

Accelerating the Rollout of COVID-19 Vaccines:

**A How-to Guide for National
Regulatory Authorities in Low- and
Middle-Income Countries**

AIMS (Access, Introduction and Monitoring
Strategies) for COVID-19 Vaccines

Guidance for Regulators / December 2020



Table of Contents

Introduction.....	1
Background.....	1
Regulatory AIMS (Access, Introduction and Monitoring Strategies) for COVID-19 Vaccines.....	2
Clinical Trials Oversight – CTO.....	2
Registration and Marketing Authorization – RMA.....	3
Licensing Establishment and Compliance – LEC.....	4
Quality Testing and Lot Release – QLR.....	5
Regulatory Inspection and Oversight – RIO.....	6
Market Quality Surveillance and Control – MSC.....	6
End-user Safety Vigilance – ESV.....	6
NRAs’ Role in Overcoming Vaccine Hesitancy and Restoring Public Trust.....	7
Additional Resources for NRAs.....	7
Acknowledgement.....	8
References.....	9

Accelerating the Rollout of COVID-19 Vaccines: A How-to Guide for National Regulatory Authorities in Low- and Middle-Income Countries

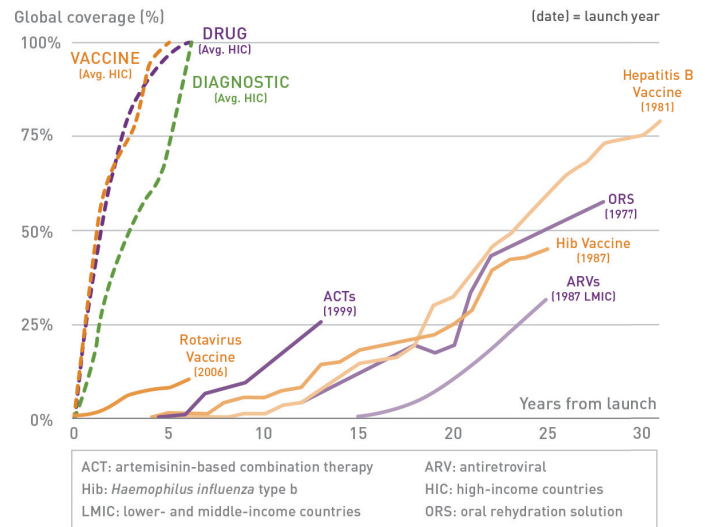
Introduction

National regulatory authorities (NRAs) in low- and middle-income countries (LMICs) urgently need to establish and/or strengthen critical regulatory areas and related functions to safeguard the quality, safety, and effectiveness of future COVID-19 vaccines. The actions NRAs take now will not only enable a sustainable and quality-assured supply of efficacious vaccines to fight the pandemic but will also help preserve public trust. NRAs review, pre-approve, inspect, and help ensure the quality of lots before they are released for use. NRAs also monitor the safety of COVID-19 vaccines throughout the post-marketing phase. Additionally, NRAs should collaborate with national immunization programs (NIPs), national pandemic response teams, and public and private health system stakeholders in their countries to introduce vaccines, facilitate access, and foster trust in their communities. Thus, the introduction of COVID-19 vaccines provides a critical opportunity to strengthen quality assurance and safety regulations that will help address the current pandemic and prepare for future public health crises.

This paper proposes immediate actions that NRAs in resource-limited settings can take now to prepare to accelerate COVID-19 vaccine introduction and minimize delays in scale-up. The paper recommends practical approaches to consider while responding to the ongoing pandemic.

Background

The COVID-19 pandemic has caused massive disruptions to global medical product supply chains and myriad challenges to health systems worldwide. As the pandemic began, short-term reductions in manufacturing capacity, temporary holds on exports from some countries, and skyrocketing demand for touted—but often unproven—COVID-19 treatments constrained the supply of medical products worldwide. These disruptions, coupled with long-standing vulnerabilities in global supply chains, led to immediate shortages of critical medicines and medical products, such as hand sanitizer and personal protective equipment (PPE). This imbalance between supply and demand also contributed to a corresponding surge in the prevalence of substandard and falsified medical products.^{1,2}



While drugs, diagnostics, and vaccines typically scale within the first two years of launch in developed countries, they often take decades to scale in lower- and middle-income countries.

