



Meeting Report

Enabling the evaluation of COVID-19 vaccines with correlates of protection



Arnaud Marchant^a, Pierre Van Damme^b, Stanley Plotkin^c, Pieter Neels^d,
 Maria Cristina Cassetti^e, Jakob Cramer^f, Marion F. Gruber^g, David Goldblatt^h, Deborah Kingⁱ,
 Wendy Hartig-Merkel^j, Joris Vandeputte^{d,*}

^a Institute for Medical Immunology (IMI), European Plotkin Institute for Vaccinology (EPIV), Université libre de Bruxelles, 808 Route de Lennik, 1070, Brussels, Belgium

^b Centre for the Evaluation of Vaccination, European Plotkin Institute for Vaccinology (EPIV), Vaccine & Infectious Disease Institute, University of Antwerp, Faculty of Medicine & Health Sciences, Vaccinopolis/University of Antwerp, Drie Eikenstraat 663, 2650, Edegem, Belgium

^c University of Pennsylvania, 18902, Doylestown, Pennsylvania, United States

^d International Alliance for Biological Standardization (IABS), Rue Mina-Audemars 3, 1204, Genève, Switzerland

^e Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Health (NIH), 20852, United States

^f Coalition for Epidemic Preparedness Innovations (CEPI), Gibbs Building, 215 Euston Rd, Bloomsbury, London, NW1 2BE, United Kingdom

^g International AIDS Vaccine Initiative (IAVI), 125 Broad Street, New York, NY, 10004, United States

^h Infection, Immunity, and Inflammation Department, Great Ormond Street Institute of Child Health, University College London and Great Ormond Street Children's Hospital, NHS Foundation Trust, 30 Guilford Street, London, WC1N 1EH, United Kingdom

ⁱ Wellcome Trust, Gibbs Building, 215 Euston Road, Bloomsbury, London, NW1 2BE, United Kingdom

^j P95 Epidemiology & Pharmacovigilance, Koning Leopold III Laan 1, 3001, Leuven, Belgium

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ABSTRACT

In February 2023, a meeting about correlates of protection (CoPs) against COVID-19 was organized by the International Alliance for Biological Standardization, the European Plotkin Institute for Vaccinology, and Vaccinopolis. The meeting aimed at reviewing the evidence, drawing conclusions, and identifying knowledge gaps.

Collection of evidence is not straightforward. Neutralizing antibodies correlate with protection and are used for immunobridging studies within and between vaccine platforms for approval of new COVID-19 vaccines. In preparation for the next pandemic, it is vital that rapidly authorized initial vaccines are available to perform immunobridging studies very early. Additional components of the immune response likely contribute to protection against symptomatic infection. Current evidence is strongest for T lymphocytes and binding antibodies. Further studies are needed to consolidate this evidence and define their potential role in the evaluation of vaccines. For evaluation of mucosal vaccines, identifying CoPs against infection and transmission is key; further research is needed to identify and standardize methods suitable for clinical studies. CoPs for broadly protective beta-coronavirus vaccines remain a critical area of research.

The knowledge, expertise, and capacity exist to conduct clinical studies using different designs in different populations to discover and validate CoPs, facilitating and accelerating evaluation of novel vaccines/vaccination platforms.

1. Introduction

A meeting was held in February 2023 at the Vaccinopolis facility (University of Antwerp, Belgium), about correlates of protection (CoPs) against COVID-19 caused by the novel SARS-CoV-2. The meeting aimed to review the evidence, draw conclusions, and identify knowledge gaps.

The meeting was organized by International Alliance for Biological Standardization (IABS), the European Plotkin Institute for Vaccinology (EPIV) and Vaccinopolis, with the support of the Coalition for Epidemic Preparedness and Innovations (CEPI), the Wellcome Trust (WT) and the US National Institutes of Health (NIH).

The opening session, chaired by **Stanley Plotkin**, Emeritus Professor of Pediatrics, University of Pennsylvania, began with a presentation by

* Corresponding author.

E-mail addresses: arnaud.marchant@ulb.be (A. Marchant), pierre.vandamme@uantwerpen.be (P. Van Damme), stanley.plotkin@vaxconsult.com (S. Plotkin), pieter.neels@vaccine-advice.be (P. Neels), ccassetti@niaid.nih.gov (M.C. Cassetti), jakob.cramer@cepi.net (J. Cramer), MGruber@iavi.org (M.F. Gruber), d.goldblatt@ucl.ac.uk (D. Goldblatt), D.King@wellcome.org (D. King), wendy.hartig-merkel@p-95.com (W. Hartig-Merkel), joris.vandeputte@vaccim.eu (J. Vandeputte).

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Christina Cassetti of the US NIH who reviewed ‘Operation Warp Speed’, which delivered effective vaccines in the briefest possible time. She stressed that right from the beginning, data were collected on immune responses to permit effective vaccines to be used and improved as rapidly as possible. **Jakob Cramer**, Head of Clinical Development at the

hemagglutinin-inhibition antibody) and biomarkers for which no threshold value is established (anti-SARS-CoV-2 NAb). She noted that IB can be done in the absence of an agreed-upon serological threshold value if the biomarker measured is shown to be associated with protection. SARS-CoV-2 NABs were used to infer effectiveness and autho-

