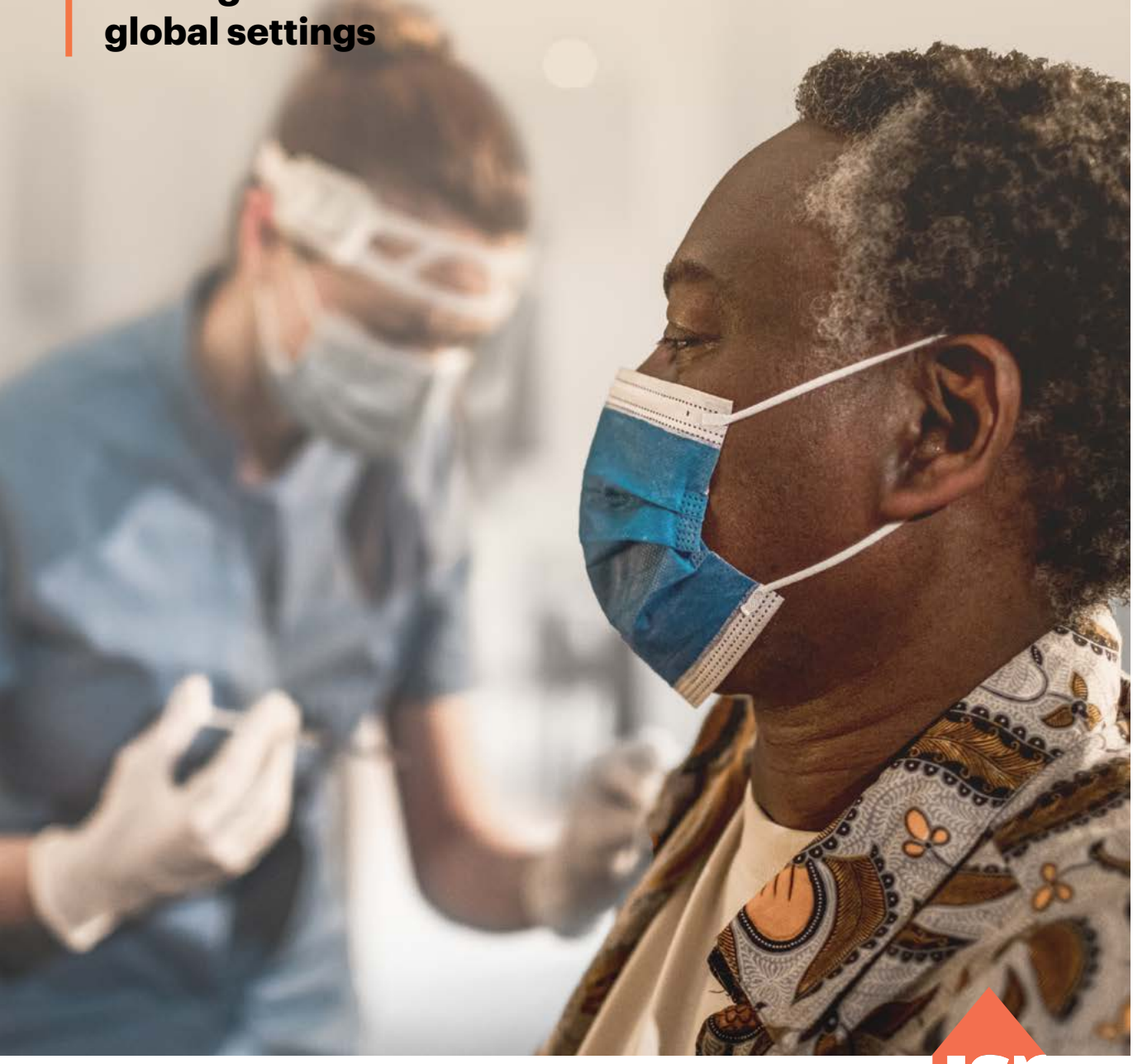
Confronting Substandard and Falsified COVID-19 Vaccines:

Strategies and tools for use in global settings

August 2021



usp®

Table of Contents

Confronting Substandard and Falsified COVID-19 Vaccines:

Strategies and tools for use in global settings

Objectives:

