Vaccine Research and Development: Key Lessons and Ways Forward

AVAC
Global Health Advocacy, Access & Equity

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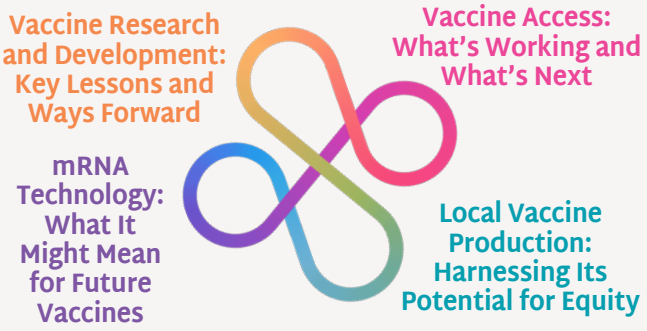
Ensuring equitable access to safe, effective, and affordable vaccines involves advocacy across multiple areas. This issue brief on the vaccine research and development (R&D) process is one of a series of four briefs, which provide a roadmap for advocacy to advance the development of essential vaccines for HIV, COVID-19, tuberculosis, and other global public health threats, and approaches to ensure equitable access to these life-saving vaccines. Additional topics cover the role of mRNA technology, the need for local vaccine production, and issues around global access.

The world still lacks vaccines for some long-standing infectious diseases – due to both significant scientific challenges and the lack of a lucrative market for them – and these issues are further illuminated with emerging pathogens.

FROM THE LAB TO THE JAB

A series of advocate's guides



This is one in a series of four advocate's guides highlighting key advocacy issues to ensure equitable access to safe, effective, and affordable vaccines. All four briefs can be found at avac.org/FromLabToJab

Key Points

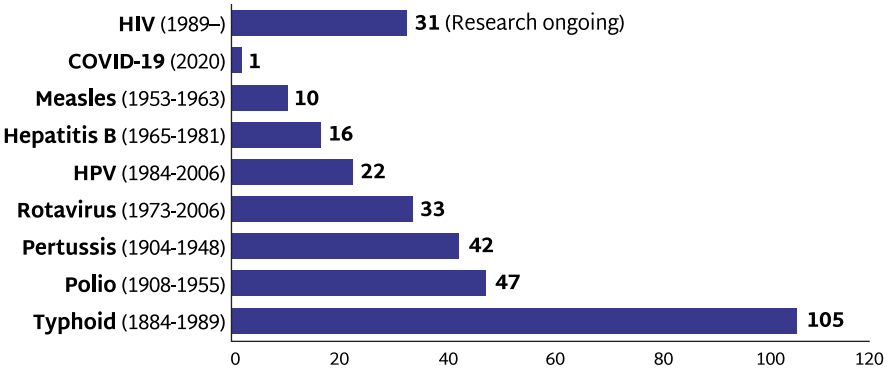
- HIV vaccine research enabled rapid development of COVID-19 vaccines.
- Although COVID-19 set a new standard for rapid vaccine R&D, the initial vaccines, which were first developed in 2020, could be improved upon.
- There is urgent need for continuing advocacy for, and meaningful community participation in, vaccine R&D.

Vaccine development has traditionally been a lengthy, complex process, sometimes taking over a century following the identification of a disease. New technology has enabled more rapid development of vaccines, especially through the mRNA platform.