Abbreviations			
ACE	Angiotensin-converting enzyme	IB	Immunobridging
Ad	Adenovirus	ICS	Intracellular cytokine staining
ADCC	Antibody-dependent cellular cytotoxicity	IM	Intramuscular
AIM	Activation-induced marker	IN	Intranasal
BSL	Biosafety level	INF	Interferon
BTI	Breakthrough infection	IPV	Inactivated polio vaccine
CEPI	Coalition for Epidemic Preparedness and Innovations	NAb	Neutralizing antibody
CHIM	Controlled human infection model	NHP	Non-human primate
CMI	Cell-mediated immune	NIH	National Institutes of Health
CoP	Correlate of protection	NITAG	National immunization technical advisory group
DSMB	Data and safety monitoring board	NP	Nucleoprotein
EC	Ethics committee	OPV	Oral polio vaccine
EPIV	European Plotkin Institute for Vaccinology	PCR	Polymerase chain reaction
FDA	United States Food and Drug Administration	RBD	Receptor binding domain
GMP	Good Manufacturing Practices	RCT	Randomized controlled trial
GMT	Geometric mean titer	RSV	Respiratory syncytial virus
HIV	Human immunodeficiency virus	TCID	Tissue culture infectious dose
IABS	International Alliance for Biological Standardization	VE	Vaccine efficacy
		WT	Wellcome Trust

CEPI, explained how the organization targets 100 days as the goal for vaccine development and that work has begun on candidate vaccines against organisms that could potentially cause new epidemics. **Deborah King**, Vaccine Research Lead at the WT, explained that the Trust is keen on identifying CoPs to permit rapid vaccine development and licensure early in epidemics.

Ilse de Coster, University of Antwerp, described the features of Vaccinopolis, the new human challenge facility at the University of Antwerp where the meeting was held. Vaccinopolis forms, along with the Institute for Medical Immunology (Université libre de Bruxelles), the EPIV (www.epiv.eu), which is a joint effort of the University of Antwerp and the Université libre de Bruxelles to promote studies of vaccine immune responses and CoPs using controlled infection in isolation units monitored by biosafety level (BSL)-2 and BSL-3 laboratory studies.

2. Presentations on current evidence of CoPs against COVID-19

2.1. Why do we need CoPs against SARS-CoV-2?

The following session was opened by **Dan Barouch**, Professor, Harvard University, who has conducted extensive studies of SARS-CoV-2 infection in macaque monkeys. He concluded that whereas neutralizing antibodies (NABs) are protective against infection, cellular responses modify the severity of infection. This has become particularly evident with the advent of the Omicron variant. Cases of infection despite vaccination are related to low NAB responses and low T-cell responses. Experimental depletion of CD8⁺ T cells also results in severe infections.

Marion Gruber (formerly of the US Food and Drug Administration [FDA]), discussed the importance of CoPs (also referred to as immune markers) in the development and licensure of preventive vaccines. Immune markers serve different regulatory purposes including forming the basis of approval of new vaccines. Biomarkers are used as endpoints in clinical immunobridging (IB) studies to infer effectiveness of vaccine candidates whereby the strengths of the biomarker vary from scientifically well-established biomarkers (e.g., anti-hepatitis B antibody) to biomarkers “reasonably likely” to predict protection (influenza

rization of SARS-CoV-2 vaccines directed against SARS-CoV-2 variants of concern, as well as approval of new SARS-CoV-2 vaccines based on a different platform than the licensed comparator vaccines. For next generation SARS-CoV-2 vaccines, inference of effectiveness should not be based on NABs alone but also would require a thorough characterization of the immune response of the new vaccine versus a licensed comparator. She concluded that SARS-CoV-2 NAB may be used as CoP to predict the effectiveness of certain future “pan-variant” SARS-CoV-2 vaccines, but that further research is needed to establish biomarkers to demonstrate the effectiveness of broadly protective SARS-CoV-2 vaccines including vaccines administered via different routes of administration and/or if the outcome of interest (e.g., protection from infection rather than severe disease) is changed.

Hanna Nohynek, Finnish Institute for Health and Welfare, gave insights into the work of national immunization technical advisory groups (NITAGs). These NITAGs must evaluate vaccines proposed for licensure even if circulating SARS-CoV-2 strains have changed from the original Wuhan virus. The fact that infection takes place on mucosal surfaces also introduces a variable. Efficacy must be evaluated against infection and disease, inasmuch as CoPs may differ between the two.

2.2. Serum antibodies

Serum antibodies to structural proteins of SARS-CoV-2 are induced following natural infection, and the majority of those with neutralizing activity are targeted at the spike protein receptor binding domain (RBD).

David Montefiori, Professor, Duke University Medical Center, described how NABs have proven to correlate with VE in multiple studies but emphasized that *binding* antibodies (to the whole spike protein and to the RBD) have also been demonstrated to correlate well with VE. The two major categories of assays that measure NABs are pseudovirus assays and live virus assays. These are widely used but not standardized, so wide variations can occur. Several antibody effector functions that may be important for COVID-19 vaccines and that probably deserve more attention than they have received to date are antibody-dependent cellular cytotoxicity (ADCC), phagocytosis,

complement, antibody isotypes/subclasses, and Fc receptor binding.

Miles Davenport, Head Infection Analytics Program, The Kirby Institute, University of New South Wales, described how protection from *symptomatic* infection was first approached by comparing clinical trials of different vaccines and relating the geometric mean titers (GMTs) of NAb elicited in vaccinees with the protective efficacy measured in the individual clinical trials [1]. This “vaccine comparison method” has also been used for binding antibodies against the ancestral virus, which also correlates well with VE. A systematic review of all published data until January 2022 reported on protection over time and against specific SARS-CoV-2 variants and estimated the titers based on the knowledge of the half-life of the antibody and the drop in titer (which is again estimated from another meta-analysis) [2]. Protection at low antibody levels could be predicted accurately at some time after vaccination and in the context of different variants. NAb curves are thus predictive of protection, both across different vaccines and variants and across time. These curves appear to be predictive of both symptomatic and severe infection, with the caveat that most data were collected from naïve individuals; for those with hybrid immunity, further study is required.