- **Clarify challenges related to substandard and falsified COVID-19 vaccines.**
- **Highlight relevant policies at the global, regional, and country levels to combat the threat.**
- **Explore practical approaches and tools to prevent, detect, and respond.**
- **Proposes strategies and interventions to various stakeholders invested in medicines quality.**

Introduction

The world has never seen a global vaccine rollout on the scale of the COVID-19 response. Ten to fourteen billion doses of vaccine are estimated to be required to protect the global population against death and severe illness while controlling transmission. Vaccine manufacturers, regulatory authorities, logistics experts, healthcare systems, and healthcare practitioners are facing the challenge of producing and delivering these billions of doses while ensuring that every dose administered is safe and effective. Currently, the world is falling short in this effort.

High global demand and insufficient supply have resulted in the vastly inequitable global distribution of COVID-19 vaccines, and these factors also have created economic incentives for the deliberate falsification of vaccines. While ensuring authenticity of vaccines is fundamental, it is not sufficient to guarantee quality. The particularities of COVID-19 vaccines, such as the ultra-cold chain requirements and evolving stability and expiry data, also create conditions for vaccines to degrade and become substandard during distribution, storage, and handling.

The problem of substandard and falsified (SF) COVID-19 vaccines is a global challenge that is likely to intensify. Acute shortages of vaccines in many low-and middle-income countries (LMICs) followed by eventual surges of supply provide both motive and opportunity for a rise in SF vaccines. This issue impacts individuals, our ability to control the pandemic, larger societal health, public trust, and social justice. Ensuring vaccine quality is integral to equitable access.

This paper clarifies the challenges related to SF COVID-19 vaccines, highlights relevant policies to combat these, explores practical approaches and tools to prevent, detect, and respond to this threat, and proposes strategies and interventions to stakeholders in medicines quality.

Definitions

Substandard medical products are authorized by national regulatory authorities but fail to meet either national or international quality standards or specifications – or in some cases, both.

Falsified medical products deliberately or fraudulently misrepresent their identity, composition or source. [1]