Figure 1: Years to Scale-up (Source: Gates Foundation)

Against this backdrop, government health agencies, academic institutions, and the biopharmaceutical industry are working together to develop a broad range of COVID-19 vaccines and treatment options. Researchers are using various technologies and platforms including viral-vectored, protein subunit, nucleic acid (DNA, RNA), live attenuated, and inactivated vaccines. As of publication, more than 50 vaccine candidates are at different phases of clinical trials, including several that have either submitted for emergency use authorization to stringent regulatory authorities or have released Phase 3 efficacy results.³

Safe and effective vaccines for COVID-19 will be critical in the pandemic response. At the same time, rapidly developing, evaluating, and producing vaccines at scale presents considerable challenges.⁴ Likewise, widespread uptake and acceptance of effective vaccines will face numerous hurdles. First, although vaccine manufacturers have announced cumulative capacity to produce as many as nine billion doses by the end of 2021, most of these doses are earmarked for high-income countries (HICs) through direct contracts with the manufacturers, leaving LMICs anticipating insufficient supplies. In addition, rapid approval of vaccines with limited efficacy and incomplete safety information could feed and

amplify COVID-19 vaccine hesitancy and may ultimately undermine public trust in other routine vaccines.^{5,6}

In LMICs, widespread scale-up of novel medical products (i.e., drugs, diagnostics, and vaccines) has persistently lagged behind HICs. In most cases, new medical products take decades to scale up in low-income settings (Figure 1).⁷ A similar delay in access to future COVID-19 vaccines would not only jeopardize health in LMICs but would also imperil progress against the pandemic response globally.

Initially, donors and initiatives such as COVAX (co-led by Gavi, the Coalition for Epidemic Preparedness Innovations, and the World Health Organization) are likely to provide access to COVID-19 vaccines in LMICs.⁸ A sustainable, uninterrupted supply of vaccines will only be possible when those vaccines are produced, supplied, and distributed regionally.

Regulatory AIMS (Access, Introduction and Monitoring Strategies) for COVID-19 Vaccines

Accelerating access to quality-assured, efficacious, and safe vaccines in LMICs requires seven regulatory functions over the course of three phases: vaccine development phase; supply chain preparedness phase; and introduction, scale-up and regulatory monitoring phase. Figure 2 outlines the steps in vaccine rollout and relevant regulatory functions for sustainable impact.

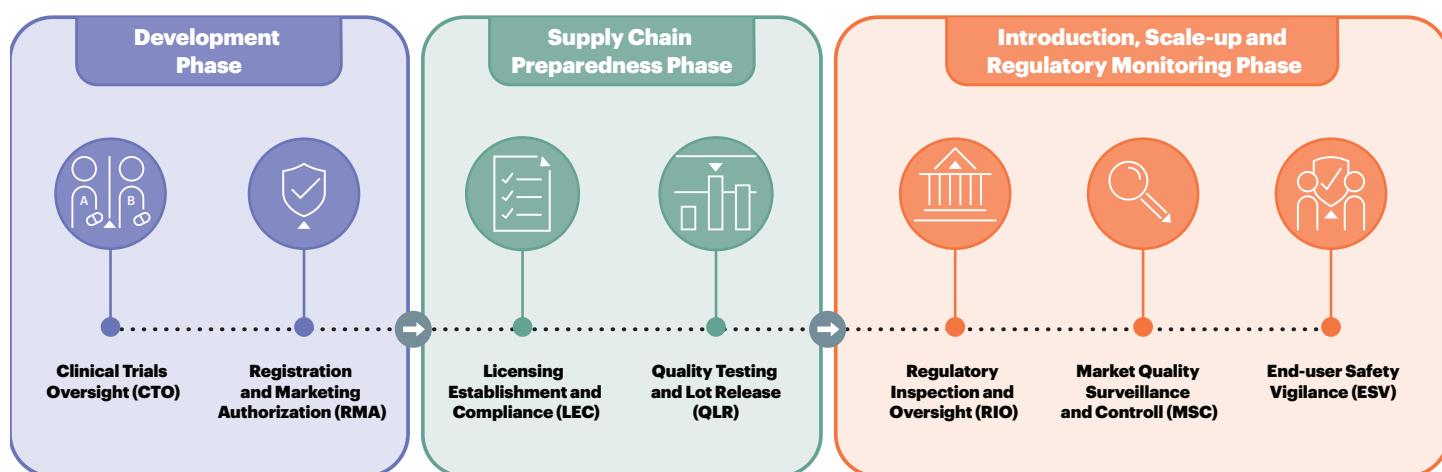


Figure 2: Regulatory functions involved during vaccine development, introduction, and scale-up

Clinical Trials Oversight – CTO

Multiple LMICs are actively involved in ongoing clinical trials of COVID-19 vaccines (e.g., Figure 3).⁹ In recent years, biomedical research in many LMICs – including African countries – has grown in sophistication and substantially expanded the R&D portfolio for diseases endemic in LMICs.