Merryn Voysey, Associate Professor and Head of Statistics in Vaccinology, University of Oxford, presented CoP analyses for SARS-CoV-2 from the U.K. phase 3 clinical trial of the Oxford AstraZeneca vaccine during the winter 2020–2021 (i.e., most of the cases were either SARS-CoV-2 Alpha or earlier variants). The trial used both binding antibody assays and NAb assays, and both were shown, in a correlates-of-risk analysis, to be associated with protection [3]. Remarkably, the plots and relative risk curves from this trial and a Moderna phase 3 trial were very similar, with CoPs found to be consistent across vaccines [4]. T-cell and other antibody assay data will be available for the trial participants soon, and an integrated analysis of a variety of immunological markers (CoPs) will aid in assessing the proportion of protection afforded by each immunological marker.

Peter Gilbert, Professor of Biostatistics, University of Washington, summarized the current CoP gaps and potential areas for increasing CoP research, which included extending studies to include a variety of clinical outcomes, utilizing more sensitive assays to assess CoP at low levels of NAb, establishing population-level meta-analyses of existing data, collecting more data on Omicron BTIs (limited data available at the time of the meeting), using test-negative-designs for post-approval studies, integrating vaccine and monoclonal antibody studies and accounting for SARS-CoV-2 sequence and immunophenotyping to improve the understanding of CoPs following immunization with an ancestral strain and BTI with a variant.

2.3. Circulating T lymphocytes

B and T lymphocytes have co-evolved and cooperate to provide immunity to viral infections. This session addressed the role of circulating T lymphocytes in natural and vaccine-induced immunity to SARS-CoV-2 and the challenge of measuring T-cell responses in large clinical studies.

John Wherry, Professor, University of Pennsylvania, emphasized the importance of differentiating protective immunity against infection, disease, and transmission. Studies of BTIs indicate that systemic vaccination has a limited impact on the kinetics of viral clearance from the upper respiratory tract but limits viral replication and spread, thereby preventing lower respiratory tract infection and severe symptoms. Studies suggest that prolonged viral exposure in the upper respiratory tract activates pre-existing memory B cells and the production of cross-reactive NAb, recognizing the viral variant causing the BTI. BTI is also associated with the rapid priming and expansion of non-spike-specific CD4 and CD8 T lymphocytes. Within the spike protein, previous vaccination focuses the T-cell response on the RBD rather than the S2 domain. Together, these data indicate that intramuscular (IM) vaccine-induced immunity does not prevent infection, at least in the upper respiratory tract, and suggest that BTI is associated with a spread in antigen

repertoire recognized by antibodies and T cells that could contribute to the limitation of viral spread and prevention of symptoms.

Arnaud Marchant, Professor, Université libre de Bruxelles, discussed the evidence supporting a role of circulating T cells as a CoP against COVID-19. Studies of primary infection support a role for T lymphocytes in preventing the development of severe disease. Evidence of a role of T cells in vaccine-induced immunity remains scarce. This is partly due to the high correlation observed between antibody and T-cell responses to vaccination in healthy individuals and the difficulty to disentangle the relative role of the two immune effectors. Studies of immunocompromised patients with defective antibody responses to vaccination may help reveal a role for T lymphocytes. In kidney transplant recipients, Kemlin et al. [5] recently observed that both NAb and cell-mediated immune (CMI) responses predict the risk of BTI following mRNA vaccination. The highest risk of BTI was observed in patients with low antibody and CMI responses, whereas the lowest risk was observed in patients with high responses of the two immune effectors. These data support an independent role of T lymphocytes induced by mRNA vaccination in protection against COVID-19 and the interest in conducting CoP studies in immunocompromised populations.

Robbert van der Most, responsible for the biomarker strategy at BioNTech, discussed laboratory methods to identify T-cell CoPs following vaccination. Tuberculosis vaccine trials provided proof of principle that CMI analysis can be performed in cohorts of thousands of subjects. Pilot studies are needed to assess the characteristics and performance of the available assays and to select those that are suitable for large clinical trials. Several assays are available to assess T-cell responses. The gold standard is intracellular cytokine staining (ICS) following antigen stimulation of peripheral blood mononuclear cells. Although this assay is labor intensive and challenging to standardize, it has been successfully applied to phase 3 trials. Whole blood ICS or secreted cytokine assays simplify sample processing procedures. Other assays deserve more attention, including interferon (IFN)- γ release, TruCulture® or non-antigen-specific T-cell activation assays. T-cell receptor sequencing has recently been proposed and requires further evaluation for the sensitive detection of T-cell responses. The ideal assay would be simple and easily scalable. Small-scale studies can be used to explore correlations between simpler assays with the gold standard and with other immune parameters, including antibodies or transcriptomics.

2.4. Mucosal immunity

Several efforts are currently ongoing to develop COVID-19 vaccines that are delivered mucosally and aim at blocking infection and transmission in addition to protecting against disease [6]. Understanding the CoPs for mucosal vaccines is critical to identify the most promising vaccines and facilitate their regulatory approval.

