federal Office of Public Health (FOPH), journalists, and the general public. We further were in close exchange with the FOPH and provided specific analyses, results, and assessments on demand. This collaboration ensured rapid translation of scientific insights into evidence-based guidance for disease prevention.

Research Project

Investigation of healthcare-associated outbreaks of SARS-CoV-2

Stephen Harbarth, HUG Genève
Samuel Cordey, Walter Zingg

The Covid-19 pandemic hit the world, its healthcare systems, and the infection prevention and control (IPC) community by surprise, leading to numerous nosocomial outbreaks with high morbidity and mortality. It brought along new challenges in the management of transmission of nosocomial respiratory infections.

Background

At the beginning of the pandemic, it was widely thought that healthcare workers (HCWs) were victims of nosocomial Covid-19 and that the source of their infections was the patients hospitalized with Covid-19 for whom they provided care. Transmission of SARS-CoV-2 was thought to be unidirectional, and transmission events between HCWs among themselves as well as to patients were considered negligible. This misunderstanding of transmission dynamics led to numerous nosocomial outbreaks.

Aim

Our aim was to reconstruct nosocomial outbreaks that occurred in 3 hospital sites in the Geneva University Hospitals (HUG) during the first pandemic wave in spring 2020, combining epidemiological with genetic data, in order to understand transmission dynamics and improve IPC practices; establishing viral transmission pathways of the outbreaks and reconstructing transmission trees; identifying the directionality of transmission (i.e. HCW to HCW, HCW to patient, patient to HCW, community to HCW); and determining risk factors for nosocomial SARS-CoV-2 infection.

Results

We analyzed nosocomial outbreaks of SARS-CoV-2 in 3 hospital sites in the Department of Rehabilitation and Geriatrics of HUG, involving both patients and HCWs. Due to the dense nature of these outbreaks, there was limited genetic variability in the SARS-CoV-2 strains, which had not enough time to accumulate mutations between transmission events, leading to uncertainty in individual transmission (i.e. person-to-person) events. Despite this challenge, we were able to make certain inferences by applying sophisticated modelling techniques. We have shown that in these “Covid-free” hospital zones, SARS-CoV-2 was almost exclusively imported by HCWs. We have also shown that even in a single ward there may be concurrently circulating strains, linked to multiple importation events.

The particular transmission dynamics varied according to the context. In a small rehabilitation clinic where no acute admissions occur, we showed that there was a significantly greater fraction of infections attributable to HCWs (71 %) than expected, given the number of HCW cases (47 %). HCWs were thus the main drivers of nosocomial SARS-CoV-2 cross-infection to other HCWs, and especially patients, for whom approximately 80 % of infection events were attributable to HCWs.

In another rehabilitation hospital, we showed that in a single ward there were 4 separate importation events, all by HCWs, with subsequent transmission to other HCWs as well as patients. When analyzing seroprevalence data of a cohort of HCWs, we found that both communities as well as work-related exposure were important predictors of SARS-CoV-2 seropositivity.

Furthermore, we analyzed the risk of nosocomial infection in patients, and found that frailty (indicated by a Clinical Frailty Scale >5) was associated with seven-fold higher odds of nosocomial infection. This can stem from biological phenomena whereby there is increased susceptibility to acquiring an infection (e.g. due to immunosenescence), or from differences in contact patterns because frail patients require more assistance for daily activities.

Specific contribution to tackle the current pandemic

Our research has added to the growing body of evidence that there is a complex interplay between HCWs and patients in transmission of SARS-CoV-2 in healthcare settings. Our results have provided meaningful insights into the transmission dynamics in these nosocomial outbreaks, and have, along with other studies, contributed to adapting local, national, and international recommendations for prevention and control of nosocomial outbreaks of SARS-CoV-2.

Research Project

The influence of risk perception on tourism behaviour

Timo Ohnmacht, Hochschule Lucerne

Global mobility and the increase in tourism flows are a driving factor in the emergence and spread of pandemics. Against the backdrop of continuing uncertainty about pandemic recurrence, safe travel should be facilitated.

Background

In order to explain the Swiss population's intention to travel during the Covid-19 pandemic and to explain the acceptance of travel measures, the theory of planned behavior was combined with the Health-Belief Model to determine the most important factors influencing (preventive) health behavior when travelling during the Covid-19 pandemic.

Aim

Based on the theoretical model, the aim was to explain the travel intention during the Covid-19 pandemic as well as the acceptance of measures by the Swiss resident population when travelling. A further aim was to develop intervention strategies based on the most important influencing factors and to provide tourism service providers and health authorities with a toolbox to develop target group-specific interventions with the aim of facilitating safe travel.

Results

In terms of travel intention during the pandemic, it has been found that the most important variable of travel avoidance is the perceived susceptibility to the coronavirus when travelling. The higher the perceived susceptibility to contracting coronavirus while travelling, the lower the intention to travel. The second most important variable is the perceived benefit of non pharmaceutical interventions (NPIs) while travelling. The higher the perceived effectiveness of NPIs in containing Covid-19 during travel, the higher the intention to travel during the pandemic. Another important variable is risk-taking behavior during leisure time. The riskier the leisure behavior, the more willing people are to travel during the pandemic.

The most important variable explaining the acceptance of measures is the perceived severity of a course of disease with Covid-19. The higher the perceived severity of a course of disease with Covid-19, the higher the acceptance of measures when travelling. Furthermore, older people show a higher acceptance of travel measures than younger people. The third most important variable explaining the acceptance of travel measures is the attitude towards NPIs. The higher the (positive) attitude towards NPIs when travelling, the higher the measure acceptance when travelling.

Regarding specifically tested measures (vaccination passport, hygiene masks, travel warnings, rapid tests, FFP2 masks, PCR tests, 10-day and 14-day), it can be stated that the attitude towards all these measures is positive. Also, all measures are perceived as equally effective in containing Covid-19. Among the measures tested, the hygiene mask is particularly noteworthy. Compared to all other measures, the hygiene mask shows the highest (positive) attitude as well as the highest support from close people. Behavioral control (correct wearing) is also highly pronounced and the intention to travel is highest under this measure.

Specific contribution to tackle the current pandemic

Based on the findings, destination managers, tourism practitioners and health authorities can derive target group-specific interventions to enable safe travel on the one hand and to increase the acceptance of protective measures both in general and among residents on the other. In this way, psychological resilience can be strengthened, and economic damage averted in the event of a pandemic flare-up.

Research Project

Cognitive impairment due to Covid-19

Julie Péron, Université de Genève
Frédéric Assal

As early as April 2020, and based on clinical observations in the acute phase of the infection, the continuing presence of neuropsychological disorders beyond the acute phase of Covid-19 has been postulated.

Aim

The objective of the COVID-COG project was to assess the possible short- and long-term neuropsychological consequences of Covid-19 at 6 months and 12 months after the infection.

Results

The persistence of cognitive disorders 6–9 months and 12–15 months post-infection was confirmed. These disorders were not linked to the severity of the respiratory form in the acute phase. Three distinct clinical phenotypes have been identified with the most discriminant variable being self-awareness of cognitive disorders: Some patients displayed a lack of awareness of their disorders, but with objective memory disorders. Patients at the other end of the spectrum reported numerous complaints, notably fatigue, but only displayed mild attentional and executive disorders. A third group of patients had normal performances and congruent complaints.

These disorders were associated to alterations of brain functional connectivity. Several hypotheses have been put forward to explain the persistence of these neurocognitive symptoms, but many questions remain unanswered.

Specific contribution to tackle the current pandemic

These results have been confirmed by numerous other cohort studies worldwide, referring to this condition as the post-Covid syndrome. In 2021, the COVID-COG team was the first to publish a paper reporting heterogeneity in the profiles of neuropsychological disorders, placing Switzerland as a world leader in the field of neuropsychological post-Covid syndrome. This enabled us to provide highly responsive clinical recommendations and guidelines to clinicians and information to patients.

Research Project

The effect of the COVID-19 pandemic on mental health

Georgia Salanti, University of Bern
Stefan Leucht

A meta-ecological study within a living systematic review platform, crowdsourcing, and several methodological innovations created the MHCOVID framework that answered the question: *How did the Covid-19 pandemic and the containment measures affect our mental health?*

Background

The length and intensity of social isolation and the fear of infection have adverse effects on public mental health. The efficiency of the measures taken by governments to contain the spread of the virus has to be considered in combination with their potentially detrimental impact on mental health. At the start of the project, it was not clear to what extent the Covid-19 pandemic and its containment measures influenced mental health. This is because the numerous relevant studies were presenting conflicting results.

Aim

We aimed to assess the trajectory of mental health symptoms during the pandemic and examine dose-response relations with characteristics of the pandemic and its containment measures. Further, we aimed to examine how individual characteristics such as age, gender and comorbidities modified people's mental health during the pandemic.

Results

In a total of 43 longitudinal studies (331,628 participants) we found that changes in symptoms of psychological distress, sleep disturbances and mental wellbeing, varied substantially across studies. On average, depression and anxiety symptoms worsened in the first two months of the pandemic; thereafter the trajectories were very heterogeneous. We found a linear association between worsening of depression and anxiety with increasing numbers of reported SARS-COV-2 cases and increasing stringency in governmental measures. Unpublished results: We are currently reviewing data from 176 cross-sectional studies. The average prevalence of mental health problems in women was higher than in men; however, these differences were comparable to epidemiological differences observed before the pandemic. The prevalence of mental health problems was also higher in adults compared to children, adolescents or elderly people.