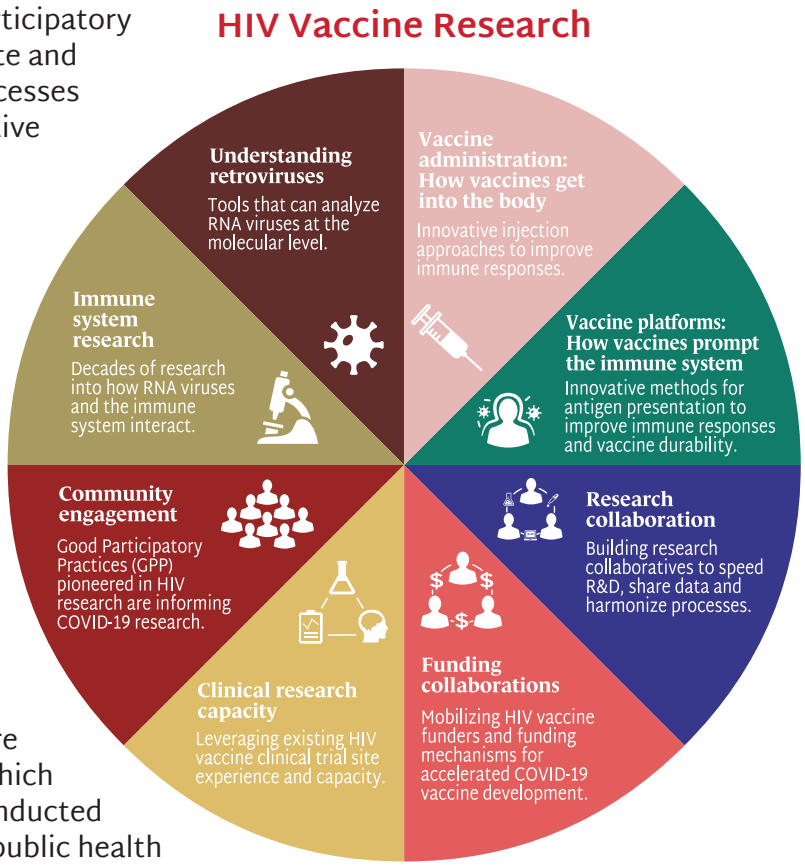
Progress in COVID-19 research was accelerated by decades of HIV vaccine research. It has increased the understanding of immune function and responses, and contributed vaccine platforms,

Vaccine Development in History

Time to develop a vaccine: Duration between discovery of microbiologic cause of selected infectious diseases and development of a vaccine



research processes and partnerships, participatory practices and robust advocacy to expedite and enhance COVID-19 vaccine research. Processes developed in HIV research (such as adaptive and pragmatic designs for clinical trials and running them in parallel, rather than sequentially, preparing for large-scale vaccine production and securing public and private commitments to enable vaccine access before final trial results) sped up development of COVID-19 vaccines, as did the partnerships and collaborations forged by HIV vaccine research, which enabled data-sharing and rapid development and distribution of COVID-19 vaccines. Good Participatory Practices (GPP) sprang from HIV prevention research; these practices ensure meaningful community participation across the continuum of biomedical research and are essential for stakeholder engagement, which guarantees that COVID-19 research is conducted in alignment with ethical, scientific and public health standards. In addition, HIV vaccine advocates have the knowledge and experience to counter stigma and address misinformation in their communities.



In turn, breakthroughs in COVID-19 vaccine research, such as licensing the first use of the mRNA platform, have advanced HIV vaccine science, and, more broadly, vaccine development.

Benefits From, and Progress in, HIV Vaccine Development

Since the first HIV vaccine trial in 1987, more than 250 trials have advanced the knowledge of HIV's structural biology and identified potential immunogens and novel systems for vaccine delivery. Although research has yet to yield a preventive HIV vaccine, it has contributed to efforts to develop other vaccines by increasing the understanding of human immune responses. HIV vaccine trials have built local and sustainable research capacity by equipping laboratories, training technicians and scientists on good clinical practices and in areas that are broadly applicable to other biomedical research, and enabling by laboratory accreditation. HIV vaccine research has advanced the practice of, and reaped the benefits from, meaningful community participation.

New approaches to an HIV vaccine are in early-stage research: mRNA-based vaccines that might stimulate production of broadly neutralizing antibodies (bNAbs, which can target multiple strains of HIV, and prevent it from infecting cells); and "immune progrmming", by using cytomegalovirus (CMV) to induce potent, long-lasting T cell responses to HIV that may be applicable to other infectious diseases and cancer; and replicating viral vector-based vaccines, which include an HIV envelope gene, to deliver antigen-making instructions that trigger immune responses.

COVID-19 Vaccine Research: Looking Back to Move Forward

There are valuable lessons from COVID-19 vaccine development.