Yongjun Sui, associate scientist, US NIH, discussed studies of non-human primates (NHPs) immunized with an adjuvanted subunit COVID-19 vaccine IM, and boosted with the same vaccine, either IM or intranasally (IN), and showing significant differences in the immune responses depending on the route of immunization [7,8]. While IM immunization elicited higher serum neutralizing and binding antibodies, IN immunization induced in all animals detectable levels of dimeric mucosal IgA and higher levels of IFN type 1, an important cytokine in the prevention of SARS-CoV-2 infection. Even if the IN-vaccinated animals had a lower systemic immunity, their clearance of virus in the nasal and bronchial compartment was significantly faster than that of the systemically vaccinated animals. This suggests that high levels of dimeric IgA in the mucosa and IFN type 1 might correlate with viral clearance from the respiratory tract.

Mark Connors, Chief HIV-Specific Immunity Section, Laboratory of Immunoregulation, US NIH, reviewed knowledge about mucosal immunity derived from trials of a replicating adenovirus type 4 (Ad4) vaccine platform, which can also be viewed as CHIM studies because it is a live-attenuated virus. In these studies, the virus was administered

orally, by an IN spray, or was directly applied to the tonsils. While in seronegative individuals, the virus is typically shed for 21 days, in seropositive individuals, shedding is limited to less than a week, even though IgA in their upper airway was limited or undetectable on the day of infection [9]. This suggests that restriction of the challenge virus may be mediated by a recall response. Although seropositive individuals were likely infected years beforehand and had little to no measurable immune response in their upper airways, they were able to restrict the Ad4 challenge virus. In these challenge studies, the route of infection affected the durability of the immune responses. When given by the oral route, good immune responses were seen at 60 days, but by six months, they had waned. In contrast, when applied to the tonsils or given by an intranasal spray, the immune responses to the challenge agent were more durable, as titers were unchanged from the day 60 peak when participants returned 3–5 years later [9]. These studies suggest that protective and durable mucosal immunity may be induced in the respiratory tract with replicating Ad vectors. Durability, if the vector replicates sufficiently, is likely to be years to lifelong [9].

Ryan Thwaites, lecturer in respiratory immunology, Imperial College London, discussed compartmentalization of immune responses at the mucosal level and implications for the induction of mucosal immunity and for the analysis of response to mucosal immunization. Production of mucosal antibodies depends on plasma cells in submucosal glands that can only be stimulated by mucosal immunization. Evidence for compartmentalization of vaccine responses comes from studies of SARS-CoV-2 pre-infected subjects showing an increase in serum, but not nasal, IgA following parenteral COVID-19 vaccination. Controlled human respiratory syncytial virus (RSV) infection studies showed that high titers of mucosal antibodies may be required to prevent infection. Whereas mucosal T cells may reduce the severity of RSV infection, their role in protection against infection may be limited. Susceptibility to infection correlates with innate immune effectors, indicating that mucosal immunity probably involves the coordinated action of multiple immune effectors.

Advancing the field of mucosal vaccines demands the development of standardized and validated tools and assays for collection and analysis of respiratory samples. This will enable data comparison across different vaccines. Basic research is also needed to understand if antigen persistence in the mucosa correlates with more complete and durable protection. Finally, more research is needed to elucidate the CoPs for mucosal vaccines. CHIMs could play an important role in elucidating, in a controlled setting, the precise nature and scale of mucosal immune responses that are correlated to protection against infection and disease.

2.5. T- and B-cell memory

The session discussed T and B cell memory in the context of duration of protection against COVID-19.

Mehul Suthar, Associate Professor, Emory University, summarized data on durability of humoral and cellular immunity following SARS-CoV-2 infection and vaccination. Very little knowledge was gained about durability of immunity following SARS-CoV-1 and MERS infection. SARS-CoV-2 infection induces durable humoral and T-cell responses in most individuals, although high variability is observed between subjects. Antibody half-life is longer for the SARS-CoV-2 spike protein and shorter for the nucleocapsid protein. Durability of antibody response is much shorter with mRNA vaccination, even after booster immunization, whereas an intermediate half-life is observed after vaccination of pre-infected subjects. BTI with variants of concern induces a bias in the antibody response to the infecting strain, although omicron infection induces a quite balanced repertoire of cross-reactive antibodies. The relatively rapid decay of antibodies following mRNA vaccination increases the need to adapt vaccines to emerging strains. Inducing more durable responses with vaccination would reduce to chase new variants with adapted vaccines.

Alessandro Sette, Professor, La Jolla Institute for Immunology,

discussed the role of T cells in immunity to COVID-19 and available assays to measure T-cell responses to vaccination and infection. Although intracytoplasmic staining following short term stimulation of antigen-specific T cells has been the gold standard assay, the activation-induced markers (AIM) assay provides a more sensitive detection of T-cell subsets such as follicular helper cells. Stimulating T cells with megapools including hundreds of peptides also provide sensitive detection of response to multiple SARS-CoV-2 antigens in populations with diverse peptide recognition repertoires. Also, megapools including SARS-CoV-2 spike-derived peptides and megapools containing peptides derived from other SARS-CoV-2 proteins can discriminate T-cell responses induced by vaccination versus infection. Differences can also be observed between asymptomatic BTIs that are associated with spike-focused T-cell responses and symptomatic BTIs that induce T-cell responses against a larger set of SARS-CoV-2 antigens. Using AIM assay and peptide megapools provided insight in the durability of T-cell immunity and in the potential role of T cells in protection against BTI caused by SARS-CoV-2 variants of concern.

2.6. CoPs against beta-coronaviruses/sarbecoviruses

This session focused on the current knowledge of broadly protective immune responses against Sarbecovirus and Merbecovirus lineages, or more broadly against beta-coronaviruses.