High heterogeneity in study findings suggests that different populations responded differently to the stress factors induced by the pandemic and the measures for its containment. The average symptoms score for depression and anxiety increased during the first two months of the pandemic by variable amounts; they also increased with increasing stringency of the containment measures and cumulative number of reported cases. However, heterogeneity was large and some studies reported improvement in sleeping, psychological distress and mental wellbeing during the pandemic or in depression and anxiety, particularly after the first three months. It is possible that these differences between study findings are attributable to factors other than differences in age, sex, social inequalities, or country wealth.

The implications of these findings for the current and future pandemics are twofold. First, the small and uncertain impact of containment measures on mental health should be politically weighted against the level of certainty with which the distancing measures efficiently contain the spread of the virus. Second, the high heterogeneity suggests that some populations clearly experience a substantial increase in mental health problems, particularly in the beginning of the pandemic and with increasing number of reported cases.

Specific contribution to tackle the current pandemic

Even if the true impact of the pandemic is small in terms of increase in symptoms, this small increase concerns a large number of people creating a public health emergency. This shall urge once again governments and health organizations in Switzerland and abroad to put in place structures and public mental health interventions for those who need it.

Research Project

Development of a real-time SARS-CoV-2 biosensing system to improve health-worker safety

Walter Zingg, University Hospital Zurich
Jing Wang

We focused on real-time detection of airborne SARS-CoV-2 and developed a new air sampler prototype as well as a novel optical biosensing platform to monitor airborne virus concentrations in healthcare settings and public spaces. Based on this data, we performed an infection risk assessment and gained a better understanding of virus aerosol behaviour.

Background

As the SARS-CoV-2 virus continues to spread and new variants emerge, monitoring airborne viruses remains crucial in key settings like hospitals and public spaces. Novel, real-time biosensing systems for pathogens that are suitable for on-site monitoring are a great benefit to ensure the safety of key locations such as healthcare facilities. Such systems help to detect outbreaks and places of problematic air quality. Measuring the airborne SARS-CoV-2 grants a deeper understanding of airborne virus transmission and allows for infection risk assessment.

Aim

The primary goal was to develop a reliable tool for real-time monitoring of airborne SARS-CoV-2. The viral aerosol sampling system and photothermal biosensor should enable fast on-site detection and be applied in a real-world scenario. This project also aimed to model the infection risk based on the collected data, as well as provide a better understanding of virus aerosol dynamics. The system should be useful to gather epidemiological data in the absence of widespread testing and help to inform safety protocols, such as mask mandates in key areas, especially healthcare settings.

Results

We successfully validated a biosensing platform for detecting airborne SARS-CoV-2 using synthetic sequences and clinical samples including the WHO SARS-CoV-2 RNA standard for validation. The system was then employed in a hospital setting as a proof of concept. The results showed varying concentrations of the virus in different areas of a hospital, indicating factors like mask usage, ventilation, and individual virus shedding affect airborne virus levels. We also detected virus presence in hospital hallways, even with closed isolation room doors.

Further we started collecting daily samples of key locations to monitor the virus concentration over time. These results were shared via QR-code for real-time monitoring. In a nursing home, increased virus levels were correlated with staff members later testing positive for Covid-19. This shows that the system can detect problematic air conditions.

Long-term monitoring was performed during spring of 2023 in a hospital cafeteria, where the collected data mirrored the epidemiological situation, showing that the system can be used to monitor infection waves. We further aimed to quantify the infection risks in the measured areas based on exposure time, PPE use, and activity levels. It demonstrated that even in low-risk scenarios, there's a risk of infection without masks.

To complement this, we conducted controlled lab experiments with a surrogate coronavirus (HCoV-229E). This provided valuable data for comparison.

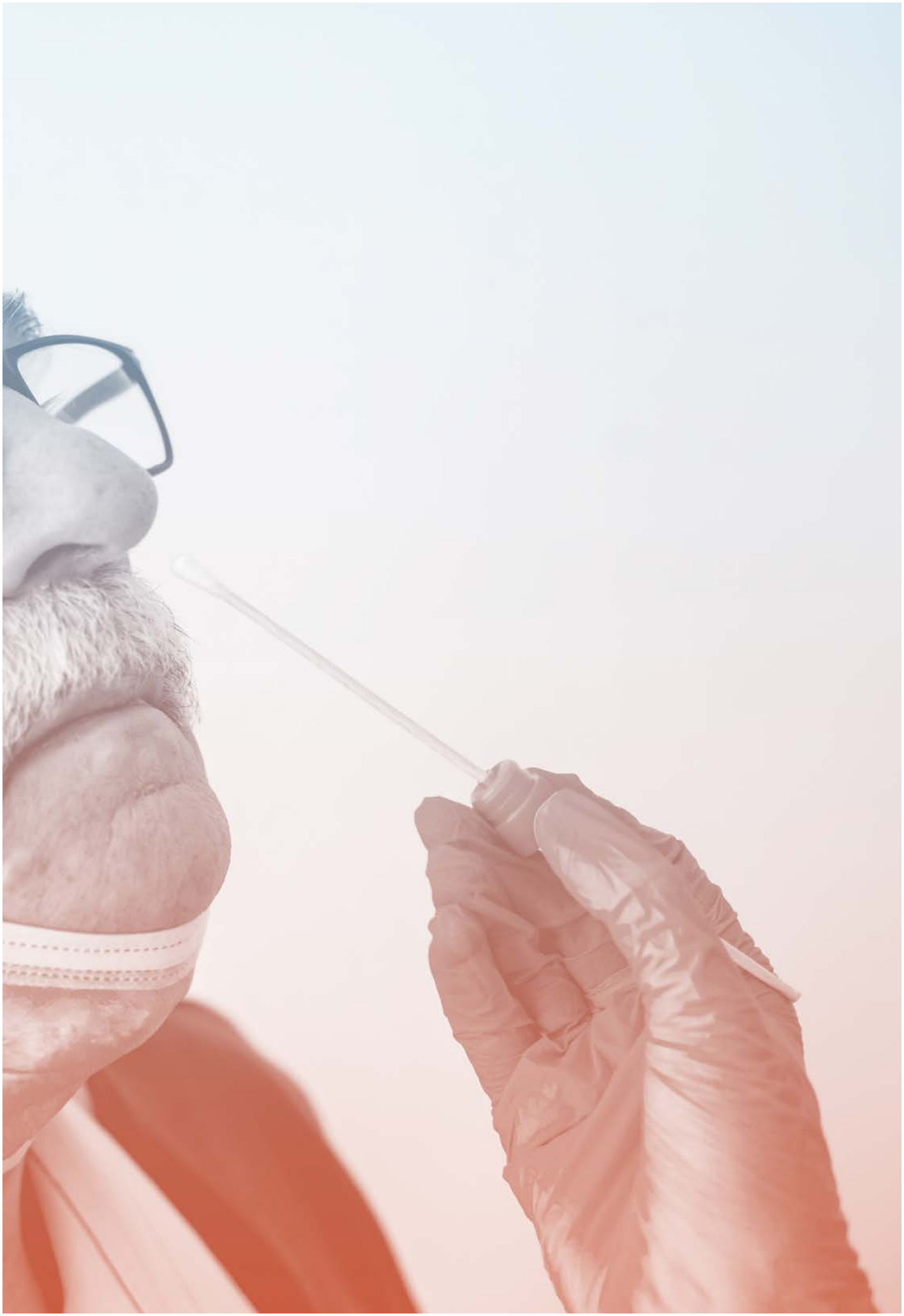
We improved our air sampling setup by adding additional sensors for monitoring air quality parameters, such as CO2, humidity, and airborne particulate matter.

We also studied different primer sets for SARS-CoV-2 PCR tests, recommending specific sets for cost-effective and reliable SARS-CoV-2 identification. Finally, a clinical mask study showed no positive cases, possibly due to low infection rates during the study period. Focus group discussions highlighted challenges like communication difficulties and mental strain due to pandemic uncertainties.

The study successfully validated the biosensing platform for SARS-CoV-2 detection. It demonstrated varying virus concentrations in different areas of healthcare facilities. Notably, even low-risk scenarios posed infection risks without masks.

Specific contribution to tackle the current pandemic

In this project, we developed and applied a new tool for monitoring airborne SARS-CoV-2 in real-time. It provides an early warning of problematic air quality and likely places of transmission. The data can also inform decision makers on the necessity and efficacy of safety measures. The data collected correlated well with the epidemiological situation, offering an alternative to widespread population testing. Applying this tool in healthcare settings allows for the improvement of staff and patient safety as well as increase our basic understanding of airborne virus transmission.



Summary Module 3
Vaccine, drug and diagnostics development


Barbara Rath, Vaccine Safety Initiative, Berlin and New Orleans
Bettina Ernst, Innosuisse Innovation Councillor, Preclin Biosystems AG

This research module has been a dense array of projects dedicated to improving the understanding of pathophysiological and immunological mechanisms of Covid-19 disease, as well as the advancement of preventive and diagnostic capabilities in Switzerland and beyond considering the challenges and time pressures of a pandemic.

The selected projects have been creating progress in their assigned areas, and the SNSF has been prudent to allow interaction between project teams during conferences in Interlaken and Thun. From a stakeholder perspective it will be critical to continue monitoring the output of the projects under the viewpoint of sustainable outcomes that will benefit Switzerland in the long run while strengthening pandemic preparedness in the long term.