Box 1. Definitions

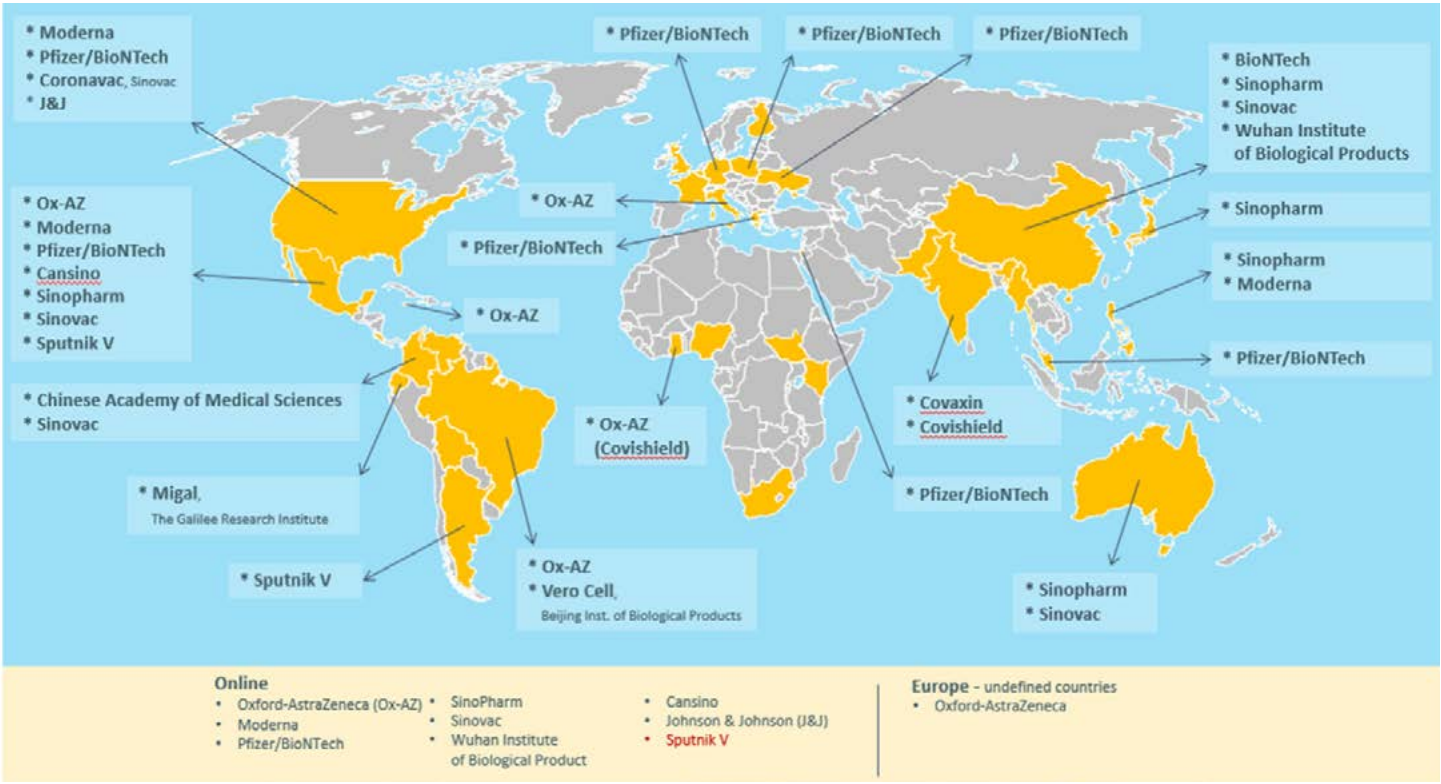


Figure 1. News media reports of SF COVID-19 vaccine data through 31 May, 2021. Countries in yellow have reports involving vaccines listed *(Used with permission of The Infectious Diseases Data Observatory (IDDO) at the University of Oxford)*

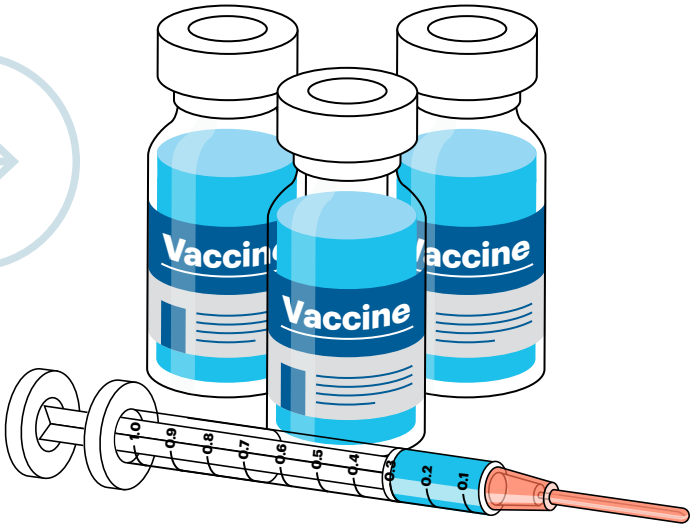
Issue

Even before the COVID-19 pandemic, SF medicines posed a major threat to global health. Poor-quality medicines cause more than one million deaths per year, reduce the effectiveness of medical treatment, waste household and national resources, and can contribute to the emergence of antimicrobial resistance.

Falsification of medicines is usually driven by economic incentives. In the past, vaccines were less frequently reported as falsified compared with other categories of medicines [2] [3]. However, COVID-19 vaccines bring enhanced challenges. The economic incentives to falsify COVID-19 vaccines are significant and are already driving global reports of diverted and SF vaccines (Figure 1). The complexity of supply chains and extended options for distribution, including online outlets, social media, and the dark web, expand opportunities for the proliferation of substandard and especially falsified vaccines. Authentic vaccines can also be subject to illegal diversion followed by re-emergence into the vaccine supply chain, making it impossible to ensure the quality of the product before administration.

The complexity of supply chains and extended options for distribution, including online outlets, social media, and the dark web, expand opportunities for the proliferation of substandard and especially falsified vaccines.

Some recent examples of reports of SF COVID-19 vaccines include a falsified version of the Pfizer vaccine containing an anti-wrinkle treatment in Poland (not administered to anyone), 80 people in Mexico who received a falsified version of the Pfizer vaccine available for sale on social networks, over 2000 people in Mumbai who received falsified COVID-19 shots during a vaccination drive, and over 800 people in Uganda who received water in place of authentic vaccines [4] [5] [6] [7].



