World Health Organization

Advancing the development of pan-sarbecovirus vaccines

Next steps

25 March 2022

R&DBlueprint

Powering research to prevent epidemics

BACKGROUND

In continuation to the scientific discussions on COVID-19 vaccines research, WHO R&D Blueprint organized a consultation to identify vaccine research priorities to facilitate further contributions of vaccines to achieve improved control of the pandemic everywhere.

During this consultation (the second specifically addressing this topic) global experts reviewed the available evidence, enumerate knowledge gaps, and outlined research priorities related to pan-sarbecovirus vaccines.

The objectives of the meeting were to:

- review scientific advances and development approaches to enable the development of a pan-sarbecovirus vaccine ;
- outline novel approaches for evaluation of pan-sarbecovirus vaccines, including in the context of the different variants of concern and;
- discuss how we can prospectively evaluate vaccines intended to protect against viruses that are not yet circulating.

The recordings of the meeting are available at the following link:
https://youtu.be/1pGBXU9Hsd8

Why is there a need to accelerate the development and evaluation of pan-sarbecovirus vaccines?

Variants of SARS-2 beta coronavirus may continue to escape neutralizing antibodies induced by vaccines against prior variants The reservoir of beta coronaviruses in bats is large and new crossovers to humans is likely If we prepare now, the time required for large scale vaccine manufacture will be reduced and lives will be saved

If they can be developed and deployed, pan sarbecovirus vaccines are expected to protect against future variants and future crossovers of related coronaviruses to humans. This is of particular importance because evolving variants are becoming increasingly able to evade neutralizing responses to current vaccines.

The technology to make pan-sarbecovirus vaccines appears to be available. A supply of such a vaccine might be able to stifle a small outbreak of a new coronavirus. Once developed, shown to be safe and immunogenic, a large amount of a new vaccine can be manufactured quickly and used to deal with the adaptation of a new beta coronavirus to humans.

For additional information on this topic, you can review the following presentation
https://cdn.who.int/media/docs/default-source/blue-print/1.-plotkin_r-d_who-consulation_25march2022.pdf?sfvrsn=931b0b0b_7

Critical knowledge about these viruses

Sarbecoviruses SARS, MERS, and SARS-CoV-2 can cause severe pulmonary disease and each have diarrhea and fecal shedding as a prominent feature. In each case, comorbidities and age increase the risk of severe disease. SARS-CoV-2 also infects the upper respiratory tract and overall has lower mortality than MERS or SARS (though if disease is severe, mortality is similar to that of SARS). Long COVID is seen with SARS-CoV-2. Goals for vaccination should include prevention of severe disease and long COVID.

For additional information on this topic, you can review the following presentations:
https://cdn.who.int/media/docs/default-source/blue-print/3.-aljabr_r-d-who-consultation_march-25-2022-.pdf?sfvrsn=8942e747_7

https://cdn.who.int/media/docs/default-source/blue-print/6.-perlman_r-d-who-consultation_march-25-2022.pdf?sfvrsn=9b6eb8a6_7

Increasing numbers of coronaviruses are being identified and the substantial genetic diversity among them increases the difficulty of developing vaccines with broad immunity to these viruses.

Climate change may alter diversity and likelihood of crossover to humans of additional sarbecoviruses, most of which have bat hosts. Completely new coronaviruses could emerge in humans due to mutations or due to changes in contact between humans &

infected vectors or host (which can be influenced by weather and changing opportunities for animal exposure). Animal reservoirs present challenges and opportunities for control.

For additional information on this topic, you can review the following presentations:
https://cdn.who.int/media/docs/default-source/blue-print/4.-koopmans_r-d-who-consultation_march-25-2022.pdf?sfvrsn=166aab82_7

https://cdn.who.int/media/docs/default-source/blue-print/5.-karesh_ecohealth_r-d-who-consultation_march-25-2022.pdf?sfvrsn=f1052ffe_7

Development of vaccines – approaches and challenges

There are important differences among sarbecoviruses that could affect the likelihood of achieving a pan-sarbecovirus vaccine. For example, SARS and SARS-CoV-2 use the ACE-2 receptor, unlike many other sarbecoviruses including MERS. The goal of a broadly specific vaccine addressing ACE2 binding sarbecovirus may thus be more achievable as compared with a pan-sarbecovirus vaccine.