The module exemplifies how this can be achieved and how each of the projects can help to shed light on a specific aspect of Covid-19 disease, the timely diagnosis of infection, the monitoring of disease activity and correlates of protection, the dissemination of disease across the body, the risk of severe or Long Covid and the possibility of protection through novel vaccines.

Outstanding research projects and their achievements

Thomas Fraefel's group developed an oral vaccine based on recombinant B. subtilis carrying specific SARS-CoV-2 antigens. They successfully demonstrated that the vaccine candidates were safe and had no adverse effects on animal welfare and that they were able to stimulate the immune system and elicit both humoral and cellular immune responses against SARS-CoV-2.

Steve Pascolo and his group developed and successfully optimized mRNA vaccination strategies that provide a much lower mRNA dose per administration (using the ng range instead of the 10–100-ug range currently used in marketed mRNA vaccines). This reduces production costs while increasing the stability of the mRNA carrier.

The Plückthun project developed a variety of adenovirus vectors encoding therapeutic payloads for the prevention and treatment of Covid-19 at all stages of disease progression. The team then validated these vectors in several in vitro assays as well as in preliminary in vivo mouse models, and successfully demonstrated the functionality of the gene delivery system and the optimized route of administration (aerosol-based delivery).

Sebastian Maerkl research group developed, validated and implemented a novel microfluidics-based nano-immunoassay to support important large-scale sero-surveillance programmes. This project is an exceptional case of an NRP 78 funded project that has directly and immediately contributed to improved pandemic response.

Christian Münz' research team focused on research to better understand the role of T-cell immunity in Covid-19 infection. They analysed the phenotype and antigen specificity of SARS-CoV-2-specific T cells comparing immunological features of infection, vaccination and in Long-Covid syndrome. This included analysis of T-cell responses to different viral proteins following "natural" Covid-19 infection versus mRNA-vaccination. Specifically, they assessed clinical - including neurocognitive - and quality of life parameters and compared these to several innate and adaptive immune changes before and after 1 month of administration of paraprobiotics.

Sandrine Gerber's group engineered a microfluidic platform for real-time detection of the SARS-CoV-2 virus

based on multifunctional silica membrane biosensors. Upon completion of the project, a pre-industrial system was successfully realized and is currently undergoing electronic and optical testing to fully characterize it.

The research group of Cristina Müller engineered radioligands for non-invasive imaging and quantification of ACE2 (functional receptor on cell surfaces through which SARS-CoV-2 enters host cells) by PET to provide clinicians with a tool to investigate the dynamics of ACE2 expression as a function of age, sex, pre-existing morbidity, medication, and environmental factors to enable (early) risk stratification.

Leverage preexisting models and platforms in pandemic situations

The research module on vaccine, drug and diagnostics development illustrates that preexisting models and platforms can be leveraged in pandemic situations to generate – maybe not a marketable product but – important progress in therapeutics, diagnostics and/or vaccine prevention of viral infections of pandemic potential. It is interesting - and was discussed during the NRP 78 Closing Conference in Thun in 2023 - that in the extreme time pressure and high workload for clinical staff at the beginning pandemic, basic science teams have had greater resources and capacity to develop concrete plans taking their research to the next level, whereas rapid access to in vivo models, BL3 laboratory facilities and clinical research teams remained somewhat of a bottle neck.

Many of the successful projects in this module have been able to make considerable achievements but will require additional national and possibly international collaboration to sustained monetary and personnel resources to advance to the next stages of pre-clinical and clinical development or to industry adaptation, piloting and scaling novel tools and approaches.

Many of the infectious disease specialists and respiratory virus experts were busy handling cases in clinical routine care, advising governments and hospital leadership in times of an acute crisis. It is hoped that now, as the tempo returns. To more of a normal place, sustained funding will be provided to help advance towards the next stages of pre-clinical and clinical development. Pre-clinical and clinical research will show which approaches are most promising and ultimately, successful in real-life settings. This will require decades of commitment in some cases, several years in others. The diversity of approaches selected for NRP 78, however, underlines the innovative power of major strategic funding calls with close supervision and scientific exchange among teams throughout.

All in all, NRP 78 has been an excellently run research programme, which resulted in significant innovation and impactful scientific output for the years to come. It is hoped that several of these approaches will ultimately translate into tangible benefit to patients and their families.

Research Project

Advancing the technological readiness level of a biologically-contained vaccine against SARS-CoV-2

Cornel Fraefel, University of Zurich
Claudio Aguilar, Catherine Eichwald

More than 380 vaccine candidates were under development during the Covid-19 pandemic. These candidates use inactivated or attenuated viruses, viral vectors, viral proteins, or viral nucleic acids. On contrast, our strategy uses the safe probiotic bacterium Bacillus subtilis as a vaccine vector for stimulation of the immune system.

Background

Based on a technology recently published by our group, we designed an innovative vaccine with live recombinant spores of B. subtilis. After oral administration, the spores bypass the stomach barrier and reach the intestine, germinating and developing into functional biofilms that express SARS-CoV-2 antigens. We had previously shown the success of this technology in the vaccination of animal models, eliciting both humoral and cellular immune responses against the fluorescent protein mCherry, and to paramyosin and tropomyosin from Echinococcus granulosus.

Aim

The aim was to develop an oral vaccine based on recombinant B. subtilis displaying specific SARS-CoV-2 antigens and to investigate the SARS-CoV-2 antigen-specific immune responses induced in a mouse model after vaccination. The SARS-CoV-2 antigens are expressed as fusion proteins to the abundant biofilm matrix protein TasA. This vaccination platform can be easily adapted to deliver emerging antigens such as those in new variants of SARS-CoV-2 or with antigens from other pathogens.

Results

We successfully designed a B. subtilis strain that shows a strict dependence on the molecule theophylline for survival. Since theophylline is not naturally present in the environment, it warrants the biological containment of the strain. Using this as genetic background, we were able to express selected antigens of SARS-CoV-2 as chimeric proteins to TasA, a crucial protein for biofilm formation in B. subtilis. We demonstrated that the fusion proteins were correctly expressed and that they do not interfere with the overall physiology of B. subtilis, including biofilm formation or sporulation. Importantly, these vaccine strains do not carry genes conferring antibiotic resistance. A remarkable characteristic of B. subtilis is the ability to produce spores. The spores are extremely resistant to environmental conditions and can be administered via the oral route. We tested these newly generated vaccine candidates in a mouse model, administering the vaccine as a spore preparation via the oral route. First, we thoroughly investigated the optimal in-vivo experimental conditions necessary for the vaccine candidates to thrive in the mouse model, including its safety. After these steps were completed, we tested the candidates expressing SARS-CoV-2 epitopes for their ability to elicit an immune response in the mouse model. Our results show that the vaccine candidates were safe and did not show negative effects on the wellbeing of the animals. The vaccine candidates were able to stimulate the immune system and were able to induce both humoral and cellular immune responses against SARS-CoV-2.

Specific contribution to tackle the current pandemic

We have successfully designed a safe, effective oral vaccine candidate against SARS-CoV-2, the causative agent of the Covid-19 pandemic. After oral administration, the vaccine stimulates the immune system and elicits both humoral and cellular responses against the virus. The vaccine candidate can be easily adapted to accommodate different antigens, like emerging virus variants of SARS-CoV-2. Since it is based on spores of B. subtilis, it can be administered in combination with different spore preparations targeting several antigens of the virus in one single dose.

Research Project

New microfluidic platform with integrated DNA biosensor for the detection of SARS-CoV-2

Sandrine Gerber, EPFL Lausanne
Francesco Bertoni, Igor Stefanini

We developed a portable microfluidic device for the detection of unamplified SARS-CoV-2 virus in human saliva sample down to 10 aM sensitivity, based on the fluorescent detection of hybridization events at the surface of silica-based DNA biosensors.

Background

Along with the emergence and spread of Covid-19 pandemics, arose the need for fast, accurate and large population scale virus detection methods. Mass testing proved to be efficient for decreasing the disease prevalence. However, the gold-standard RT-qPCR diagnostics, which rely on specialized personnel and biomedical environment, is not deployble in areas of high population mixing and in developing countries. The development of a portable device for massive and fast viral screening is therefore highly desirable.

Aim

The project aimed at the design and engineering of a microanalysis platform for SARS-CoV-2 viral charge detection in human saliva samples, without recourse to nucleic acid amplification. The target system should provide an automatic and fully integrated screening workflow, including RNA extraction from collected samples, capture of viral sequences by highly sensitive and specific sensing surfaces, and readout through optical fluorescence microscopy.

Results

We first developed a test bench multi-component microfluidic device composed of an input well, a pre-treatment chamber for RNA extraction, a screening chamber loaded with DNA biosensors and an output well allowing for digital fluorescence microscopy readout of hybridization events at the sensing surfaces.

From a large collection of sequencing data of SARS-CoV-2 (NCBI Nucleotide GenBank), a sliding windows approach led to the identification of 1,000 DNA probes targeting highly polymorphic regions of the SARS-CoV-2 genome with length between 20- and 50 bp. In silico selection pointed toward a 24- bp-long ssDNA probe specific for SARS-CoV-2 virus.

We implemented fully covalent functionalization strategies for conjugation of the selected DNA probe to naked or amino-coated borosilicate slides. A variation on spacing units, including molecular, peptidic and polymeric components, provided an efficient methodology for fine tuning the hybridization density at the DNA sensing surface with one of the highest densities reported so far. The robustness of the chemical conjugation approaches for the immobilization of DNA probes led to high stability of the resulting sensing surfaces.