Until very recently, vaccine clinical trials have been conducted primarily in HICs within the context of their immunization schedules, which often differ from the WHO-recommended immunization schedules. Conducting vaccine trials in LMICs is critical to identify issues with co-administration of other vaccines and potential adverse events. Also, it is observed that vaccine stability profiles in HICs were often not in compliance with the NIP conditions in LMICs and the finished product presentations were sometimes not consistent with the necessary programmatic suitability for LMIC use.

In 2006, WHO created the African Vaccine Regulatory Forum (AVAREF) as an informal, continent-wide regulatory platform to improve regulatory oversight of clinical trials and to promote human resource capacity, best practices, common technical requirements and the efficiency and transparency of regulatory processes.¹⁰

CTO protects the safety and rights of clinical trial participants and ensures that trials are adequately designed to meet scientifically sound objectives. Importantly, endpoints critical to select a vaccine candidate for scale-up can be reviewed independently by NRAs participating in such forums.

TESTING COVID-19 VACCINES IN AFRICA

Clinical trials are under way in many places on the continent; other sites have capacity or are developing it. These trials can help to ensure that vaccines are effective in African populations.

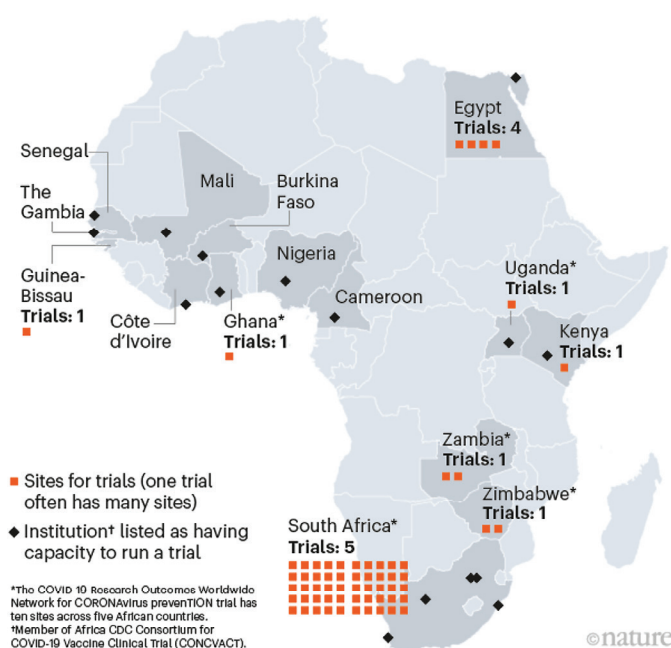


Figure 3: Testing COVID-19 Vaccines in Africa
(Source: Nature)

Key CTO Strategies for NRAs:

1. Engage with clinical researchers (for countries where clinical trials are taking place) and evaluate trial results for their own populations and their NIPs.
2. Share outcomes of clinical trials with other NRAs.
3. Review clinical trial applications, post comments, and stay current on clinical trial outcomes and implications for its own population.

Registration and Marketing Authorization – RMA

The RMA function carried out by NRAs ensures that only authorized vaccines enter the supply chain for healthcare systems, while ensuring proper evaluation of the safety, efficacy, and quality of each product. The traditional process of registration in LMICs includes three steps: 1) SRA approvals, 2) WHO prequalification (PQ), and 3) in-country NRA approvals. A new vaccine is tested for safety

and efficacy through multiple clinical trials; products also must meet appropriate manufacturing quality standards before they can be registered for marketing.^{11,12} During the pandemic response, the goal of each NRA should be to reduce registration time and to make safe, efficacious vaccines available to its population as quickly as possible.