There is concern that the incentives driving the proliferation of falsified products are high in many resource-constrained countries which currently lack adequate access to COVID-19 vaccines. The generally weaker regulatory systems of resource-constrained countries increase the opportunities [8]. This becomes a vicious cycle where falsified vaccines further aggravate the inequities faced by LMICs.

Beyond illicit behavior, there are other challenges. Countries may seek to legally swap, sell, or donate vaccines that are already within their borders, including returning vaccine delivered by COVAX [9] [10]. Countries receiving vaccine doses through these transactions may face additional challenges to ensure their quality and appropriate use.

Substandard vaccines can enter the supply chain at points where there are lapses in manufacturing or where less robust manufacturing processes are used to produce and release bulk ingredients for vaccines or the final vaccine doses. Production concerns have already been raised by regulatory bodies [11] [12].

Substandard vaccines can also result from use errors and inadvertent mistakes during manufacturing, distribution, storage, handling, and administration. These risks are increased due to the unique context of the COVID-19 vaccine rollout, which increased the potential for confusion. Table 1 highlights potential differences between COVID-19 vaccines and other vaccines that may contribute to conditions leading to substandard vaccines.

Substandard and falsified vaccines may arise for different reasons, but both lead to compromised quality and similar negative consequences.

Issue	COVID-19 Vaccine Characteristics that May Differ from Other Vaccines
Vaccine Type	• Different vaccine platforms (mRNA, adenovirus, protein, inactivated, etc.) sourced from multiple producers may be in use at the same time in a given country.
Storage and Distribution	• Storage temperature, preparation, and use specifications vary across vaccines. Expiration can vary according to temperature conditions. • Select vaccines require ultra-cold chain. • Manufacturers are collecting real-time stability data concurrent with the rollout leading to: o Short initial shelf-life. o Evolving information on expiry dates and storage temperatures.
Policies	• Vaccine administration targets adult populations with the potential use of novel delivery strategies. • Country policies and manufacturer recommendations may be less aligned (e.g., open vial policies, perspectives on pre-drawing).
Data and Labeling [13]	• In some cases, use of manufacturing dates rather than expiry dates. • Optional use of QR codes/websites to provide updated information on expiry. • For vaccines moving across different temperature conditions within the cold chain, there can exist a need to dynamically re-adjust expiry dates (dynamic labelling). • Bar codes on secondary packaging with optional use on primary packaging. • Vaccine vial monitors (VVMs) not widely used, although they remain a preferred characteristic in UNICEF tenders.

Table 1. Select issues differentiating COVID-19 vaccines from vaccines for routine immunization