Using saliva samples containing decreasing concentrations of SARS-CoV-2 virus, we established the detection limit of the screening device at 6 copies per mL (corresponding to 10 aM). Also, the absence of readout signal for saliva samples containing the MERS virus demonstrated the discrimination capacity and specificity of the system. Following validation of the test bench platform, we engineered a pre-industrial prototype of the screening device, integrating the fluorescence microscope, the microfluidic circuit and the bioimpedance measurement setup. Current developments include novel design of the sensing unit to match the requirements of bioimpedance readout and extension of the screening capacities towards other viral pathogens.

Specific contribution to tackle the current pandemic

The screening platform herein developed allows for SARS-CoV-2 screening in human saliva samples without the recourse to viral RNA amplification and with total analysis time of less than 15 minutes. Thanks to the fully automated and integrated device, the sample processing and detection technology are accessible to non-specialized personnel and can be operated outside of biomedical environments. The functionalization strategy is independent of the sequence of the immobilized DNA probe, thus offering the possibility to apply the technology to other viral pathogens.

Research Project

New technology for decentralised and low-cost mass testing

Sebastian Maerkl, EPFL Lausanne
Isabella Eckerle

The research group developed a large-scale serological profiling of SARS-CoV-2 and related human CoVs with high-throughput microfluidic nano-immunoassays.

Background

To perform sero-surveillance requires the use of immunoassays for the detection of virus specific antibodies in human blood. Existing assays require the use of serum, which must be obtained by a venous blood draw by a trained medical professional, and this procedure generally needs to be performed at a point of care such as a hospital or clinic. In this project, we addressed these aspects among others by developing a novel serological assay as well as by implementing it immediately in a joint epidemiological-virological study.

Aim

We aimed to develop new technologies to perform highly accurate, quantitative immunoassays in high-throughput and at low-cost. We wanted to eliminate the need for serum and concomitant venous blood draws by developing approaches to collect ultra-low volume capillary blood samples obtainable by simple fingerpick. These approaches were to be fully characterized and validated and these technologies were to be deployed in sero-surveillance programmes in the Geneva and Lausanne area.

Results

We set out to develop next generation technology to eliminate the major bottlenecks of existing molecular diagnostic methods. To do so, we developed a high-throughput, low-cost microfluidic system capable of analyzing over 1'000 samples in parallel while reducing the cost of the assay to 0.06 % for reagents alone as compared to standard ELISA tests. Our new method outperforms existing technologies in terms of sensitivity and specificity, which are amongst the most important parameters determining the usefulness of a molecular diagnostics assay. Furthermore, we developed up-stream sample collection and processing steps that permit untrained individuals to perform a simple fingerpick, collect a minute volume of capillary blood, and send this sample by regular postal mail to be analyzed on our next-generation molecular diagnostics platform. This enables low-cost, simple, and convenient de-centralized sample collection, coupled with highly precise centralized analysis.

We also analyzed the role of SARS-CoV-2-specific locally produced s-IgA antibodies in the nasal mucosa and compared them to functional neutralizing antibodies. We demonstrated that previous infection elicits significantly higher SARS-CoV-2 secretory component IgA (s-IgA) antibody responses, while vaccination leads to the s-IgA responses only in a minority of individuals. In addition, boosting by a third vaccine dose does not improve these responses. We showed that protection by neutralization against different SARS-CoV-2 strains was higher in previously infected individuals compared to those vaccinated only. Interestingly, neutralization of Omicron BA.5 strain was comparable in individuals with previously confirmed BA.1 or Delta SARS-CoV-2 infections. Furthermore, there is strong evidence that s-IgA substantially contributes to virus neutralization in the nasal mucosa.

Concerning viral shedding, we demonstrated that vaccination with 2 doses reduced infectious viral loads in Delta-infected individuals, whereas for Omicron BA.1 breakthrough cases, reduced infectious viral load was observed only in boosted individuals, but not in individuals vaccinated with 2 doses compared to unvaccinated individuals.

Specific contribution to tackle the current pandemic

We were able to rapidly develop and validate new technologies enabling large-scale sero-surveillance and deployed these in Geneva and Lausanne to support sero-surveillance programmes in this region. The use of this assay could contribute to findings on seroconversion in the general population as well as in children and enable child-friendly outbreak-investigations. Our findings on infectious viral loads indicate that vaccines may lower transmission risk for Delta and Omicron BA.1 variants of concern and, therefore, have a public health benefit beyond individual protection.

Research Project
Cellular immunity against SARS-CoV-2

Christian Münz, University of Zurich
Silvio Brugger, Daniel Franzen, Ilijas Jelcic, Antonia Mueller, Volker Thiel

We have examined the immune response to SARS-CoV-2 spike (S) and nucleoprotein (N) and to multiple sclerosis (MS) autoantigens after natural infection, in Long Covid syndrome and after Covid-19 vaccination. A particular focus was on SARS-CoV-1 natural infection or vaccination induce autoimmunity.

Background

Besides symptoms of upper respiratory tract infections, a wide range of organ manifestations of various severity grades has been observed after SARS-CoV-2 infection. Based on predisposing factors such as age, comorbidities, likely genetic factors and prior environmental exposures, different pathomechanisms have been implicated including damage of cells and tissues by viral infection, indirect effects by virus-specific immune responses with similar results, and the induction of autoimmune reactions.

Aim

We aimed to understand the following aspects of SARS-CoV-2-associated immunity: the phenotype and antigen specificity of SARS-CoV-2-specific T cells after infection, vaccination and in Long Covid syndrome and the induction of autoreactivity against central nervous system (CNS) /MS autoantigens in Long Covid syndrome, after infection and vaccination. With an unbiased search for cross-reactive autoantigens for SARS-CoV-2 S- or N-antigen-specific T cell clones we were reaching out for an exploratory treatment attempt with paraprobiotics in Long Covid syndrome patients.

Results

Both natural infection and mRNA vaccination induce very robust T cell responses against SARS-CoV-2 S- (infection and vaccination) and N-protein (infection) in every examined individual. In Long Covid syndrome patients, more than 50 % show reactivity against MS autoantigens to a degree that is comparable to what we observe in MS patients. Further characterization of the acquired immune cells is pending, and examination of clinical, neurocognitive, fatigue, autonomous nervous system function and quality of life parameters in relation to the immunological findings are pending.

Two vaccinees, who developed MS after mRNA vaccination have been studied in detail. In both individuals, we show by studying peripheral blood-derived S-antigen-specific T cells and also T cells from the cerebrospinal fluid (CSF) that S-Ag vaccination is able to induce cross-reactive CD4+ T cells that recognized MS autoantigens. The demonstration of molecular mimicry at the level of single T cell clones indicates that the strong S-Ag-specific T cell response can elicit a CNS autoimmune disease in predisposed individuals. However, epidemiologic data indicate that such events are very rare and more likely to occur after the natural infection.

We systematically examined clinical, neurocognitive deficits, fatigue and quality of life parameters and, in parallel, a battery of immune parameters including innate and adaptive immune changes in a small group of Long Covid syndrome patients before and after 1 month of administration of paraprobiotics, for which immunomodulatory effects had been shown previously. Our preliminary data indicate that several of the above parameters are positively altered, however, preferentially in young individuals.

Individual T cell clones from the CSF of the above vaccinees are currently being examined with an unbiased antigen discovery approach for cross-reactivity against human and also bacterial and viral targets.

Specific contribution to tackle the current pandemic

Our results indicate that both natural infection and mRNA vaccination lead to robust T cell responses against SARS-CoV-2 S- and N-Ag. Long Covid syndrome patients appear to mount cross-reactive immune responses against CNS autoantigens as well. It will be important to understand this aspect better particularly because two Covid-19 vaccinees developed MS. Paraprobiotics, probiotics and antigen-specific tolerization should be examined in more depth as possible treatment approaches for Long Covid.

Research Project

Development of a Radioligand for ACE2 PET Imaging

Cristina Müller, Paul Scherrer Institut, Villigen
Jeffrey Bode, Roger Schibli

Covid-19 shows large variability in susceptibility, progression, and symptom severity. A possible explanation for this high heterogeneity may be linked to the interindividual differences in the expression of proteins responsible for SARS-CoV-2 infection of host cells, such as the ACE2 enzyme.

Background

The Covid-19 pandemic showed large variability in disease presentation, progression, and outcome. Adequate early risk stratification is essential to avoid overburdening hospitals and intensive care units in view of future generations of SARS-CoV-2 infections. Molecular imaging using Positron Emission Tomography (PET) may serve for risk stratification by assessing the expression and regulation of key disease factors, such as ACE2 – the entry receptor of SARS-CoV-2 – thereby providing personalized treatment options.

Aim

It has been suggested that the SARS-CoV-2 entry receptor ACE2 is responsible for the individual's susceptibility to infection and disease progression. The aim of this project was to develop a radioligand for non-invasive imaging and quantification of ACE2 using PET. We aimed at providing clinicians with a tool to investigate the dynamics of ACE2 expression in relation to age, gender, pre-existing morbidity, medication, and environmental factors, and thus enable (early) risk stratification.