Evolution of SARS-CoV-2 continues with uncertain direction, which might influence the success of broadly specific vaccines. We don't know the sources of all variants—they could evolve naturally from human-to-human transmission (but may not be detected early due to undersampling), could involve replication in animals (e.g., mink, deer, or other unknown hosts), or evolve during multiple rounds of replication in the same immunocompromised human hosts. It is predicted that new variants will likely gain in capacity for immune escape and virus transmissibility.

For additional information on this topic, you can review the following presentations:
https://cdn.who.int/media/docs/default-source/blue-print/20.-krammer_r-d-who-consultation_march-25-2022.pdf?sfvrsn=c2f8d686_12

https://cdn.who.int/media/docs/default-source/blue-print/7.-wang_vaccine-strategies_r-d-who-consultation_march-25-2022.pdf?sfvrsn=4e1a3fc6_12

https://cdn.who.int/media/docs/default-source/blue-print/8.-saunders_r-d-who-consultation_march-25-2022.pdf?sfvrsn=168ff052_7

https://cdn.who.int/media/docs/default-source/blue-print/11.-jiang-lu_r-d-who-consultation_march-25-2022.pdf?sfvrsn=56e6da37_7

https://cdn.who.int/media/docs/default-source/blue-print/11.-jiang-lu_r-d-who-consultation_march-25-2022.pdf?sfvrsn=56e6da37_7

https://cdn.who.int/media/docs/default-source/blue-print/12.-bjorkman_vaccine-strategies_r-d-who-consultation_march-25-2022-.pdf?sfvrsn=6e2d2797_7

https://cdn.who.int/media/docs/default-source/blue-print/13.-levy_r-d-who-consultation_march-25-2022.pdf?sfvrsn=7bc3e78b_7

Evaluation of vaccines and anticipated challenges

There will be pre-clinical and clinical challenges in developing these vaccines, many of which can be addressed by focused research. Improved virological understanding of sarbecoviruses, including their antigenic breadth, potential for antigenic drift, identification of conserved epitopes will be essential.

Animal models (both large and small) that can allow for evaluation of vaccines against infections caused by the large number of viruses in this group against which protection is desired, as well as lead to improved understanding of COVID ARDS and enhanced disease will also be important.

Panels of standards that are relevant to key sarbecoviruses will be needed to aid in assay development, including identification of standardizable approaches to measuring cell-mediated immunity.

Additional research into the immunology of these infections is also essential, including the role of cross-virus immunity in protection as well as in vaccine response, and better definition of protective immune responses and the kinetics of their development will also be needed. It will be important to address biosafety considerations associated with working with additional coronaviruses.

Coronavirus-specific neutralizing antibodies are often very strain-specific, suggesting the importance of inducing cross-neutralizing antibodies.

Various strategies can be considered to increase the breadth of neutralizing antibodies, recognizing that very strong neutralizing responses are more likely to be cross-protective than weaker responses.

Cell-mediated responses and non-neutralizing humoral responses are also considered key to increasing duration and breadth of protection, since these responses are less vulnerable to receptor-binding-domain mutations. Mucosal responses could also play an important role in protection induced by some vaccines.

Identifying ways to evaluate vaccines that will lead to regulatory authorizations and NITAG recommendations will also be important.

Clinical trials, if needed, will need to be done in increasingly seropositive populations. Immunobridging approaches proposed for use with SARS-CoV-2 vaccines may also have utility in evaluating more broadly protective vaccines. In-deployment studies and controlled human infection models (CHIM) may play a role where immunobridging is not supported (for CHIM, recognizing the difficulty of making appropriate challenge strains and assuring protection of study participants).

In general, it is considered feasible to use criteria that have been agreed upon for SARS-CoV-2 vaccines to make more broadly specific vaccines available initially.