Mihai Azoitei, Assistant Professor, Duke Human Vaccine Institute/Duke University, presented the antigenic potential of the SARS-CoV-2 spike protein. SARS-CoV-2 uses the RBD on the spike protein to bind to the angiotensin-converting enzyme (ACE) 2 receptor to gain access to target cells. The pre-fusion spike protein (the target of most licensed vaccines against SARS-CoV-2) contains three regions that may be targeted by antibodies: RBD, fusion protein and stem helix. The RBD is one of the most diverse regions of coronaviruses, and targeting the more conserved regions of the RBD may provide a strategy to induce broadly protective responses. Antibodies to the fusion peptide and stem helix are known to be broadly protective; fusion peptide antibodies are reactive with both alpha and beta-coronaviruses, while stem helix antibodies are highly reactive with beta-coronaviruses. However, the spike protein poorly induces responses to the stem helix and fusion peptide regions, and novel approaches are needed to induce broadly protective responses using the spike protein as an antigen.

Antonio Bertoletti, Professor, Duke-NUS Medical School, looked at the nature of T-cell responses in asymptomatic and symptomatic infection. T cells are an important component of the antiviral immune response induced by SARS-CoV-2 infection, with diverse T-cell responses being beneficial, as T cells can tolerate mutations. Early induction of a multi-specific T-cell response is associated with control of SARS-CoV-2 infection. Mild disease is associated with induction of nucleoprotein (NP)-specific T cells in the acute phase, and these become more dominant in the memory phase, along with spike-specific responses. T-cell responses to accessory proteins are also observed; however, their association with disease severity is inconsistent between cohorts and not fully understood.

Multi-specific mucosa-resident T cells were also observed after infection in the nasal compartment. Dominance of NP-specific responses was observed in the nasal compartment in contrast to blood, where responses tend to be spike-specific. Together, such data indicate that antigens beyond the spike protein may be needed to induce robust protection against multiple coronavirus strains.

Pamela Bjorkman, Professor, California Institute of Technology, and Mihai Azoitei presented their research developing broadly protective vaccines. Mihai Azoitei's approach to generating a pan-beta-coronavirus vaccine was to combine immunogens in a nanoparticle, displaying multiple copies of the RBD to elicit antibodies against each of these regions. Studies in NHPs demonstrated good neutralization activity in a pseudovirus assay, including against the Omicron variant XBB1.5. Based on these promising data, Good Manufacturing Practices

(GMP) material is now being produced for a phase 1 clinical study with this approach. While RBD-focused responses are important, fusion peptide and stem helix-specific responses may also be needed to induce broad protection. To address this challenge, Azoitei's group has also designed "epitope scaffold" fusion peptide and stem helix immunogens. These are protein immunogens whose aim is to expose target epitopes that would otherwise be occluded. This approach has also shown promising preclinical data and will enter clinical trials later this year.

Pamela Bjorkman has also developed a nanoparticle-based vaccine using a bacterial protein onto which any antigen can be fused. It can have 60 copies of RBD attached and can be homotypic or mosaic with RBDs from multiple strains or lineages. The aim of the approach is to activate B cells recognizing less accessible, more conserved regions, driving a response that would be broadly protective. The approach is currently in preclinical development, with studies in ACE2 transgenic mice showing a protective effect of mosaic nanoparticles, and deep mutational scanning shows that this vaccine drives production of the more conserved antibody responses.

2.7. SARS-CoV-2 human challenge studies

The session was about SARS-CoV-2 human challenge studies and how they can accelerate understanding of CoPs.

Chris Chiu, Professor, Imperial College London, indicated that CHIMs can help understand better the questions on CoPs in terms of virus interaction and immune responses. The key strengths of CHIMs are that they are conducted with well characterized viral strains and standardized dosing of inoculation of all study participants, immediately controlling for viral and environmental factors and eliminating them as confounders. Along with careful selection of participants, a very consistent and usually high infection rate can be achieved (usually 50–70 %). Small sample sizes are therefore needed for statistical power to demonstrate clinical efficacy signals early during clinical development of vaccines and other interventions. The other major advantage of CHIMs, for the purpose of understanding host immunity in CoPs, is that it is possible to study inoculated individuals in detail immediately before and throughout the whole post-inoculation period, i.e., at the beginning, middle, and end of infection. For example, aspects such as the time when the virus and the immune response appears and disappears, growth and decay rates, and time of peak responses can be estimated at great precision. In contrast, these would be difficult to estimate with any accuracy from intermittent sampling in field studies.

In the first COVID-19 CHIM trial, a pre-alpha GMP virus was manufactured and studied in a high-containment quarantine unit in a hospital with an infectious disease unit providing full access to high-level clinical care and very close clinical monitoring. Antivirals were available. 'Long COVID' being a concern, long-term follow-up (up to a year after the viral inoculation) was conducted. Extensive independent scrutiny and public engagement were ensured for overall acceptance. Intranasal inoculation of 10 TCID₅₀ of the D614G-containing wild-type SARS-CoV-2 in 34 seronegative 18–30-year-old volunteers generated sustained infection in 53 % of them. Virus replication quickly reached high levels in the upper respiratory tract, mostly associated with mild and largely upper respiratory tract that peaked around day 4–8 after inoculation. Viral load correlated positively with the timing and size of IFN responses, but IFN levels did not correlate with more rapid control of viral load. The onset of viral load detection correlated with the start of antibody production, but the amount of virus did not correlate with the size of the antibody peak. In contrast, the size of the activated T cell response negatively correlated with viral clearance and therefore the total amount of virus produced. In non-infected individuals, there was evidence of abortive or transient infection associated with rapid recruitment of innate and adaptive immune cells that suggested a role in protection for pre-existing cross-reactive immune responses against seasonal coronaviruses.