Results

This project delivered ACE2-targeting peptides based on the structure of DX600, modified with a chelator for complexation of a radionuclide (68Ga/67Ga) to enable nuclear imaging using PET or Single Photon Emission Computed Tomography (SPECT). Among those radiopeptides, 67Ga-HBED-CC-DX600 showed the most promising characteristics regarding the uptake in ACE2- expressing cells and xenografts. As the radiopeptide did not show undesired uptake in non-targeted tissues, it may potentially be useful for non-invasive imaging of ACE2. While this radiopeptide served to establish preclinical cell and animal models and understand potential critical aspects in the context of ACE2 imaging, it would not fulfill the requirements for clinical translation. In parallel, we developed an 18F-based small-molecular-weight radioligand for non-invasive visualization of ACE2 using PET. Such a radioligand could potentially be produced under Good Manufacturing Practices (GMP) using an automatic synthesis module as is required for radiopharmaceutical production for patient application. While the radioligand showed promising features, a further optimization of the chemical structure will be necessary to improve its pharmacokinetics and prevent undesired accumulation in the intestinal tract. Although the ultimate radioligand could not be identified yet, we are convinced to achieve this goal in a follow-up project that will be focused on lead-structure optimization. Ultimately, clinicians may profit from such a PET agent, not only to assess Covid-19 patients, but also patients with cardiovascular disease to provide them with more individualized treatment options.

Specific contribution to tackle the current pandemic

The goal was to develop a tool serving clinicians to understand ACE2 expression and regulation as a potential predictor of severe Covid-19 outcome. Only when we understand the role of key players in the context of a SARS-CoV-2 infection, it will be possible to address unfavorable conditions in certain population groups by specific interventions and to provide individualized treatments for specific patients at risk. The understanding of these mechanisms may also be of value to fight future generations of corona viral infection and cardiovascular diseases in general.

Research Project

An optimized mRNA vaccine against COVID-19

Steve Pascolo, University Hospital Zurich

Vaccines in the form of in vitro transcribed (ivt) mRNAs have proven to be the swiftest to produce during the Covid-19 pandemic. On March 16, 2020 Moderna injected the first participant with an ivt mRNA vaccine against SARS-CoV-2. The present project aimed to further optimise mRNA vaccines against Covid-19.

Background

For non-replicating mRNA vaccines developed by BioNTech, CureVac and Moderna, the amount of mRNA per injection is between 12 and 100 µg. For 100 µg doses, vaccinating the whole Swiss population would require 2 kg of purified mRNA, i.e. at least 400 litres of transcription reaction mixture. This cannot be achieved easily and quickly because it requires expensive infrastructures and large amounts of raw materials. Self-amplifying mRNA requires much lower amounts of material than non-replicating mRNA.

Aim

We aimed to generate an optimal and safe self-amplifying mRNA vaccine for subcutaneous, intramuscular, or intranasal administration that induces a strong antibody response against SARS-CoV-2. The amounts of mRNA could be a thousand-fold lower than the amounts required for the current non-replicating mRNA vaccines.

Results

We expected to identify a formulation of an mRNA vaccine against SARS-CoV-2 that will induce a strong antibody response after an injection of a very small amount of vaccine mRNA, in the range of one nanogram mRNA per mouse. The outcome would be a safe, efficacious, versatile, and inexpensive mRNA vaccine against coronavirus that can also form the basis for easy and quickly manufactured vaccines against any new viral diseases.

Specific contribution to tackle the current pandemic

Our work shall provide a method for designing and producing an mRNA vaccine that can induce strong antibody responses against the SARS-CoV-2 virus with a minimum amount of injected mRNA. Using this method, we predicted that we could vaccinate the whole Swiss population with just 5 grams of spike-coding mRNA. This amount of mRNA could easily be produced within a small GMP certified infrastructure using small amounts of reagents (e.g. nucleotides and enzymes).

Research Project

A Trojan horse for lung delivery of coronavirus therapies

Andreas Plückthun, University of Zurich

The SARS-CoV-2 virus is taken up via the lung. The build-up of a protection by a passive and active immune reaction would be especially effective in this organ. We used our technology of synthetic adenovirus with aerosols to achieve production of therapeutics and vaccines directly in the lung.

Background

Our research group had developed a robust and highly versatile platform for generating non-replicative, high-capacity gutless adenoviruses that can be retargeted to transduce specific cell types using adapters to cell-surface biomarkers, used to deliver large payloads of up to 36 kb, such as secreted neutralizing antibodies (nAbs) and/or complex vaccine cocktails, generated with extremely high purities, and coated with an engineered shield that reduced immune-based clearance.

Aim

We aimed to adapt our delivery platform for combatting Covid-19. Using our addressable, retargeted, shielded delivery system (SHREAD) based on gutless adenovirus without viral genes intrapulmonary as aerosols, we aimed for adapting it for lung tropism, as this is the organ where SARS-CoV-2 first infects the body. For therapy, we aimed to have the lung directly produce therapeutic antibodies, and as a vaccination, for developing robust mucosal immunity and memory responses, produce the antigen.

Results

We developed and tested several new adenoviral retargeting adaptors for biomarkers present on airway epithelial cells (AECs) and antigen presenting cell (APC) subtypes. From our existing pool of retargeting adapters, we had identified several in our portfolio that can already be applied in the mucosal SARS-CoV-2 applications described here. However, we discovered that the most effective targeting was achieved by coating with lactorferrin, which we had previously discovered as a molecule involved in natural adenovirus infections of the lung.

Next, we developed an aerosol-based system to deliver the particles to the lung in a mouse model. This was compared to intratracheal delivery, which was expected to give an independent estimate on the effectivity of infecting lung tissue. In both cases excellent transduction of lung tissue was seen, demonstrating that this aerosol-based route of administration is extremely promising.

Third, we developed the high-capacity viruses to encode a series of therapeutic modalities and, in a complementary approach, immunogens. Particularly, we generated constructs encoding the anti-spike antibodies REGN10933 and REGN10987 in either IgG format, but also in IgA format, which would be especially potent for a response in the lung mucosa. We investigated these in their original human format, but also as a murinized chimeric molecule to test them in mice, and we tested the anti-spike DARPin MP0420. In a second set of experiments, we compared different spike constructs as immunogens. All constructs are expressed excellently in our viral system.

Finally, we could show in mouse experiments, using an aerosol-based delivery of our gutless virus system and the optimized retargeting, that in the lung excellent expression of the therapeutic antibody is observed, which demonstrates the validity of this concept. Notably, no expression in off-target tissues is seen.

Specific contribution to tackle the current pandemic

The strategy developed here could show a potentially very efficient system for in-vivo production of a therapeutic modality and an immunogen in the lung. It is possible that they would be more effective than current approaches, because of the production and very long residence in the relevant tissue, where they can have a maximal protective effect. Since the components are completely modular, they can be adapted to different strains, different viruses, and even different lung diseases.

Summary Module 4
Clinical research and therapeutic interventions to improve treatment


Giacomo Grasselli, University of Milan
Emanuela Keller, Innosuisse Innovation Councillor, University Hospital Zurich

At the beginning of the pandemic pathogenesis of microvascular complications and organ dysfunction in Covid-19 was unknown. With the project "Devils dance: complement, NETs and thrombosis in Covid-19", Sacha Zeerleder investigated the systemic inflammation in severe Covid-19, leading to multiple organ dysfunction. Specifically complement activation with subsequent neutrophil activation of the innate immune system in the form of neutrophil extracellular traps (NETS) as well as the pathogenesis of microvascular complications on endothelial cell level have been studied. Complement activation and markers for NETs significantly increased with disease severity and were associated with lethal outcome. An innovative approach to specifically measure cell-free DNA released from endothelial cells into the systemic circulation has been developed, as well as an assay with high transfer potential to investigate microvascular endothelial damage in other severe diseases as sepsis by other pathogens as bacteria and fungi. Measurement of complement activation and markers for NETs is a suitable tool to assess disease severity, can help to predict outcome and to monitor efficacy of therapeutic interventions in Covid-19. The project findings, furthermore, offer tools to monitor therapeutic complement inhibition on different levels, which is important to design clinical studies for complement therapeutics emerging in the near future.

The aim of the project "Neutralizing multivalent antibodies against coronaviruses" led by Philippe Plattet, was to develop «new generation» neutralizing antibodies targeting several functional regions of the spike protein of the virus in order to block its entry into the cells. A synthetic nanobody (sybody) pair, Sb#15 and Sb#68 could be identified. Cryo-EM confirmed that Sb#15 and Sb#68 engage two spatially discrete epitopes. Resistant viruses emerge rapidly in the presence of single binders. The bispecific sybody may not only have an increased neutralization potency but may mitigate the emergence of new SARS-CoV-2 escape mutants. The project provides the groundwork that multi-domain antibodies with broad spectrum activity could be engineered in the future. The platform technology may not only be of major importance to fight SARS-CoV-2 (and novel variant of concerns), but also of value against other viruses.

The project "Rapid Hybrid Structure Determination of Coronavirus Protein-RNA Complexes as a Basis for Drug Screening for the Treatment of Covid-19" led by Frédéric Allain serves to understand interactions between protein-RNA complexes which is important for drug development and might be helpful for future pandemics with coronavirus. The multimodal approach applying NMR spectroscopy and cross-linking with ultraviolet light coupled to mass spectrometry as well as model development based on integrative structural biology is highly innovative. The approach – to target specifically the protein-RNA interface – will be of interest to pharmaceutical companies offering novel ways for drug discovery.