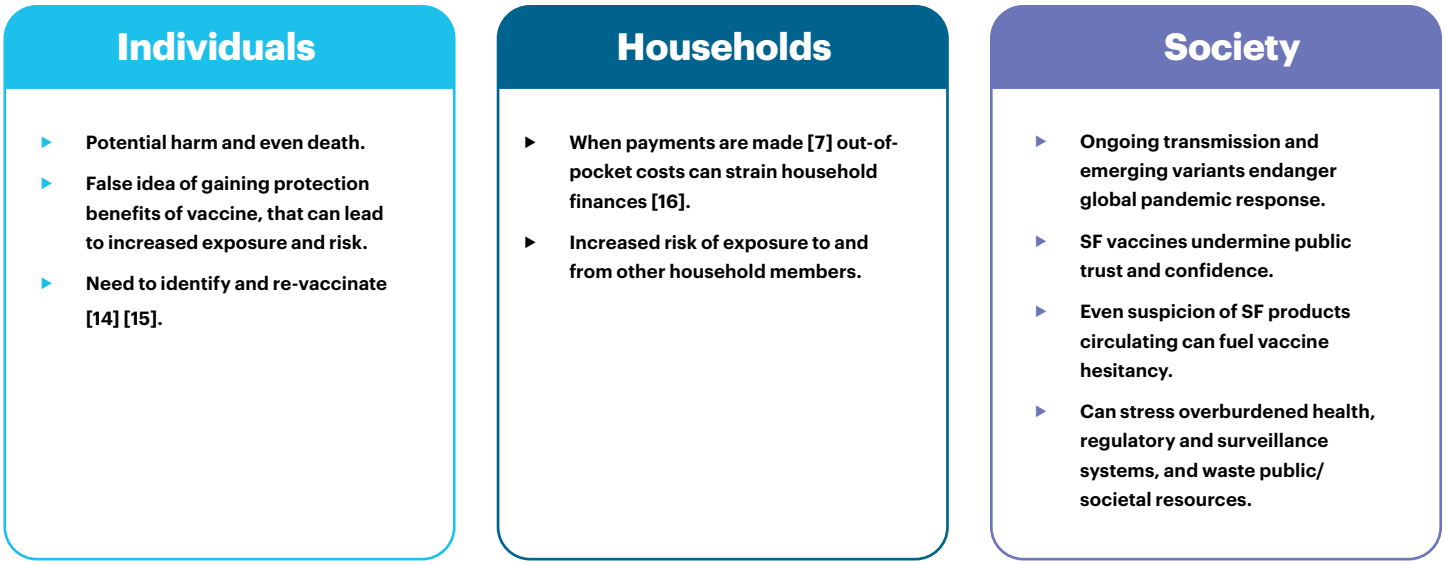


Figure 2. Impacts of poor-quality vaccines on individuals, households, and society

Why act?

Constrained access to medicines and vaccines is a contributing factor to SF product proliferation, but it is also exacerbated by SF products. Equitable access and assurance of product quality are fundamentally linked. Vaccines of poor quality can have serious negative impacts on individuals, households, and society. Figure 2 highlights some of these impacts.

SF COVID-19 vaccines cause considerable damage in terms of lives and well-being, equity, pandemic control, health system strain, financial costs, and trust. This damage merits focused and concerted action.

Interventions to address SF COVID-19 vaccines

In the fight against SF COVID-19 vaccines, several practical approaches and tools exist and can be adapted to vaccines in general and COVID-19 vaccines in particular. The World Health Organization's "Prevent, Detect, and Respond" (PDR) framework is a cornerstone strategy to address SF medical products [3]. USP has also addressed SF medicines with a Global Public Policy Position: Combatting Substandard and Falsified Medicines. This paper builds on these platforms and other established approaches, but with a practical focus on adaptations specific to COVID-19 vaccines.

Prevent

Fundamental actions in this area include developing strong legal and regulatory frameworks as well as promoting multi-stakeholder cooperation at the national and global levels. These actions may be less visible than some others, but they are the foundation upon which to build other actions. Every effort should be made to strengthen these frameworks as rapidly as possible, with the understanding that the process takes time. A USP white paper provides guidance to regulatory authorities in LMICs regarding measures to support the COVID-19 vaccine rollout. The Pan-American Health Organization has also put forth guidance that addresses gaps in regulatory readiness in the context of COVID-19 vaccine introduction [17].

Also vital is ensuring the integrity of the supply chain, including manufacturing. Access to COVID-19 vaccines can improve with a decentralized model for manufacturing, but having more players within highly global supply chains also increases the risk that substandard vaccines and ingredients used to make them will enter the supply chain. USP has educational programs that provide support for quality and manufacturing.

Training and support materials for all those involved in handling and administering COVID-19 vaccines is also crucial. Public standards, such as those highlighted in *USP-NF General Chapter <1079> Risks and Mitigation Strategies for the Storage and Transportation of Finished Drug Products* are relevant to COVID-19 vaccines, but the COVID-19 context may require adaptation or enhancement of certain practices.

Given the different temperature storage requirements for the different COVID-19 vaccines, as well as the initial, very limited availability of vaccines with VVMs, it is crucial to maintain widespread availability of reliable temperature monitoring devices throughout the supply chain. Also critical are the procedures for identifying temperature excursions, reporting these, and assessing appropriate action [18].

Because of the rapid development of COVID-19 vaccines, real-time stability and expiry data are evolving. Consequently, some vaccines are carrying manufacturing dates instead of expiry dates, and it is important to train supply chain and healthcare workers to handle expiry dates correctly as well as inform them and the public as to why these may change. Public health officials should designate clearly where and how workers can access trusted, real-time information relevant to vaccine expiry dates and should outline processes by which queries can be addressed rapidly.