SARS-CoV-2 Delta and Omicron challenges are planned. A BTI model

would enable proof-of-concept clinical trials to obtain efficacy readouts of next-generation vaccines, particularly in terms of transmission and cross-strain protection.

Helen McShane, Professor, University of Oxford, presented a dose-escalation human experimental infection study. The study was conducted in close collaboration with Chris Chiu's group to ensure that the same pre-alpha SARS-CoV-2 strain was used for inoculation. Moreover, the studies had a shared data and safety monitoring board (DSMB) and similar protocols and assays to enable as much cross-comparison between the studies as possible. The study was done in 36 healthy 18–30-year-old volunteers with pre-existing immunity. Natural infection occurred at least three months before including, and the longest interval was between six to nine months. The dose-escalation challenge ranging from 10¹ to 10⁵ TCID₅₀ per person, did not result in productive or sustained infection in any volunteers. Nevertheless, five volunteers across dose groups showed a 'transient infection', defined by polymerase chain reaction (PCR) positivity (live virus was detected in only one person). This occurred independently of the length between prior infection or vaccination. Preliminary data supported the finding of immune responses which distinguished these five volunteers from the remaining 31 uninfected volunteers.

3. Discussion

Each of the above sessions was followed by a panel discussion. In the following, these panel discussions are summarized.

3.1. Do we have a consensus on the purpose of CoPs for COVID-19 vaccines? Do we make the best use of available antibody data? Do we need additional data and for which purpose? Can we define CoPs against infection?

The panel discussion was chaired by Stanley Plotkin and the panelists were Dan Barouch, Marion Gruber, Hanna Nohynek, David Goldblatt, David Montefiori, Miles Davenport, Merryn Voysey, Peter Gilbert, Margaret Ackerman from Dartmouth College, Cristina Cassetti from the US NIH, Marco Cavaleri from the European Medicines Agency (EMA), Adam Hacker from the CEPI, Elizabeth Miller from London School of Hygiene & Tropical Medicine, Pieter Neels from Vaccine Advice, Dean Smith from Health Canada, and Jerry Weir from the US FDA.

The regulators clarified that immune markers are already used for regulatory decisions, including approval of new SARS-CoV-2 vaccines consisting of different platforms and vaccines directed at variants of concern. Anti-SARS-CoV-2 NABs are used in IB studies to infer effectiveness of the new vaccines even though there is no defined threshold. Demonstrating non-inferiority and/or superiority on GMT levels and seroconversion in IB studies comparing the candidate vaccine to an authorized vaccine with demonstrated efficacy is sufficient for inferring effectiveness of the candidate vaccine. Vaccines from different platforms have been compared and authorized in this way but rely on a good understanding of the induced immune characteristics of the licensed comparator and the new vaccine candidate. Vaccine-induced protection against infection is, however, relatively short-lived and correlates with a decline in NABs. Moreover, current vaccines do not impact shedding. Real-world evidence for ongoing vaccine-induced protection from severe disease and death suggests that there are other mechanisms (e.g., T cells) that might mediate such protection, and thus, one should still invest in generating new assays to measure other aspects of humoral immunity and making efforts to identify T-cell correlates.

The complexity of generating efficacy data was discussed, particularly in the context of the inability to conduct large-scale placebo-controlled randomized controlled trials (RCTs) for COVID-19 vaccines. Variant viruses are less susceptible to killing by serum from individuals vaccinated with ancestral virus, and thus, new vaccines containing variant virus are being developed. The fact that many of the world's population have now been exposed to vaccines or infection complicates

new vaccine evaluation as responses to new vaccines or boosters are influenced by previous exposure. While IB studies are critical, real-world evidence of the impact of vaccine on a variety of clinical outcomes is important and best gathered from large cohort studies.

3.2. Are T cells important for protection against diverse clinical outcomes? Is there a link to antibodies? What do available data tell us - can we use them? What other data do we need and for which purpose? How can other vaccine-preventable disease models inform the identification of COVID-19 CoPs?

The panel discussion was chaired by Arnaud Marchant and the panelists were John Wherry, Robbert van der Most, Miles Davenport, Martina Sester from Universität der Saarlande, and John Tsang from Yale University.

The panel discussion addressed the role of T cells in protection against different clinical outcomes of SARS-CoV-2 infection and the knowledge gaps that need to be filled to define the role of T cells as a CoP.

There was broad consensus on the role of T cells in protection against severe disease. Identifying a T-cell CoP against severe COVID-19 would involve recruiting patients in the first days after infection and would require a large sample size. It was recognized that designing and implementing such a trial is challenging. The role of T cells in protection against symptomatic infection was debated. The interest in viral shedding as a study endpoint was discussed. For regulatory authorities, a CoP against viral shedding would be useful as a proof of concept, but evidence for protection against disease would be important. Disentangling the role of T cells and antibodies is another challenge. Given the redundancy of the immune system, conducting studies in patients with a deficit in antibody responses would likely help define the role of T cells.

The relative role of antibodies and T cells in protection against SARS-CoV-2 variants was debated. The correlation between reduced vaccine-induced immunity against variants with reduced NAb activity, where T-cell responses are preserved, argues for a predominant role of antibodies. On the other hand, some protection, especially against severe disease, is observed when NAbs are undetectable, whereas variant-specific T-cell responses can be measured, suggesting an independent role for T cells. However, low assay sensitivity limits the analysis of the role of correlates, including NAbs, at low levels of protection. Also, differences in infectivity likely contribute to reduced vaccine-induced immunity and should be considered in the interpretation of CoP data.