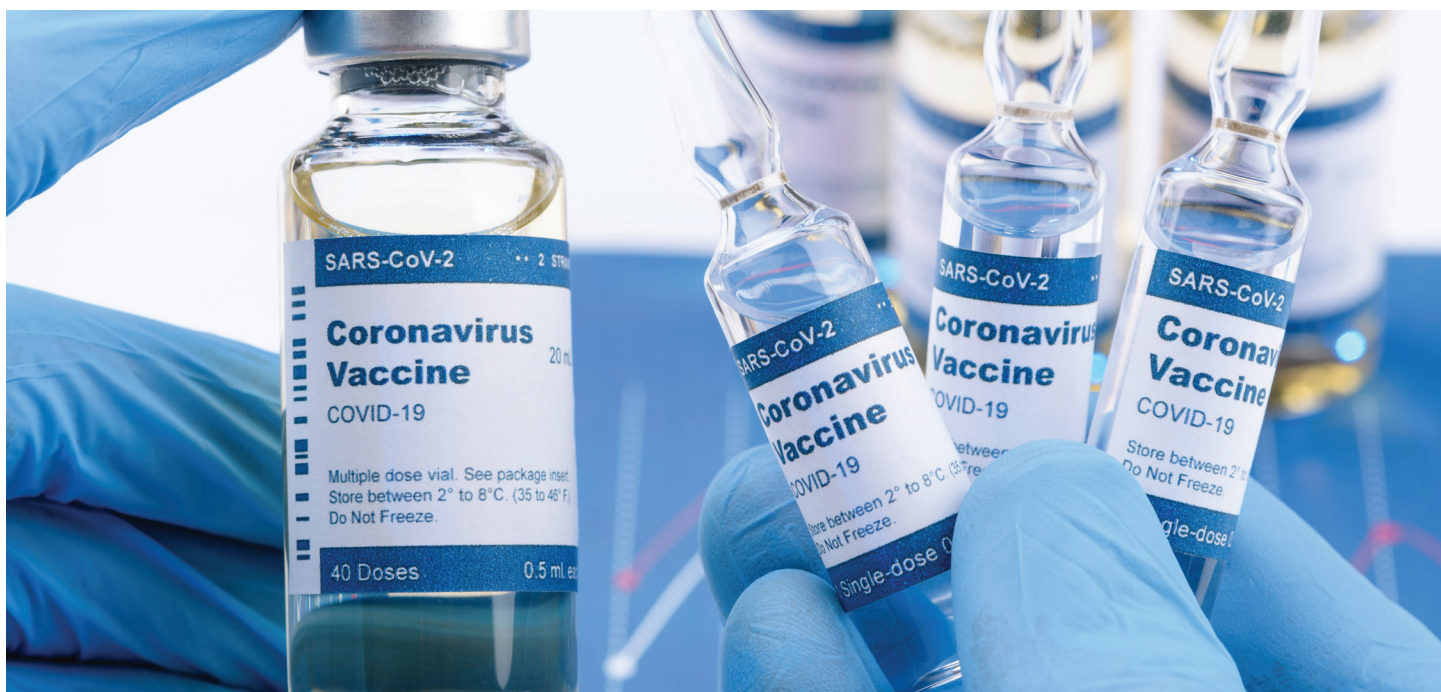
Countries that rely on medical products procured through the UN and donor-funded models must await PQ before NRA approval. International aid agencies that fund the purchase of vaccines and essential medicines for LMICs—such as Gavi, UNICEF and the Global Fund—typically require PQ assessment as a prerequisite for procurement. The process of bringing a new product to market often stretches over a decade or longer and depends on actions of other stakeholders beyond the control of NRAs in LMICs.

Although the stepwise verification process is followed routinely, it is time-consuming during an ongoing pandemic response. NRAs may wish to seek efficiencies in the stepwise verification process to reduce review time during an ongoing pandemic response.

In the past, NRAs often repeated assessments of quality, safety and efficacy already performed by SRAs or PQ, such as dossier review, product sample testing, and manufacturing site inspections. NRAs sometimes explained this redundancy as a requirement to ensure that SRA and PQ-approved products are the same as those received in their countries. Mandatory individual NRA review can add one to two years to the process. Furthermore, duplicating efforts in this way also contributes to reduced access to products because biopharmaceutical companies—whether innovator or generic—may deprioritize distribution of products to LMICs because of various risks to return on investment.