General guidance on COVID-19 vaccine supply and logistics is available [19]. However, information on appropriate practices for distribution and handling should be readily available for workers and in all places where vaccines are being moved, stored, and administered. The development and widespread use of guides for vaccine handling, adapted for different country contexts, would serve this purpose. USP has developed COVID-19 Vaccine Handling Guides – one specific to the United States and another for international use – that provide highly accessible, practical, and detailed information to workers on safe and efficient practices for vaccine distribution and administration. The guides are designed to help maximize the availability of quality vaccines and efficiency in administration while minimizing wastage.

Importantly, safe practices extend beyond vaccine administration. Clear guidance regarding the disposal of waste and vials [20] and training of workers are important. Vials can potentially be re-used for falsified products, hence their secure disposal is essential. The vials may also contain leftover unused vaccine. Some vaccines, such as the viral vector vaccines, must be disposed of in compliance with local guidance for genetically modified organisms or biohazardous waste.

Developing awareness across all stakeholders in a country is important. One example of such an approach is the WHO Global Surveillance & Monitoring System (GSMS) for Substandard & Falsified medical products, launched in 2013 [3]. The GSMS hosts a database of SF medical product records and incidents and an online portal, which are linked to a network of focal points and provides thematic analyses, services (global alerts, target market surveillance lists, etc.),

and training and workshops. This system improves the quantity, quality, and analysis of accurate data concerning SF medical products with the aim of using these data to drive action to improve prevention, detection, and response. This creates a virtuous cycle which links efforts to detect and respond to SF events with stronger measures of prevention.

Additionally, WHO hosts a mechanism for its Member States on SF medical products [21]. This Member State mechanism aims to: (a) protect public health and promote access to affordable, safe, efficacious, and quality medical products; and (b) promote prevention and control of SF medical products and associated activities.

Public awareness is also critical and depends upon effective messaging clarifying that legitimate COVID-19 vaccines are only available through official channels (and not the internet), sharing knowledge of known SF incidents, providing information on how to report suspected SF incidents, and sharing knowledge to reframe expectations on issues such as stability data and expiration dates.

Summary of Proposed Strategies and Interventions for Prevention

Strategies	Interventions	Addresses Substandard, Falsified, or Both	Possible Timeframe for Implementation and Impact: Short (2021)[1] or Medium/ Longer (2022+)[2]
Strengthen the fundamentals upon which quality is built into systems	Strengthen legal and regulatory frameworks	Both	Medium/Longer (2022+)
	Ensure use of quality standards in production	Substandard	Short (2021)
Develop and ensure wide availability of procedures and tools to help health care workers manage increased complexity	Ensure temperature monitoring equipment & protocols for heat excursions and waste management are widely available	Substandard	Short (2021)
	Develop and distribute handling guides	Both	Short (2021)
	Develop readily accessible, trusted real-time information on vaccines available in country and relevant expiry dates	Both	Short (2021)
Expand knowledge	Communicate with and educate public on SF vaccine prevention & detection	Both	Short (2021)

Table 2. Summary of Proposed Strategies and Interventions for Prevention

1. Interventions with the possibility – if given appropriate attention and resources – to be implemented and have impact more immediately (within 2021), noting that timelines can and will vary across countries and regions.
2. Interventions that generally require more time to develop. Efforts can and should commence in 2021 (or already have), but widespread availability or impact is not expected until 2022 or later. Again, timelines can and will vary across countries and regions.

Detect

While it is optimal to prevent SF products from entering the supply chain, it is also essential to have the ability to detect these products as they move from production through the entire supply chain. The first focus of effort is at the point of entry into the supply chain, with lot release serving as the measure that bridges prevention and detection activities. National Regulatory Authorities (NRAs) or National Control Laboratories (NCLs) ensure that there is independent lot release of vaccines. In many cases, this can result in laboratory testing in the country of production as well as in the receiving country, but the need to expedite access to quality COVID-19 vaccines has motivated WHO to call for countries receiving them to rely on lot certificates issued by responsible NRAs or NCLs that are operating at maturity level 3 or 4 (according to WHO benchmarking [22]). WHO is facilitating exchange of lot release data throughout its entire WHO-National Control Laboratory Network for Biologicals (WHO-NNB) [23]. It is possible for countries to effectively use regulatory reliance as well as leverage information from manufacturer in-house testing and production summaries to conduct lot release [24][25].