How T-cell responses should be measured for CoP studies was then discussed. T cells could contribute to protective immunity through different mechanisms, and T-cell effector functions and characteristics can be measured in multiple ways. How to deal with this diversity and complexity to identify T-cell CoPs was debated. On the one hand, prospective studies evaluating a defined parameter using a standardized assay are needed. On the other hand, there is still uncertainty about how the adaptive immune system should respond to control BTIs. Basic science studies are needed to understand protective immunity and inform clinical studies of CoPs. Defining the articulation between these complementary research approaches is very important. Stepwise approaches evaluating multiple parameters in small-scale studies may help select key T-cell assays that should be tested in large-scale clinical studies. This selection would also involve the potential for the assays to be standardized and scalable. Such approaches have been used for other infectious diseases, such as tuberculosis and HIV, and they could inform strategies for SARS-CoV-2 vaccines.

3.3. Can we use available data on mucosal immunity? What data do we need and for which purpose?

The panel discussion was chaired by Cristina Cassetti and the panelists were Peter Wright from Dartmouth College, Yongjun Sui, Mark Connors, and Ryan Thwaites.

A lot of what we know about the role of mucosal immunity and vaccine protection comes from studies of polio vaccines. The *live-attenuated* oral polio vaccine (OPV) replicates extensively in the gastrointestinal tract and induces not only a serum antibody response but also robust mucosal immune responses that protect individuals from viral replication in the intestine following a second exposure to OPV. In contrast, the *inactivated* polio vaccine (IPV), induces very good serum antibody levels (and protection from paralytic disease) but no measurable mucosal immune response. Vaccination with IPV provided no protection against viral replication in the intestine following OPV challenge [10]. We do not know how much of the knowledge gained through studying polio virus (which is an enteric infection) can be applied to COVID-19 (a respiratory infection).

More studies are needed to understand whether the mucosal compartments in the body (e.g., intestinal vs. nasopharyngeal mucosa) are linked. A clinical study of an Ad4 recombinant influenza vaccine that was given orally as an enteric capsule has demonstrated that it was able to induce measurable pharyngeal immunity [9].

Within the respiratory tract, there are important differences: while the upper respiratory tract is dominated by dimeric IgA antibodies, the most common type of antibody in the lung is IgG, which some believe derives from leakage of serum antibodies into the lower respiratory tract. This might explain why systemic immunity from IM vaccination (e.g., mRNA COVID-19 vaccines) is more effective to protect the lung than the upper respiratory tract. Additional studies are needed to understand the role of dimeric IgA antibodies in protecting the nasopharyngeal cavity.

CHIMs for COVID-19, although challenging to implement because of pre-existing immunity, can be an important tool to advance vaccine development, as they can help elucidate the role of mucosal immunity in vaccine protection, the duration of mucosal immunity, and best practices to collect mucosal samples. For example, CHIM studies could measure differences in viral shedding in the upper respiratory tract in volunteers immunized IM versus IN. Careful studies could also be conducted to correlate mucosal immune responses in the upper respiratory tract with protection from viral replication. CHIM studies could also help elucidate if there is antigen persistence in the mucosa following infection and if this correlates with the duration of protection. In addition, the techniques to collect nasal samples (nasal absorption swabs) could be optimized and standardized using a robust CHIM model. This would be an important pre-requisite for conducting studies on mucosal CoPs. Salivary collection from the crevicular area is not currently recommended because of leakage of serum antibodies.

The regulators are supportive of CHIM models as a tool to generate critical data that can support the authorization of a vaccine, but they feel that additional data from field clinical trials will also be needed.

3.4. Could we use immunological memory as a CoP against SARS-CoV-2?

The panel discussion was chaired by Jakob Cramer and the panelists were Mehul Suthar, Alessandro Sette, Antonio Bertolotti, and Merryn Voysey.

While protection against SARS-CoV-2 disease is mediated by both humoral (antibodies) and cellular immune mechanisms, their contributions to immediate versus delayed immune protection, as well as to cross-protection against variants, differ. Both branches of the immune system include immunological memory mechanisms that are important for immune protection in the long(er) term. Nevertheless, no harmonized and validated approaches exist to assess immune memory to support evidence generation with regard to long(er)-term protective vaccine effects, which is why immune memory markers to date have been less relevant in the context of regulatory decisions or pragmatic vaccine use recommendations. Therefore, there are more questions than answers regarding the role of immune memory as a CoP in the context of SARS-CoV-2 vaccine development:

- Is the humoral or the cellular immune memory more important in providing long(er)-term protective effects against SARS-CoV-2?
- What impact does immune memory have against SARS-CoV-2 infection versus COVID-19 disease?
- How can the effect of immunological memory markers on clinical infection/disease endpoints be established in clinical trials?
- How can immunological assays to assess humoral/cellular immune memory be standardized and harmonized to be acceptable for regulatory decisions/vaccine use recommendations?
- Even if immune memory is present (and can be measured), will immune memory be activated rapidly enough upon re-infection to (re-)mount a protective immune response before an infection proceeds to severe disease (particularly for infectious diseases with a rather short incubation period)?
- What can we learn from other diseases where measurable antibodies decrease over time or drop below detection limits while long(er)-term vaccine protection is maintained, e.g., hepatitis B or Japanese encephalitis?

The importance of long(er) term protective effects in the context of public health effects of vaccines should not be underestimated, and further research in this field is to be encouraged.

3.5. What is the path to broadly protective beta-coronavirus vaccines? Imprinting and diversity of T- and B-cell repertoires

The panel discussion was chaired by Deborah King and the panelists were Mihai Azoitei, Antonio Bertoletti, Pamela Bjorkman, and Christian Gaebler from Charité – Universitätsmedizin Berlin.