Key RMA Strategies for NRAs:

1. Develop or adapt guidelines for emergency use authorization and licensure of new vaccines and monoclonal antibodies for COVID-19.
2. Prepare and train staff to conduct GxP (Good Practices) inspections for quality guidelines and regulations for vaccines, such as Good Clinical Practices (GCP) and Good Manufacturing Practices (GMP) inspections.
3. Review legal mandates for vaccine registration, conduct joint reviews, and prioritize value-add activities for their individual reviews to minimize traditional one- to two-year delays observed after PQ.



4. Establish a system to ensure that only authorized vaccines are manufactured, imported, distributed, sold, and/or supplied to end users.
5. Assess staff skills and resources to conduct dossier review (i.e., review of data on quality, safety and efficacy submitted by the applicant) and should establish similar standards for imported and locally manufactured medical products.
6. NRAs in resource-poor settings that are unable to review due to resource constraints or lack of experience may wish to accept decisions from SRAs—such as US FDA, EMA or PQ—or results of regional reviews.

legal provisions, regulations, and guidelines to ensure that licensing of facilities throughout the supply chain is based on compliance with GxP. The laws of the country should empower the NRA to issue, suspend or revoke licenses for manufacturers that do not meet regulatory requirements.

Public and private sector supply chain stakeholders—including manufacturers, distributors, wholesalers, importers, exporters, cold-chain managers, and retailers—should possess a license to operate issued by the NRA. An inspection for confirmation of compliance with GxP is required in order to grant or re-grant a license or for approval of a substantial modification.

Key LEC Strategies for NRAs:

1. Assess its country's demand and evaluate public and private supply chain stakeholders to understand licensing needs and communicate licensing requirements to those stakeholders.
2. Support technology transfer and joint ventures to build capacity of local manufacturers and improve access to new vaccines.
3. Collaborate with national immunization and public health programs to understand the burden of disease, as well as vaccine introduction and scale-up plans, to assess geographic priorities for stakeholder licensing.
4. Legal actions for non-compliant actors.

Licensing Establishment and Compliance – LEC

To protect public health, NRAs' licensing and inspection activities are critical to safeguard the quality, safety and efficacy of medical products used within or exported out of countries. In LMICs that typically receive vaccines through organizations such as Gavi or UNICEF, NRAs may not have experience with licensing and compliance. In any country with plans to locally manufacture COVID-19 vaccines, the NRA is responsible for coordinating licensing activities and requires published and readily available



Quality Testing and Lot Release – QLR

Vaccine quality testing helps to ensure access to quality vaccines. When a manufacturer applies for new or revised marketing authorization, testing by the NRA could corroborate the manufacturer's test results. As a component of the market surveillance process, laboratory testing is intended to check compliance with the registration specifications of medical products on the market and detect substandard and falsified medical products.

NRAs have a responsibility to evaluate and independently verify the quality of each lot produced prior to release. Lot release of vaccines by NRAs is a critical function of vaccines regulation and involves the independent assessment of each lot of a licensed vaccine before it is released onto the market. The impact of substandard vaccines from poor-quality lots may not be known for years, and safety issues with a lot may not be known immediately after administration. Due to these delays, independent review of manufacturing and quality control data on every lot may be necessary before vaccines from that lot are administered to people.

Key QLR Strategies for NRAs:

1. Build capacity among staff to develop and review a common format (called CTD – Common Technical Document) to assemble all the quality, safety and efficacy information for authorization or approval of new vaccines.
2. Collaborate with national quality control laboratories to improve their capacity for lot-release testing.
3. Access to suitable quality control laboratories with skilled technicians and resources to perform quality testing of vaccines.
4. Collaborate with WHO Collaborating Centers for Biological Standardization, other networks such as AVAREF, and other countries participating in clinical trials in their regions to facilitate development, validation and assessment of assays and allow for comparability of results from different assays.
5. NRAs with limited domestic capabilities should arrange joint review, reliance agreements and formal recognition so that they can rely on lot testing conducted by other regulators.
6. Release a batch processing record and a summary protocol for each batch for the purpose of lot release, following WHO guidelines.
7. Retain all manufacturing batch records for at least one year after the expiration date of the batch of the biological product; these should be readily retrievable for inspection. NRAs should retain these documents for longer periods, as they provide useful information related to adverse events from immunization (AEFI) and other investigations.