However, enhanced regulatory reliance does not obviate the need for laboratory testing capacity for COVID-19 vaccines. Not all vaccines will arrive as direct consignments from producers or from countries with the appropriate regulatory maturity, as some will inevitably cross borders due to swaps, donations, and sales. Furthermore, laboratory testing of select samples collected at various points in the supply chain constitutes an important component of post-market surveillance. While expanding laboratory capacity for COVID-19 vaccines at the country level is a challenge,

particularly in resource-constrained settings, doing this through regional and/or other network-based approaches is an important way of ensuring access to testing while minimizing the resource implications and complexity for individual countries. The value of expanded regional capacity for lot release was already highlighted prior to the COVID-19 pandemic by WHO [26] and has only increased in importance within the context of the pandemic.

To support laboratories that are developing and validating assays for COVID-19 vaccines, USP has developed Vaccine Quality Assessment Toolkits. The toolkits are presented by vaccine platform (not specific to any one vaccine) with a focus on the final vaccine product. This resource also includes a Compendial Assay Toolkit which provides information on assays for sterility and endotoxins.

Two types of testing that are not fully available at this time are vaccine-specific identity assays (beyond testing manufacturers perform themselves) and field-based screening methods. The ability to carry out independent testing through vaccine-specific assays is an important regulatory function that complements the support manufacturers provide in verifying the authenticity of the product. One place to start may be the development of a spectral reference library for all existing COVID-19 vaccines that can be built into potentially suitable devices (e.g., Raman, near infrared, etc.) for detecting SF COVID-19 vaccines. Whereas several field-based screening tools using various methodologies exist for medicines, there is not yet one available for COVID-19 vaccines. Because laboratory-based testing is difficult to access, time-consuming, and costly, the value of screening tools that can be deployed

Platforms being used to develop vaccines against COVID-19

Toolkits for additional platforms will be added as these vaccines are authorized for COVID-19