During 2020, the world went from having no COVID-19 vaccines to having several desperately needed vaccines, with unprecedented speed. Decades of HIV vaccine and other research, and substantial government funding, enabled the rapid development of COVID-19 vaccines.

Although these vaccines saved nearly 20 million lives, worldwide, in just a year,[1] their clinical trials had limitations, such as:

- Lack of head-to-head trials and the absence of a standardized vaccine trial protocol, which prevented comparisons of vaccine safety and efficacy.
- Use of different COVID-19 symptoms (which triggered testing) across trials, and lack of universal and regular COVID-19 testing for all trial participants; only symptomatic trial participants were tested for COVID-19. It is likely that many infections were undetected, because 45% of people with COVID-19 are asymptomatic. This led to an overestimation of the effectiveness of vaccines for preventing infection, and, ultimately, mistrust and vaccine hesitancy.
- Different primary endpoints were used across vaccine trials, most of which focused on prevention of symptomatic infection; some – but not all – also assessed efficacy for preventing serious illness, hospitalization, and death from COVID-19. The failure to assess all of these endpoints led people to undervalue the importance of COVID-19 vaccines.
- Short follow-up periods prevented an assessment of the durability of vaccine-induced protection against infection, serious illness, hospitalization and death.
- Exclusion or under-enrollment of certain groups, such as pregnant people, people living with HIV, people with immunocompromising conditions, and older people.
- Conducting trials in areas where different viral variants were circulating, without collecting crucial information about the dominant variants in different countries and regions. Some variants are better able to evade vaccine-induced protection against infection than others; the lack of information undermined the ability to assess how effective the tested vaccine was for preventing infection on a variant-by-variant basis.
- Lack of transparency about trial protocols and results, including clear communication about adverse events.
- Widespread, misleading "science by press release." Numerous product developers announced vaccine trial results in press releases, which cited only the data selected by pharmaceutical companies; it took weeks to months before complete results were available in peer-reviewed journals.

Research on approved vaccines focused on products developed in high-income countries. There were fewer studies on vaccines developed and approved in low- and middle-income countries. This led to non-evidence-based notions that vaccines developed outside of high-income countries were less effective.

The absence of sufficiently funded global surveillance systems for capturing information on adverse events has created and fed mistrust, misinformation and vaccine hesitancy.

What the World Needs Now

Current COVID-19 vaccines greatly reduce incidence of severe illness, hospitalization, and death. But the level of antibodies from a COVID-19 vaccine (or SARS-CoV-2 infection) wanes within months. In addition, SARS-CoV-2 keeps changing, and some of its variants are better able to evade immune responses than others.

The world needs next-generation vaccines that offer longer-lasting protection against a broader range of SARS-CoV-2 variants. Until recently, all COVID-19 vaccines were based on the original virus, called the Wuhan strain (although the most recent COVID-19 vaccines are designed to target certain Omicron subvariants). Instead of having multiple booster doses, the world needs COVID-19 vaccines with the following characteristics:

- Affordable, accessible and appropriate, with options that are suitable for different global contexts
- Safe, effective and suitable for all ages, and in immunocompromised and pregnant people
- Tolerable, with minimal, mild side effects
- Able to elicit rapid, robust immune responses, including in people with preexisting immunity
- Able to prevent severe disease
- Will protect against all coronaviruses
- Offer at least one full year of protection, without the need for booster doses
- Could be aimed at viral targets that are less likely to mutate than the SARS-CoV-2 spike protein, which is used in current vaccines
- Could be given as a nasal spray or inhaled, to increase immunity where SARS-CoV-2 enters the body. This could enhance protection and provide an easy-to-use alternative.

Getting the COVID-19 Vaccines We Need

As of March 2023, the World Health Organization reported that there are 199 COVID-19 vaccines in pre-clinical development, and 183 in clinical trials.[2] Most are injectable; but 16 candidates are intranasal, 5 are oral, 2 are inhalable, and 1 is an aerosol.