Regulatory Inspection and Oversight – RIO

NRAs—supported by a comprehensive set of legal provisions, regulations, and guidelines—should have provisions in place to evaluate compliance with best practices and oversee activities across the all supply chain stakeholders through inspections. It is important to have a local mandate to inspect the establishments of vaccine-related marketing authorization holders, manufacturers, importers, exporters, and distributors for compliance with national standards and GxP guidelines.

Many LMICs encounter challenges in implementing cold chain systems to secure the quality of vaccines for their NIPs. Many COVID-19 vaccine candidates require ultra-low temperature storage conditions that may not be readily available, compounding these challenges.

Key RIO Strategies for NRAs:

1. Assess and identify legal provisions to carry out routine inspections of vaccine supply chain stakeholders in the public and private sectors, as well as assessing financial and human resource needs for implementation of inspections.
2. Compile lists of facilities that will be inspected for GxP and national mandatory compliance.
3. Evaluate potential resources and needs to address cold chain requirements.
4. Impose stringent legal actions for non-compliant actors to improve public trust and mitigate potential impacts on the pandemic response.

Market Quality Surveillance and Control – MSC

The risk of poor-quality vaccines entering the supply chain is higher during a pandemic, due to the high demand for vaccine candidates from all countries. Post-marketing surveillance and control will play a crucial role in ensuring vaccine quality, safety, and compliance with the registration specifications of approved vaccine candidates (i.e., verifying compliance with marketing authorization and good practices guidelines). Key regulatory functions in the context of vaccine post-marketing surveillance and control activities are primarily concerned with four processes:

- (1) control of import activities, (2) prevention, detection and response to substandard and falsified vaccines, (3) market surveillance program for monitoring the quality of vaccines throughout the supply chain, and (4) control of promotional, marketing and advertising activities.

Key MSC Strategies for NRAs:

1. Design active market surveillance strategies to assess safety issues and review and validate the quality of vaccines available in their supply chains.
2. Collaborate globally or regionally with SRAs to share test results and compare different assays to test vaccine quality.
3. Ensure guidelines for vaccine storage are up-to-date and widely distributed.
4. Develop, review and/or update national deployment and vaccination plans to ensure vaccine quality is maintained throughout the supply chain.
5. Deploy and use temperature monitoring devices and refrigeration systems to support and monitor the vaccine cold chain.

End-user Safety Vigilance – ESV

End-user vaccine vigilance—defined as the science and activities related to the detection, assessment, understanding and prevention of adverse effects or other problems in end users—is extremely important for ensuring that only safe, effective, quality vaccines are used. Post-vaccine serious effects (i.e., adverse events from immunization – AEFI) often lead to public concerns and could erode confidence in vaccines as well as regulatory and health systems. If not adequately addressed, these concerns could have significant negative implications for vaccine uptake and scale-up. A post marketing vigilance system for vaccines is therefore essential, especially since COVID-19 vaccine candidates are likely to roll out at a faster pace than other vaccines and hence will have shorter safety surveillance before market approval. Given that the spread of COVID-19 is higher in minority and resource-poor communities due to poor hygiene and higher population density, the potential health impact of vaccines on these communities needs to be ensured through safety vigilance.

Key ESV Strategies for NRAs:

1. Strengthen passive reporting systems, such as AEFI, as well as capacity for case identification and investigations.
2. Develop regulations and guidelines for manufacturers' mandatory reporting of potential quality issues and development of product complaint handling programs.
3. Design active vaccine safety surveillance studies, registries, and other systems to enable the identification of rare adverse reactions not detected during preapproval and to better understand the rate of known adverse events for vaccines.
4. Identify risk factors and pre-existing conditions associated with higher incidence of adverse reactions to vaccines.
5. Review past AEFI systems and adapt and establish in-country vigilance activities based on a risk management approach.
6. Engage with global and regional bodies and other SRAs and NRAs to acquire, share and exchange relevant information on medical product safety.