The project "AI-multi-omics-based Prognostic Stratification of Covid19 Patients in Acute and Chronic State" led by Alexander Pöllinger, aimed at developing an artificial intelligence multi-omics model based on imaging, clinical and laboratory data. The researchers were able to collect more than 3000 CT scan and chest X-ray exams from patients treated in Switzerland, Italy and the US. For more than 200 of these exams, clinical and laboratory data were also available. The AI-model, called AssessNet-19 demonstrated a good performance in lung lesions characterization, severity assessment based on a standardized scale (WHO severity score) and prediction of the need for intubation after 7 days. Another important goal was to predict the risk of developing severe sequelae in the chronic phase of the disease (Long Covid). This AI-based multi-omics approach may be relevant for the management of the current and future pandemics, to

identify patients at risk of developing severe manifestations of the disease both in the acute and chronic phase. This is particularly important in situations of significant mismatch between the available resources and the number of patients needing medical assistance.

Aim of the project "Canakinumab in Patients with Covid-19 and Type 2 Diabetes: A Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial" led by Mark Donath, was to assess the efficacy of the interleukin-1B inhibitor canakinumab in patients with type 2 diabetes mellitus and overweight (BMI > 25 Kg/sqm) hospitalized for Covid-19. Indeed, obese and diabetic patients are at higher risk of developing severe hyperinflammatory responses to viral infections. Patients were randomized to receive canakinumab or placebo in association with standard care (steroids and/or antivirals). The primary composite outcome of the study (length of survival, ventilation, ICU stay and hospitalization at day 29) was not met, despite patients treated with canakinumab had numerically lower number of deaths and ICU and ventilation time. In addition, patients receiving anti IL-1B therapy had lower levels of markers of systemic inflammation and improved metabolic state (i.e. they needed reduced doses of antidiabetics to achieve similar glycemic control). Probably the study was not powered to detect a significant difference in the composite outcome. However, the study shows that canakinumab may help to optimize diabetes control in overweight patients with viral infections and concomitant treatment with steroids.

The project "Recombinant human C1 esterase inhibitor in the prevention of critical SARS-CoV-2 infection in hospitalized patients with Covid-19: a randomized, parallel-group, open label, multi-center exploratory trial" led by Micheal Osthoff, aimed at assessing the efficacy of conestat alpha (recombinant C1 esterase inhibitor) to reduce the severity of disease on day 7 in hospitalized patients with Covid-19. Conestat alpha is a potent inhibitor of the complement system, of the contact system and of the kinin-kallikrein system, that seem to play a role in the progression of the disease. Of 621 patients screened in five Centers in Switzerland, Brazil and Mexico, only 85 were enrolled. The DSMB recommended early termination of the study after the second pre-planned interim analysis due to persistent baseline imbalances in the two treatment groups (despite randomization, the disease severity was higher in the conestat alfa group at baseline) and no difference in the study outcomes. In addition, there was no evidence of significant interference with the complement system and other plasmatic cascades with the study drug, thus questioning the initial hypothesis and the rationale of the trial.

The project "Enoxaparin for primary thromboprophylaxis in ambulatory patients with coronavirus: the multicenter randomized controlled OVID trial" led by Nils Kucher, addressed a very important clinical question. It is well known that Covid-19 is associated with an increased risk of thromboembolic complications. However, the exact indications and dosing of anticoagulants in different stages of the disease remain to be understood. Aim of the OVID trial was to assess whether thromboprophylaxis with enoxaparin in outpatients with symptomatic Covid-19 could reduce the risk of hospitalization and death (primary composite outcome) and of cardiovascular events. At the predefined first interim analysis, after the enrollment of 475 patients (50 % of the target sample size), the independent DSMB recommended early termination of the study for futility (no difference in the primary or any of the secondary outcomes). The study findings have been published in a very high reputation journal, confirming their relevance for the management of patients with Covid-19. Since another similar study (ETHICS trial) was performed in the same patient population, the investigators carried out an individual patient-level pooled analysis of the OVID and ETHICS trials (in total 691 patients) that confirmed the lack of benefit of treatment with enoxaparin compared to placebo. Finally, the investigators are working on a study-level metanalysis on all randomized trials of thromboprophylaxis in outpatients and they are also collecting long term outcome data from all patients enrolled in the OVID trial.

Research Project
Studying SARS-CoV-2 Protein-RNA Complexes

Frédéric Allain, ETH Zurich
Alexander Leitner

Interactions between viral proteins and the viral RNA genome are important for survival and pathogenicity of SARS-CoV-2. By combining two complementary structural biology techniques, we studied these interactions using the nucleocapsid protein as the main example and demonstrated how such interactions can be targeted for drug discovery.

Background

In the beginning of the pandemic, many fundamental aspects of interactions between proteins and RNA in coronaviruses were unknown, and gaps in knowledge remain to this day. A better understanding of these interactions helps to understand fundamental aspects of the biology of the virus and opens up additional opportunities for therapeutic interventions. Based on technology developed earlier by the participating research groups, we set out to study protein-RNA interactions in SARS-CoV-2, using the nucleocapsid (N) protein and the non-structural protein 3 (Nsp3) as targets.

Aim

Our goal was to use such newly established structural biology methods to study protein-RNA interactions between two important viral proteins (N and Nsp3) and their interacting RNAs. Specifically, in a first step, binding sites in these protein-RNA complexes would be located and models of the complexes would be built. In a second step, compounds (drug precursors, so-called fragments) would be identified that bind to the interaction regions and therefore interfere specifically with the binding between the partners. These compounds may be further developed into actual drugs.

Results

The nucleocapsid protein was the main target throughout our project. We combined the techniques of nuclear magnetic resonance (NMR) spectroscopy and cross-linking with ultraviolet light coupled to mass spectrometry (XL-MS) to study the interaction of the N protein with one of its target regions in the viral genome, the s2m element. Two different parts of the N protein (protein domains) that were known to bind RNA were separately studied and models of both domains in complex with s2m were generated. With these models in hand, we proceeded to identify drug fragments that bind to the interacting regions of the N protein domains and s2m, respectively. NMR spectroscopy identified such candidate compounds from a set of more than 600 fragments, revealing basic chemical structures that may be developed further in the future to increase the strength of the binding and to improve pharmacological properties. Together with collaboration partners from NRP 78, we are currently trying to obtain structures of the protein domains and the RNA in complex with such drug fragments by X-ray crystallography.

Research knowledge related to SARS-CoV-2 evolved quickly. One of the novel findings from other research groups was that the nucleocapsid protein undergoes a process called liquid-liquid phase separation (LLPS). LLPS causes two liquid phases to form from one solution, typically in the form of denser droplets in a surrounding liquid. In the context of the coronavirus, such processes are expected to be important for packaging of the RNA genome inside the virus, and for viral replication in the host organism. Based on these new findings, we also decided to study LLPS processes involving the N protein. Initial results generated in this project revealed conditions under which droplets form and dissolve again, and what structural changes occur in the protein and the interacting RNA when transitioning from one single phase to a phase-separated state.

With respect to our second target, Nsp3, we performed preliminary experiments to identify RNA- binding regions with model RNAs. Developing models in a similar way as for Nsp3 proved more difficult. However, as Nsp3 also became known to interact with the N protein, we started further experiments that connect the two target proteins to RNA binding.

Specific contribution to tackle the current pandemic

We could demonstrate the general validity of our approach – to target specifically protein-RNA interactions – by successfully generating structures of complexes and by identifying small molecules that bind to the targets. Our approach, which was published in final form in early 2023, will be of interest to pharmaceutical companies as an alternative way to develop antiviral drugs. Moreover, interest in LLPS is growing rapidly and offers another direction for drug development by interfering with biological mechanisms that involve phase separation.

Research Project

Canakinumab in patients with Covid-19 and diabetes

Marc Donath, University Hospital Basel

Patients with type 2 diabetes and obesity have chronic activation of the innate immune system possibly contributing to the higher risk of hyperinflammatory response to SARS-CoV2 and severe Covid-19 observed in this population. We tested whether interleukin-1β (IL-1β) blockade using canakinumab improves clinical outcome.

Background

CanCovDia was a multicenter, randomized, double-blind, placebo-controlled trial to assess the efficacy of canakinumab plus standard-of-care compared with placebo plus standard-of-care in patients with type 2 diabetes and a BMI > 25 kg/m² hospitalized with SARS-CoV-2 infection.

Aim

Patients were randomly assigned 1:1 to a single intravenous dose of canakinumab or placebo. Canakinumab and placebo were compared based on an unmatched win-ratio approach based on length of survival, ventilation, ICU stay and hospitalization at day 29.

Results

116 patients were randomly assigned with 58 in each group. One participant dropped out in each group for the primary analysis. At the time of randomization, 85 patients (74·6 %) were treated with dexamethasone [canakinumab 41 (71·9 %), placebo 44 (77·2 %)]. The win-ratio of canakinumab vs placebo was 1·08 (95 % CI 0·69-1·69; p=0·72). During four weeks, in the canakinumab vs placebo group 4 (7·0 %) vs 7 (12·3 %) participants died, 11 (20·0 %) vs 16 (28·1 %) patients were on ICU, 12 (23·5 %) vs 11 (21·6 %) were hospitalized for more than 3 weeks, respectively. Median ventilation time at four weeks in the canakinumab vs placebo group was 10 [IQR 6.0, 16.5] and 16 days [IQR 14.0, 23.0], respectively. Median glycated haemoglobin A1c (HbA1c) after four weeks in the canakinumab group vs placebo was 7·40 [IQR 6·65, 8·30] vs 7·50 ([IQR 6·68, 8·33] p=0·955) despite a lower number of antidiabetics administered in patients treated with canakinumab vs placebo (OR 0·47 [95 % CI 0·23-0·95] p=0·04). Median ratio to baseline of endogenous insulin (pmol/L) at four weeks in the canakinumab group vs placebo was 0.94 [0.59, 1.66] vs 0.64 [0.29, 1.44] (GMR 2.21 [1.09, 4.48] (p=0.029). Median ratio to baseline CRP and IL-6 was lower at 29 days in the canakinumab group vs placebo (GMR 0·47 [0·27, 0·82], p=0·01, and 0·28 [0·11-0·68], p=0·005).