Platform and Number of Candidates	
Protein subunit	59
Viral Vector (non-replicating)	25
DNA	17
Inactivated Virus	22
RNA	43
Viral Vector (replicating)	4
Virus-Like Particle	7
VVr + Antigen Presenting Cell	2
Live Attenuated Virus	2
VVnr + Antigen Presenting Cell	1
Bacterial Antigen-spore Expression Vector	1

Source: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

Trials cannot be conducted as they were in 2020. Large, placebo-controlled vaccine trials are no longer ethical or feasible, due to their high cost and changes in COVID-19 incidence. Researchers and regulators will need to identify approaches for defining and demonstrating effectiveness of second-generation COVID-19 vaccines, as well as assessing their safety. This has become more complicated, because everyone has varying degrees of immunity from past infections and/or previous vaccines, and since there is no established threshold of immunity to SARS-CoV-2. A vital next step for researchers is to identify reliable correlates of protection (which are the immune responses associated with protection from infection).

Although more information about types and levels of immune response to SARS-CoV-2 is needed, new COVID-19 vaccine trials are already relying on an approach called immunobridging. This approach infers the efficacy of a vaccine by comparing immune response markers (usually levels of certain antibodies) in recipients of experimental vaccines to those proven to predict protection against disease. Immunobridging has been used for a seasonal influenza vaccine, and to determine the efficacy of the Pfizer/BioNTech COVID-19 vaccine in people ages 16-25, and for lower doses in people ages 5-11.

In 2021, the International Coalition of Medicines Regulatory Authorities convened a workshop on future steps for COVID-19 vaccine development,[3] which included a discussion of trial designs and immunobridging. Potential criteria and considerations for immunobridging studies include:

- Determine which vaccine(s) should be replaced with comparator(s) to identify optimal effectiveness.
- Determine whether the same-platform vaccines or vaccines from different platforms should be compared (such as an mRNA-based vaccine versus a viral vector vaccine).
- The selection of viral strain (original versus variants).
- Comparator populations (age, race/ethnicity/co-morbidities).
- Vaccine dosing and scheduling.
- Reliability of the tests used to establish correlates of protection.
- Epidemiology and evolution of SARS-CoV-2 – if COVID-19 cases decrease, a vaccine could look more effective than it actually is; as the virus changes, vaccines may be less effective against emerging variants.

On April 10, 2023, the Biden Administration announced a new, $5 billion US initiative, "**Project NextGen**," which aims to expedite development of COVID-19 vaccines and therapies.[4] Project NextGen will focus on creating long-lasting and strong monoclonal antibodies, expediting development of vaccines that produce mucosal immunity (a first line of defense in the upper respiratory tract, where SARS-CoV-2 enters the body), and accelerating development of a single vaccine that will protect against all coronaviruses through public-private partnerships.

However, Project NextGen is currently being hindered by several factors, such as confusion about eligibility for the program, an uncertain regulatory pathway for novel COVID-19 vaccines, lack of infrastructure (unlike Operation Warp Speed, which used HIV clinical trials networks for COVID-19 vaccine research, Project NextGen will rely on private companies for vaccine development), and whether there will be sufficient funding for registration trials.

In addition, researchers have faced difficulty in obtaining mRNA-based COVID-19 vaccines for trials, due to a requirement for approval from Moderna and Pfizer/BioNTech in government procurement contracts. Both companies have delayed donations for research, or added stipulations for intellectual property rights to any invention discovered in trials using donated vaccines.[5,6]

Ethics of Meaningful Engagement

Communities that advance science must benefit from the results of research and be among the first to receive access to approved medical technologies. But some of the countries that hosted clinical trials for COVID-19 vaccines were left without access to these vaccines, despite ethical principles for research that are enshrined in *The Declaration of Helsinki*[7] and *Good Participatory Practice Guidelines*,[8] each of which specifies the obligation to provide post-trial access for trial participants.

In turn, science must be able to benefit from meaningful participation of community, civil society, advocacy, and activist representatives. If these stakeholders are engaged meaningfully, input can improve trial designs and vaccine uptake, and mitigate vaccine misinformation and hesitancy – all of which ensure that research can translate to real-world impact most effectively.