The confidence in our current understanding of CoPs for broader families of coronaviruses was discussed first. Panelists commented that every effort was being made to understand both humoral and cellular immunity that could provide protection against beta-coronaviruses, with active research ongoing into multiple approaches, to understand breadth, durability, and potential from escape mutations. We continue to learn from SARS-CoV-2 on the utility of new approaches such as mRNA, and more traditional approaches, such as inactivated vaccines, with innovative research being conducted to address outstanding questions.

The way in which broadly protective vaccines could be licensed, what tools could be used to demonstrate effectiveness and their limitations were discussed with input from regulators, with the critical question being how to demonstrate effectiveness of a vaccine against a virus that has not spilled over to humans yet.

Currently, although there is substantial data supporting a protective role for NAbs as a CoP for SARS-CoV-2, these need to be more widely accepted before they can be used for licensure applications of other vaccines. Currently, NAbs to other coronaviruses could only be shown to be broadly reactive, not protective. The importance of challenge studies was highlighted as being critical to bridge the gap between what is reactive and what is protective. The panel acknowledged the difficulty of developing challenge models for coronaviruses that are not yet circulating in humans, making human challenge models highly unlikely. The possibility of developing a bat model was discussed, as bats are a known reservoir of coronaviruses, but lack of understanding of their very different immune systems and lack of disease in bats means the value of such models remains unclear, and they are not well developed.

Since no accepted CoP is available in an animal model, i.e., a clear relationship between immune responses and clinical outcome, the value of animal models for coronaviruses in licensure packages was raised.

Regulators commented that we need to be pragmatic about the tools we have available and how to use them. The aim should be to demonstrate proof of concept by developing a series of datasets that would give confidence that an approach is likely to be effective and that developers should be creative to build data packages that immunologically make sense, potentially including animal data if suitable models are available,

in vitro data and functional immunity data; parallels were drawn with the licensure of vaccines for Meningococcus B, from which lessons could be learned.

Overall, CoPs for broadly protective beta-coronavirus vaccines remain a critical area of research, with many innovative approaches being tested to develop and assess such products, to be better prepared for the next introduction of a coronavirus into humans.

3.6. Using CHIMs for identification of COPs. Creating a network for COVID-19 CHIM studies (objectives of a network, study sites, laboratories, standardization, agencies)

The panel discussion was chaired by Andrew Pollard and the panelists were Chris Chiu, Helen McShane, and Pierre van Damme.

The panel discussion drew attention to the bottlenecks in developing challenge models: global access to virus strains, manufacturing costs under BSL-3 GMP, storage and stability testing, characterization of isolates, duration of manufacturing of strains (which can take up to nine months or more), absence of regulatory clarity, and uncertainty on protective immunity after infection. The need for costly and time-consuming production of challenge strains in BSL-3 under GMP or “GMP-like” conditions was debated.

The panel further agreed on the need for specialized ethics committees (ECs) for CHIM trials. The preference goes to international approaches. It has been very helpful to have the World Health Organization bring together experts right at the start of challenge studies to think about the ethics and the practicalities and published documents [11] and reports are important sources of information for the training of EC specialists. In the U.K., a specialist EC for CHIMs was established and trained based on those WHO documents. The panel further stressed the need for exchanging existing expertise and experiences.

4. Conclusions

During this very timely workshop, current understanding of SARS-CoV-2 immunity was reviewed and discussed to advance the identification of CoPs, enabling the evaluation of COVID-19 vaccines. Several important conclusions were drawn on which further research can be built.

NAbs correlate with protection against COVID-19 and are used for IB studies within and between vaccine platforms for approval of new vaccines by regulatory authorities. Beyond neutralizing antibodies, additional components of the immune response to COVID-19 vaccines are likely to independently contribute to protection against symptomatic infection. Identification of such additional CoPs would help design and evaluate novel vaccines and vaccination platforms in the general population and vulnerable patients. Among the CoP candidates, current evidence is strongest for T lymphocytes and binding antibodies and further studies are needed to consolidate this evidence and define their potential role in the evaluation of vaccines.

For the evaluation of mucosal vaccines that are currently developed, identifying CoPs against infection and transmission is key. Although progress has been made in the analysis of antibody and T-cell responses at the mucosal level, further research is needed to identify and standardize methods suitable for clinical studies. Assay selection, optimization, and standardization are required to further advance the evaluation of all CoP candidates. The workshop indicated that the knowledge, expertise, and capacity to bring selected assays to clinical trial standards are available.

Clinical studies can use different entry points to identify CoPs against infection, mild or severe disease. Identifying CoPs against natural infection or in CHIMs allows the analysis of baseline immunity as potential CoP and the use of viral shedding as a study endpoint. Again, the workshop indicated that the knowledge, expertise, and capacity exist to conduct clinical studies using different designs in different populations, and they can be used to discover and validate CoPs that would facilitate

and accelerate the evaluation of novel vaccines and vaccination platforms.

During the COVID-19 pandemic, rapidly authorized vaccines were unfortunately not accessible for early IB studies. Ensuring this accessibility in a future pandemic is very important. For that, it is necessary that authorized vaccines are legally allowed to be used for purposes beyond immunization, i.e., that they can be bought for IB studies.

The COVID-19 pandemic has stimulated an unprecedented global research effort that generated a unique understanding of the immune response to a respiratory virus. This knowledge provides a very strong basis to identify and validate CoPs enabling vaccine evaluation. Important challenges remain, but the scientific community is in a unique position to transform scientific evidence into robust tools that can be used by vaccine developers and regulators. Reaching this objective will consolidate our ability to control COVID-19 and will likely also strengthen our capacity to control future pandemics.

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