Specific contribution to tackle the current pandemic

In patients with type 2 diabetes who were hospitalized with Covid-19, treatment with canakinumab in addition to standard-of-care did not result in a statistically significant improvement of the primary composite outcome despite a numerical benefit in survival, ventilation, and ICU time. Patients treated with canakinumab required significantly less antidiabetic drugs to achieve similar glycaemic control, possibly due to increased insulin production. Canakinumab was associated with a prolonged reduction of systemic inflammation.

Research Project

Thrombosis prevention in ambulatory patients with Covid-19

Nils Kucher, University Hospital Zurich
Stefano Barco

Blood thinners for the prevention of unplanned hospital admission, death, and blood clots in high-risk (ambulatory) outpatients with symptomatic Covid-19: the OVID study

Background

The development of blood clots is a serious complication of Covid-19 that can worsen the disease and lead to death. Hospitalized Covid-19 patients routinely receive blood thinners to prevent blood clots, but it was unclear if high-risk outpatients should also receive this treatment. Since most Covid-19 patients are initially managed at home, the potential benefits of blood thinners for these patients remained unconfirmed without clinical trials that assign patients to one of the two treatment strategies (blood thinners vs. no blood thinners) on a random basis.

Aim

The OVID study hypothesized a potential benefit of blood thinners in Covid-19 patients, potentially reducing the number of hospitalizations, primarily due to thromboembolic complications or Covid-19 itself, and the number of deaths among patients receiving blood thinners. Moreover, we studied the impact of blood thinners on the development of blood clots and on the course of symptoms.

Results

As far as we know, this is the first and biggest study that aimed to investigate whether using the blood thinner heparin can help prevent blood clots in Covid-19 patients who are sick and have symptoms, but not hospitalized. Overall, 472 patients were included at 8 study centers in 2 countries (Switzerland and Germany) and followed for 90 days after inclusion in the study.

When half of the total participants were enrolled and data were collected, we checked to see if the treatment was working well enough to continue the study. The independent group overseeing the study recommended stopping the study early based on pre-planned statistical criteria. They determined that the chances of finding a clear benefit of using enoxaparin for preventing blood clots in this study were very low, given the original study design assumptions. The results of the OVID study showed that using enoxaparin did not reduce the risk of early hospitalization for any reason. The overall risk of early Covid-19-related unplanned hospitalization was 3.4 % with no differences between treatment groups.

Our study, together with the results of similar studies that used different blood thinners, does not support using blood thinners routinely for Covid-19 patients who are not in hospital, as it may not prevent severe complications due to Covid-19 leading to unplanned hospitalizations.

Moreover, we showed that early treatment with blood thinners did not improve the course of symptoms and their resolution. Although our findings point to a reduction of blood clots in outpatients with Covid-19 who received blood thinners (0.4 % vs. 1.7 % without blood thinners). More studies are needed to confirm these findings.

Specific contribution to tackle the current pandemic

The results from this large study, which included participants from different countries, showed that using a type of blood thinner called low-molecular-weight heparin did not seem to prevent Covid-19 patients from getting worse and needing to go to the hospital. Moreover, it did not speed up the resolution of symptoms and one patient out of six experienced residual respiratory symptoms 90 days after Covid-19. Based on these results, it is not recommended to routinely use blood thinners for Covid-19 patients who are not hospitalized.

Research Project

Conestat alfa in the treatment of Covid-19

Michael Osthoff, University Hospital Basel

Infection with SARS-CoV-2 may cause an exaggerated inflammatory reaction in the lung severe enough to require mechanical ventilation. This project investigated the anti-inflammatory drug Conestat alfa in patients with Covid-19.

Background

An exaggerated inflammatory reaction seems to be the main driver of Covid-19 progression up to and including lung failure. Conestat alfa is a man-made form of a protein that occurs naturally in the bloodstream and which blocks several of the inflammatory systems involved in Covid-19-related exaggerated inflammation. An animal study of the protein in coronavirus has already produced promising results.

Aim

The PROTECT-COVID-19 trial investigated whether Conestat alfa can prevent severe disease progression and the need for mechanical ventilation in hospitalized patients with Covid-19. In addition to efficacy and tolerability, the trial also assessed the level of inflammation in the two-week period following enrollment.

Results

This international, multicenter, randomized, open-label trial enrolled 84 participants with moderate to severe Covid-19 in Switzerland, Brazil and Mexico starting in August 2020. Participants were randomized to treatment with Conestat alfa for 3 days in addition to standard of care or standard of care alone. Most patients received Dexamethasone as standard of care treatment, and Remdesivir was used occasionally. Conestat Alfa was well tolerated without any safety signal despite choosing a higher than licensed daily dosage. The trial was prematurely terminated in September 2021 following a preplanned second interim analysis demonstrating relevant baseline imbalances in the two treatment groups (e.g. disease severity was higher in the Conestat alfa group at baseline) and no differences in the primary and a key secondary endpoint. Consequently, the original aim to enroll 120 patients was deemed not to be sufficient to show a difference in the primary outcome measure given the imbalances observed at baseline. Further arguments to terminate the trial were the introduction of additional effective treatments such as monoclonal antibodies in the second half of 2021 and the fact that the analysis of inflammatory systems indicated that the chosen Conestat alfa treatment regimen was not able to significantly reduce inflammation compared to the control group. tly reduce inflammation compared to the control group.

Specific contribution to tackle the current pandemic

Interventions that prevent Covid-19-induced lung failure play an important role in treating patients with the disease. Currently, Dexamethasone, Tocilizumab and Baricitinib have all shown to be effective in treating moderate to severe Covid-19 and preventing admission to the intensive care unit and mechanical ventilation. Results from this small study do not support the use of Conestat alfa in order to ameliorate the exaggerated inflammatory reaction and to prevent Covid-19 progression, although a larger trial would be desirable.

Research Project

Sybodies neutralise SARS-CoV-2 variants

Philippe Plattet, University of Bern
Dimitrios Fotiadis, Markus Seeger

The aim of our research project was to generate a new generation of antibodies composed of multiple anchoring points to effectively block the entry of SARS-CoV-2 into the cells. The small size of these antibodies may result in better penetration into the tissues, better management of the viral resistance mechanisms and the production of new drugs.

Background

The Covid-19 pandemic has produced an unprecedented global health and economic crisis. Since no vaccine or therapy was available at the start of the project, developing new treatments was a matter of urgency. The entry of SARS-CoV-2 into the cell is controlled by the spike protein (S) anchored in the viral envelope. The S protein binds to a receptor located on the target cell, ultimately resulting in the injection of genetic material from the virus into the cell. This S protein is a major target for the production of antibodies by the immune system in response to the infection.

Aim

Our project focused on the development of a new generation of neutralizing antibodies that block the entry of the virus into the cell. The antibodies generated in this project are designed to contain several mini domains derived from antibodies produced by llamas. These antibodies are fused together and simultaneously target several functional regions of the S protein.

Results

We report the identification of a synthetic nanobody (sybody) pair, Sb#15 and Sb#68, that can bind simultaneously to the SARS-CoV-2 spike RBD and efficiently neutralize pseudo typed and live viruses by interfering with ACE2 interaction. Cryo-EM confirms that Sb#15 and Sb#68 engage two spatially discrete epitopes, influencing rational design of bispecific and tri-bispecific fusion constructs that exhibit up to 100- and 1,000-fold increase in neutralization potency, respectively. Cryo-EM of the sybody-spike complex additionally reveals a novel up-out RBD conformation. While resistant viruses emerge rapidly in the presence of single binders, no escape variants are observed in the presence of the bispecific sybody. The multivalent bispecific constructs further increase the neutralization potency against globally circulating SARS-CoV-2 variants of concern. Our study illustrates the power of multivalency and biparatopic nanobody fusions for the potential development of therapeutic strategies that mitigate the emergence of new SARS-CoV-2 escape mutants.

Specific contribution to tackle the current pandemic

Multi-domain antibodies may show unparalleled therapeutic efficacy due to several factors: a neutralizing activity superior to conventional antibodies as a result of their multiple anchoring points on the S protein, a reduction in the risk of developing resistant viruses thanks to the multi-directional attack, the promising possibility of developing a drug that could be directly inhaled, and a technological approach for producing neutralizing antibodies not just against SARS-CoV-2, but potentially also against other coronaviruses.

Research Project

Covid-19 prognosis with artificial intelligence (AI)

Alexander Pöllinger, Inselspital Bern
James Duncan, Mauricio Reyes, Nicola Sverzellati

AI-based lung image analysis enhances disease severity assessment, reducing ICU overload with standardized admission criteria for Covid-19 patients. Expanded AI research is vital for integrating it into clinical practice and preparing for future pandemics.