What Can Advocates Do?

PROMOTE Good Participatory Practices; ongoing advocacy to bring GPP to public health research is imperative.

DEVELOP a community research agenda and define a "target product profile" for COVID-19 vaccines— a set of desirable criteria for future vaccines to ensure that community values, preferences and needs are reflected in COVID-19 vaccine R&D.

ENGAGE in vaccine research and development.

ADVOCATE for meaningful community participation in Project Next Gen and other initiatives for developing COVID-19 vaccines.

PRESSURE governments hosting vaccine trials to impose conditions for post-trial access.

ESTABLISH relationships with local manufacturers and governments and advocate for effective implementation of, and access to, vaccines.

CREATE AND DISSEMINATE clear and accurate information about COVID-19 risks and benefits, available in local languages, for your community.

ADDRESS vaccine misinformation and hesitation respectfully and effectively.

Resources

- **AVAC**: AIDS Vaccine Handbook
- **AVAC**: Five "P"s to Watch: Platforms, Process, Partnerships, Payers and Participatory Practices that Drive Vaccine Development
- **AVAC/UNAIDS** Good Participatory Practices. Guidelines for Biomedical HIV Prevention Trials. https://www.avac.org/good-participatory-practice

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- **Center for Infectious Disease Research and Policy**: A Research and Development Roadmap for Broadly Protective Coronavirus Vaccines: https://cvr.cidrap.umn.edu/sites/default/files/banner-download/RD.Roadmap.Broadly.Protective.Coronavirus.Vaccines_FINAL02152023.pdf
- **European Medicines Agency**: Initiatives for acceleration of development support and evaluation procedures for COVID-19 treatments and vaccines https://www.ema.europa.eu/en/documents/other/ema-initiatives-acceleration-development-support-evaluation-procedures-covid-19-treatments-vaccines_en.pdf
- **US FDA**: Development and Licensure of Vaccines to Prevent COVID-19: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19
- Singh JA et al. WHO Guidance on COVID-19 vaccine trial designs in the context of authorized COVID-19 vaccines and expanding global access: Ethical considerations: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8882397/
- **WHO**: Considerations for Evaluation of COVID-19 Vaccines (Revised) https://extranet.who.int/pqweb/sites/default/files/documents/Considerations_Assessment_Covid-19_Vaccines_v30March2022.pdf
- **WHO**: Regulation and Prequalification of COVID-19 Vaccines https://www.who.int/teams/regulation-prequalification/eul/covid-19
- **WHO**: COVID-19 Vaccine Tracker and Landscape https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

Footnotes

[1] https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00320-6/fulltext
[2] https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
[3] https://www.icmra.info/drupal/en/covid-19/24june2021 https://static1.squarespace.com/static/5e937afbfd7a75746167b39c/t/643ee03ce3538e2bb5d925bf/1681842236736/PrEP4All+Prevention+Equity+Alert+-+4-2023.pdf
[4] https://www.washingtonpost.com/health/2023/04/10/operation-warp-speed-successor-project-nextgen/
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[7] https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
[8] https://www.avac.org/good-participatory-practice

About This Brief

AVAC gratefully acknowledges many friends and colleagues as we researched and developed *From the Lab to the Jab* series. It was written by Tracy Swan, in collaboration with AVAC staff. Special thanks to Lusiana Aprilawati, Cindra Feuer, Gregg Gonsalves, Laia Ruiz Mingote, Bill Snow, Els Torreele. This publication was made possible with support from the Bill & Melinda Gates Foundation, the New Venture Fund, and PEPFAR through the United States Agency for International Development (USAID) with their support of the Coalition to Accelerate and Support Prevention Research (CASPR). AVAC does not accept funding from the pharmaceutical industry.

About AVAC

AVAC is an international non-profit organization that leverages its independent voice and global partnerships to accelerate ethical development and equitable delivery of effective HIV prevention options, as part of a comprehensive and integrated pathway to global health equity. Follow AVAC on Twitter @HIVpxresearch; find more at www.avac.org, www.prepwatch.org and www.stiwatch.org.