NRAs can actively support frontline health workers and vaccine advocacy groups by sharing trusted, credible information on vaccines

NRAs' Role in Overcoming Vaccine Hesitancy and Restoring Public Trust

The WHO has listed vaccine hesitancy as one of the top ten public health threats.¹³ Reluctance or refusal to vaccinate

despite the availability of vaccines threatens to reverse progress made in tackling vaccine-preventable diseases. Lack of confidence in vaccines is a key reason underlying hesitancy. Furthermore, many communities in LMICs equate vaccines with childhood vaccination only and are unaccustomed to participating in adult or annual vaccination programs; immunization uptake may be lower among these populations. NRAs can actively support frontline health workers and vaccine advocacy groups by sharing trusted, credible information on vaccines. Responsive regulatory oversight of COVID-19 vaccines will benefit the ongoing pandemic response and build long-lasting public trust to minimize the public health, social, and economic impacts of COVID-19 and future public health emergencies.

Additional Resources for NRAs:

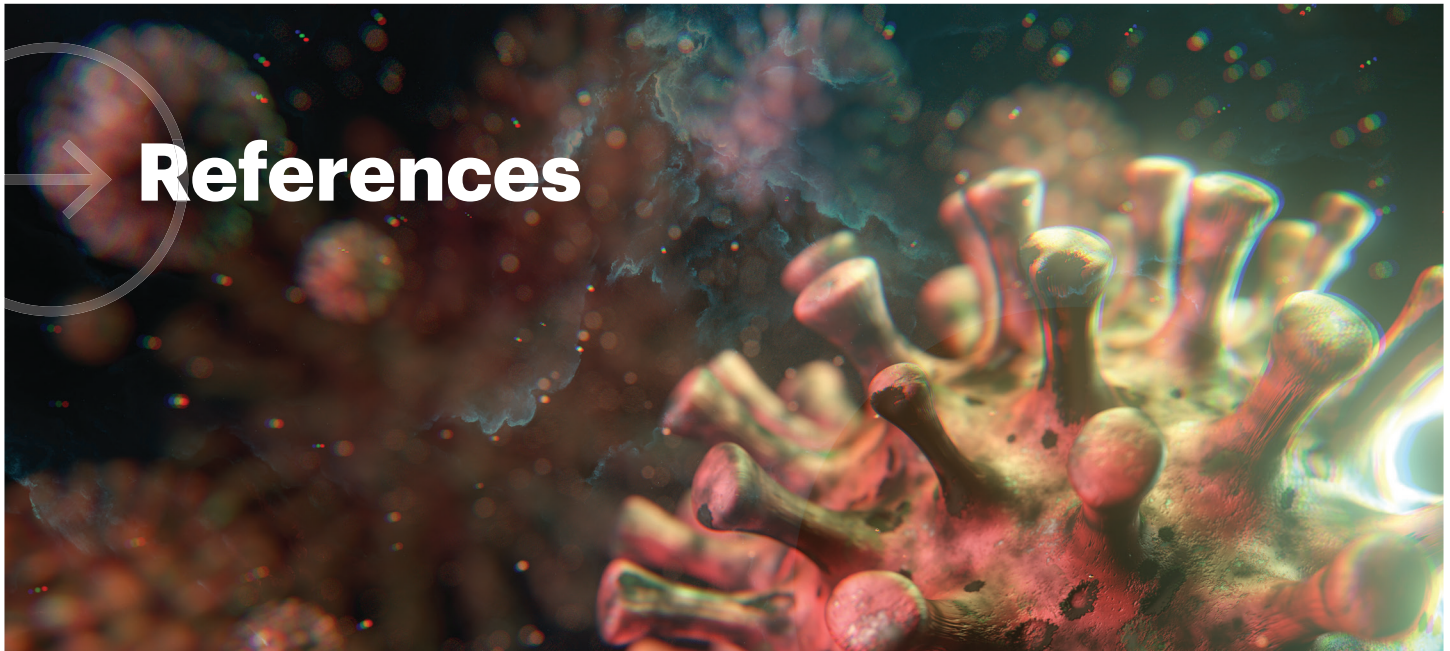
1. COVID-19 Vaccine Predictions: Using Mathematical Modelling and Expert Opinions to Estimate Timelines and Probabilities of Success of COVID-19 Vaccines. <https://www.cgdev.org/publication/covid-19-vaccine-predictions>
2. Guidelines on clinical evaluation of vaccines: regulatory expectations 8 Proposed revision of WHO TRS 924, Annex 1; WHO/BS/2016.2287 https://www.who.int/biologicals/BS2287_Clinical_guidelines_final_LINE_NOs_20_July_2016.pdf
3. Relevant WHO documents for SARS-CoV-2 vaccines and other biologicals WHO https://www.who.int/biologicals/Relevant_WHO_documents_for_SARS-CoV2_vaccines_and_other_biologicals.TZ.IK.7_Apr_2020.pdf?ua=1
4. WHO Vaccine GMP, https://www.who.int/biologicals/areas/vaccines/Annex_2_WHO_Good_manufacturing_practices_for_biological_products.pdf?ua=1
5. Post-authorization Surveillance of Medical Products during a Pandemic Emergency – July 2020 <https://iris.paho.org/handle/10665.2/52578>
6. Considerations for Regulatory Oversight of Clinical Trials in the COVID-19 Pandemic – June 2020 <https://iris.paho.org/handle/10665.2/52266>
7. Crisis Management during an Epidemic: General guidelines for efficient response coordination by national regulatory authorities – May 2020 <https://iris.paho.org/handle/10665.2/52098>