Background

Automated Covid-19 segmentation and quantification of lung involvement using deep learning hold promise. However, there are notable disparities between clinicians' and AI communities' studies regarding patient care for Covid-19. Therefore, integrating AI into clinical practice requires addressing challenges in standardized severity classification, lung lesion characterization, multi-modal imaging data integration, robust quantification of Long Covid severity, and understanding acute-to-chronic phases. These steps are crucial for optimizing patient care.

Aim

This study aimed to develop a modular AI-based approach for modeling a patient's current state and predicting the short and long progression of Covid-19 patients. The specific objectives were establishing a severity assessment system based on the WHO clinical progression scale, including chest X-rays, to predict whether patients need intubation after seven days based on baseline medical images, and to create an AI model to predict the severity of Covid-19 disease in the chronic phase.

Results

Our AI model, AssessNet-19 achieved an F1-score of 0.76±0.02 for severity classification in the evaluation set, which was superior to the three expert thoracic radiologists and the single-class lesion segmentation model. In addition, AssessNet-19 automated multi-class lesion segmentation obtained a mean Dice score of 0.70 for Ground-glass opacity (GGO), 0.68 for consolidation, 0.65 for pleural effusion, and 0.30 for band-like structures compared to ground truth. Moreover, it achieved a high agreement with radiologists for quantifying disease extent with Cohen's Kappa of 0.94, 0.92, and 0.95.

Transferable vision transformers guided by GGO and CON mask achieved an F1 score of 0.6972 and an AUC of 0.7452 for the 7-day intubation prediction task in the test set. It outperforms the vision transformer trained on DRRs and tested on XRs with an F1 score of 0.5819 and an AUC score of 0.6785. Moreover, the transferable vision transformer guided by GGO and CON mask generates natural attention maps along with prediction results, showing the important regions for model prediction.

Specific contribution to tackle the current pandemic

We provided a multi-center Covid-19 dataset: curated, labeled, diverse radiological, clinical and laboratory data, reduces biases, enhances generalizability with varied cases, severities, CT scan sources, and contrast use.

A novel AI multi-class radiomics model including seven lung lesions to assess disease severity based on the WHO-CPS scale more accurately determines the severity of Covid-19 patients than a single-class model and radiologists' assessment.

Research Project
Innate immunity in Covid-19

Sacha Zeerleder, Inselspital Bern

In the beginning of the pandemic the pathogenesis of microvascular complications and organ dysfunction in Covid-19 was not known. To Identify the main players which drive systemic inflammation in Covid-19 is key to identifying targets for therapeutic interventions.

Background

Severe Covid-19 is characterized by microvascular complications resulting in organ dysfunction and occasional death. From other diseases characterized by systemic inflammation with microvascular complications we learned that complement activation as well as neutrophil activation in the form of neutrophil extracellular traps (NETs) is a driving force in the process. Earlier work of our group demonstrated that therapeutic complement inhibition efficiently reduces systemic inflammation by blocking complement and subsequently also inhibits NET formation.

Aim

We aimed to demonstrate that systemic inflammation with microvascular complications in Covid-19 is driven by complement activation with subsequent NET formation. In detail, we aimed to assess complement activation and NETs in plasma of patients suffering from Covid-19 and to study on whether these markers are suitable to assess severity of Covid-19, to predict outcome and to follow the efficacy of therapy. In addition, we aimed to study the pathogenesis of microvascular complications on endothelial cell level.

Results

We demonstrated complement activation and neutrophil activation in the form of NETs in Covid-19 patients. Complement activation and markers for NETs significantly increased with disease severity and were highest in patients who died. Interestingly, in patients with mild disease, the markers for complement activation were only marginally increased as compared to healthy controls and normalized over time, whereas markers for NETs in these patients was comparable with healthy controls. In patients with moderate disease severity markers for complement activation and NETs were significantly increased on admission as compared to controls, but then decreased over time and markers for NETs even normalized. In patients with severe Covid-19, these markers significantly increased on admission and remained high throughout the observation period, with highest levels in patients who died. These data demonstrate complement and NETs to be among the main drivers of systemic inflammation resulting in microvascular complication with subsequent organ dysfunction in Covid-19.

To assess microvascular complications in Covid-19, histopathology of tissue biopsies must be performed. Microvascular complications finally result in death of endothelial cells. We demonstrated in the past, that through a highly regulated process DNA is actively released from dead cells into the circulation and can be assessed as cell-free DNA in plasma. We hypothesize that endothelial cell death results in the release of endothelial-cell specific DNA. Based on tissue specific differential methylation patterns using digital droplet PCR, we developed an assay to specifically measure cell-free DNA released from endothelial cells into circulation. Indeed, we demonstrate that the amount of endothelial cell DNA in the circulation of Covid-19 patients can be detected and significantly increases with disease severity, showing the highest levels in patients who died. These results demonstrate that with this assay endothelial dysfunction and/or death can be assessed in plasma.

Specific contribution to tackle the current pandemic

Based on our data, we could identify complement and neutrophils as main drivers of systemic inflammation and organ dysfunction. Measurement of complement activation and markers for NETs is a suitable tool to assess disease severity in Covid-19 and may help to predict outcome. In addition, we have a tool to assess vascular dysfunction on a molecular level by measuring circulating endothelial cell DNA in Covid-19 patients. The assays developed and applied in this project will also be of use to monitor efficacy of therapeutic interventions.


MULTI CARE

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Marcel Salathé, EPFL Lausanne (chair)
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Simonne Rufener, Federal Office of Public Health FOPH, Bern
Mirjam Mäusezahl, Federal Office of Public Health FOPH, Bern (until May 2023)

Head of Knowledge Transfer
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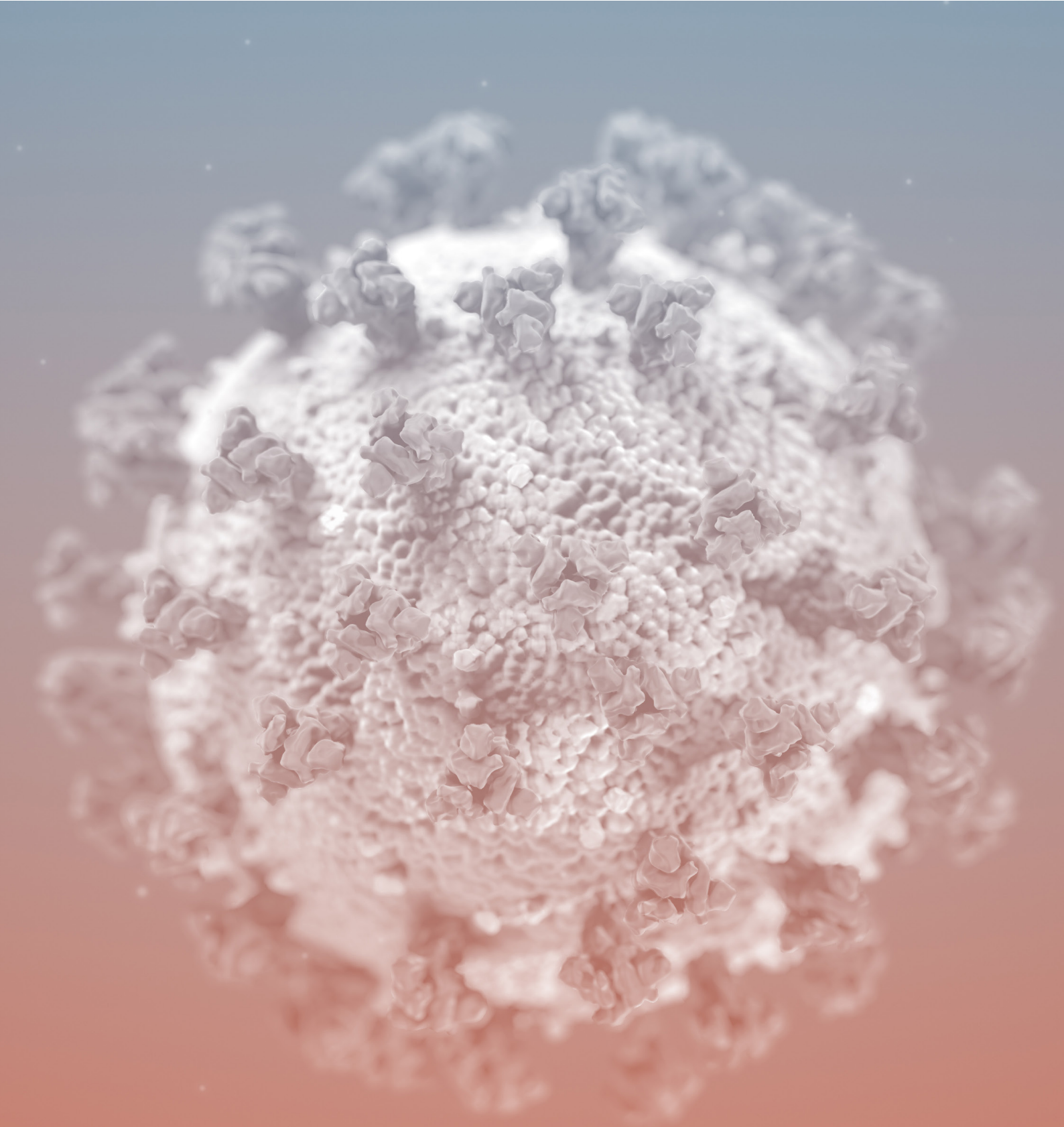

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Wildhainweg 3, Postfach
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