For additional information on this topic, you can review the following presentations:
https://cdn.who.int/media/docs/default-source/blue-print/14.-krause_framework_r-d-who-consultation_march-25-2020pptx-(2).pdf?sfvrsn=bbb2d9b9_7

https://cdn.who.int/media/docs/default-source/blue-print/16.-dhere_sii_r-d-who-consultation_march-25-2022-.pdf?sfvrsn=8c8f27b0_7

https://cdn.who.int/media/docs/default-source/blue-print/17.-schuitemaker_janssen_r-d-who-consultation_march-25-2022-.pdf?sfvrsn=d07a1fad_7

Ongoing initiatives to support the development of some vaccines

Major funders, including NIAID, INSERM, CEPI among others, as well as industry funded initiatives, are investing in new vaccine approaches and supportive science. WHO will provide a forum for follow-up discussions to facilitate exchange of ideas and to help with research coordination.

For additional information on one of such initiates, you can review the following presentation or consult the website of the partners mentioned above:
https://cdn.who.int/media/docs/default-source/blue-print/21.-costa_cepi_r-d-who-consultation_march-25-2022.pdf?sfvrsn=31838982_7

Overall conclusions and the way forward

Further progress on broadly-specific sarbecovirus vaccines is considered to be essential—with no doubt that what is learned about increasing breadth of protection against SARS-CoV-2 will have additional future implications for public health.

Numerous promising vaccine strategies are being pursued. Approaches include vaccines that present antigens that are largely conserved among these viruses, chimeric antigens, and multiple different antigens. It will be important to identify the most important antigens and epitopes globally using and independent process, including which viral proteins or portions of viral proteins should be included. Strategies for antigen presentation may be particularly important in inducing broadly specific responses.

Vaccination regimens which include multiple different but related antigens that represent different viruses, whether given at the same or different times, appear to be promising. Adjuvants could also play a role in increasing breadth and magnitude of immune responses.

Other vaccine features that will aid in deployment of these vaccines include ability to induce responses with fewer doses or mucosal administration. Many presenters, including those from industry, strongly emphasized the importance of vaccination strategies that will induce cell-mediated as well as humoral responses.

From the preliminary data presented, it seems likely that a next generation of vaccines could be developed that induced broader immunity than currently available vaccines, without needing to sacrifice efficacy.

Global experts generally agreed that it is critically important to proceed with development of vaccines with broader specificity. This will address current and future needs for SARS-CoV-2, as well as help prepare for a future possible pandemic.

WHO's aim is to contribute to accelerate the candidate vaccines assessment pathway and to contribute to highlight how global resources should be applied to their development as part of global research pandemic preparedness.

WHO is committed to continue to offer a forum for follow-up discussions to facilitate exchange of ideas and to help with research coordination. What we learn about increasing breadth of protection against SARS-CoV-2 will doubtless have additional future implications.

Globally agreed R&D Roadmaps and generic Target Product Profiles (TPPs) are being developed through broad and open consultations with leading experts and other stakeholders. The roadmap development process has been informed by a WHO generic methodology that serves as a guide to structure and harmonize roadmaps creation and implementation.

The R&D Blueprint team has also been fostering collaborations and consultations between regulators to develop WHO regulatory guidance to facilitate regulatory assessment of candidate vaccines.

Specifically, using its existing methodology, WHO will develop a Roadmap for Pan-Sarbecovirus vaccines. The WHO R&D roadmaps encompass basic research through to late-stage development, licensure and early use of products. Such roadmap will serve as a collaborative framework to underpin strategic goals and research priority areas so as to accelerate the development of vaccines to prevent and control severe emerging diseases due to priority pathogens.

In brief, key steps for the development of the WHO R&D Blueprint roadmap include the following:

1. Convene two consultation with a large group of diverse international experts, to obtain overall inputs on the needs and on key issues to consider.
2. Develop a roadmap draft, with input and support from a core group of selected subject matter experts.
3. Revise the roadmap (with support from an Expert Working Group)
4. Complete a review process by sharing the draft online and inviting inputs from all stakeholders that will be incorporated into the final draft.

Step 1 has been conducted, step 2 is underway. A critical element of such a global initiative is that it will incorporate and support not only candidate vaccines supported by major funders but also academic, biotech and and big pharma initiatives from around the world.

For additional information on this topic, you can review the following presentation or consult the website of the partners mentioned above:

https://cdn.who.int/media/docs/default-source/blue-print/22.-henao-restrepo_r-d-who-consultation_march-25-2022.pdf?sfvrsn=c90afc3d_7

https://www.who.int/observatories/global-observatory-on-health-research-and-development/analyses-and-syntheses/who-r-d-blueprint/who-r-d-roadmaps