This white paper was authored by Dr. Nagesh N Borse, Technical Program Director of Global Health Technical Services at USP.

Acknowledgments

This white paper benefited greatly from the contributions, review, and support of several individuals. The author wishes to express his gratitude to Dr. Emily Kaine for her strategic guidance and invaluable assistance. Additionally, special thanks to those individuals who provided technical input and shared their expertise on this topic, including Dianna McCarthy, Erin Wilhelm, Fouad Atouf, John Kokai-Kun, Jude Nwokike, Thierry van Bastelaer, and Victor Pribluda. Finally, the author would also like to thank Aubrey Clark, Jamie Rosen, and David Stonehouse for their support in writing, editing, and designing this paper, respectively.





References

¹Newton PN, Bond KC. 2020. COVID-19 and risks to the supply and quality of tests, drugs, and vaccines. *Lancet* 8:6 (e754-55). [https://doi.org/10.1016/S2214-109X\(20\)30136-4](https://doi.org/10.1016/S2214-109X(20)30136-4).

²Medicine Quality Research Group, University of Oxford. Medical Product Quality Report – COVID 19 Issues. Issue 2, July 2020. <https://www.iddo.org/document/medical-product-quality-report-covid-19-issues-issue-2-july-2020-main-text-plus-annexes>.

³World Health Organization (WHO). Landscape of COVID-19 candidate vaccines. December 2020. <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>.

⁴World Health Organization (WHO). Accelerating a safe and effective COVID-19 vaccine. 2020. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/accelerating-a-safe-and-effective-covid-19-vaccine>.

⁵McKinsey & Company. On pins and needles: Will COVID-19 vaccines 'save the world'? July 2020. <https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/on-pins-and-needles-will-covid-19-vaccines-save-the-world>.

⁶Center for Global Development (CGD). Vaccine Experts Speak out COVID-19 vaccines and how to prepare. 2020. <https://www.cgdev.org/blog/vaccine-experts-speak-out-covid-19-vaccines-and-how-prepare>.

⁷United States Agency for International Development (USAID) Center for Innovation and Impact (CII). Idea To Impact: A guide to Introduction and Scale of Global Health Innovations. 2015. <https://www.usaid.gov/cii/guide-introduction-and-scale>

⁸World Health Organization(WHO). COVAX: Working for global equitable access to COVID-19. <https://www.who.int/initiatives/act-accelerator/covax>

⁹Nkengasong JN, Ndembu N, Tshangela A, Raji T. 2020. COVID-19 vaccines: how to ensure Africa has access. *Nature*. 586: 197-199. <https://www.nature.com/articles/d41586-020-02774-8>.

¹⁰African Vaccines Regulatory Forum (AVAREF). <https://www.afro.who.int/health-topics/immunization/avaref>

¹¹World Health Organization (WHO). WHO Prequalification: A system for the prequalification of vaccines for UN supply. https://www.who.int/immunization_standards/vaccine_quality/pq_system/en/

¹²Ahonkhai V, Martins SF, Portet A, Lumkin M, Hartman D. 2016. Speeding Access to Vaccines and Medicines in Low- and Middle-Income Countries: A Case for Change and a Framework for Optimized Product Market Authorization. *PLoS ONE* 11(11): e0166515. <https://doi.org/10.1371/journal.pone.0166515>.

¹³World Health Organization (WHO). 2019. Ten threats to global health in 2019 <https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019>