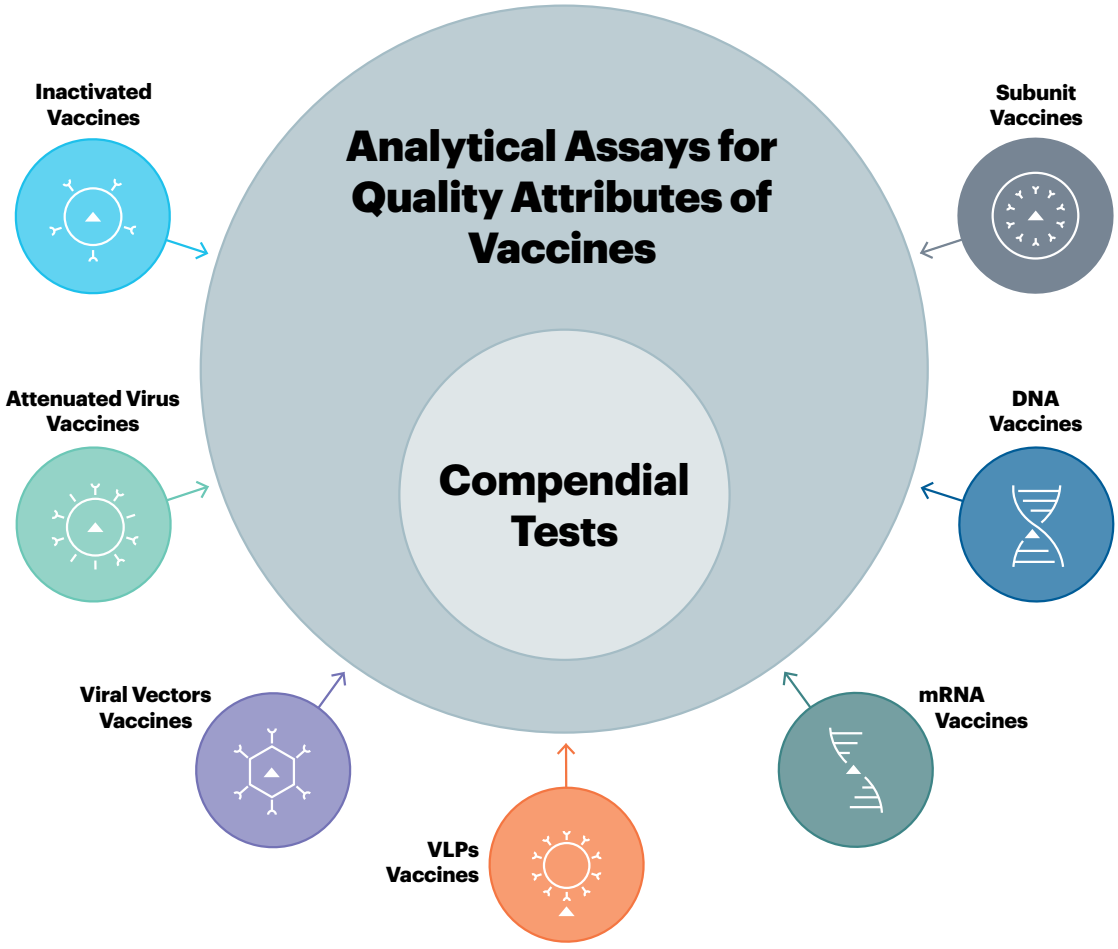


Figure 3. Vaccine Quality Assessment Toolkits

more broadly and rapidly at different points in the supply chain to detect SF vaccines cannot be overemphasized.

Other tools are also available to detect SF COVID-19 vaccines. The simplest approach involves visual inspection of the product and its packaging. While deviations in product color or sedimentation can signal quality issues, it should be made clear that vaccine appearance alone is not a robust measure for detecting issues with quality or potency. The labels on falsified products can be nearly indistinguishable from authentic products, but it is sometimes still possible to detect abnormalities, particularly if visual inspection guides, such as those developed by USP as part of the COVID-19 Vaccine Handling Toolkit, are available and clearly indicate how labels should appear. These guides are most effective when tailored and updated to reflect country labelling and vaccine availability. They should be widely distributed and available to health care workers.

Because laboratory-based testing is difficult to access, time-consuming, and costly, the value of screening tools that can be deployed more broadly and rapidly at different points in the supply chain to detect SF vaccines cannot be overemphasized.

Many LMICs use vaccines that come with VVMs on the primary packaging to measure cumulative heat exposure. VVMs were first used in 1996 and have been used to expand coverage while minimizing vaccine wastage. They can also be used to assist in the detection of falsified product (for example, boiling a vial or lid containing a VVM should result in the rapid darkening of the central square) as it is challenging for falsifiers to reproduce the exact specifications of thermochromic labels.

There are different VVMs for vaccines with different stability profiles, and newer ones have been developed for COVID-19 vaccines. WHO prequalification of vaccines includes an evaluation of their programmatic suitability for low-resource settings. Within this context, VVMs are generally considered to be a critical characteristic for prequalification and are subject to assessment and testing. However, due to evolving stability data and the need for speed and maximal access, most COVID-19 vaccines with a WHO Emergency Use Listing (with the exception of the Sinopharm vaccine [27]) do not yet have VVMs affixed. As more stability data become available, there is clear value in reassessing VVM requirements and increasing their utilization.

How to use VVMs

Do not use vaccine if inner square is the same color or darker than the outer circle.

If the expiry has not passed, vaccines with the inner square lighter than outer circle can be used.

Box 2. VVM graphic used with permission of Zebra Technologies

Efforts to develop and use traceability solutions based on global standards for medicines, vaccines, and other health products are rapidly evolving, but global progress is very uneven, particularly in the context of LMICs. The benefits of traceability systems extend beyond their ability to prevent and detect falsified products. They improve supply chain efficiency and enable rapid product recalls. The Inter-Agency Supply Chain Group (ISG) is working with countries to establish policy frameworks that support the use of global standards (such as GS1) for traceability, and WHO has made available a policy paper on traceability of medical products [28].

Developing and implementing national traceability initiatives takes time, and the high risk of SF COVID-19 vaccines and supplies in LMIC settings is driving the accelerated progress of a complementary mechanism. In August 2020, UNICEF, Gavi, and the World Bank called for the establishment of a COVID-19 Vaccine and Therapeutics Expert Advisory Board that has been instrumental in driving the establishment of a Global Trust Repository [29]. This initiative – managed by a

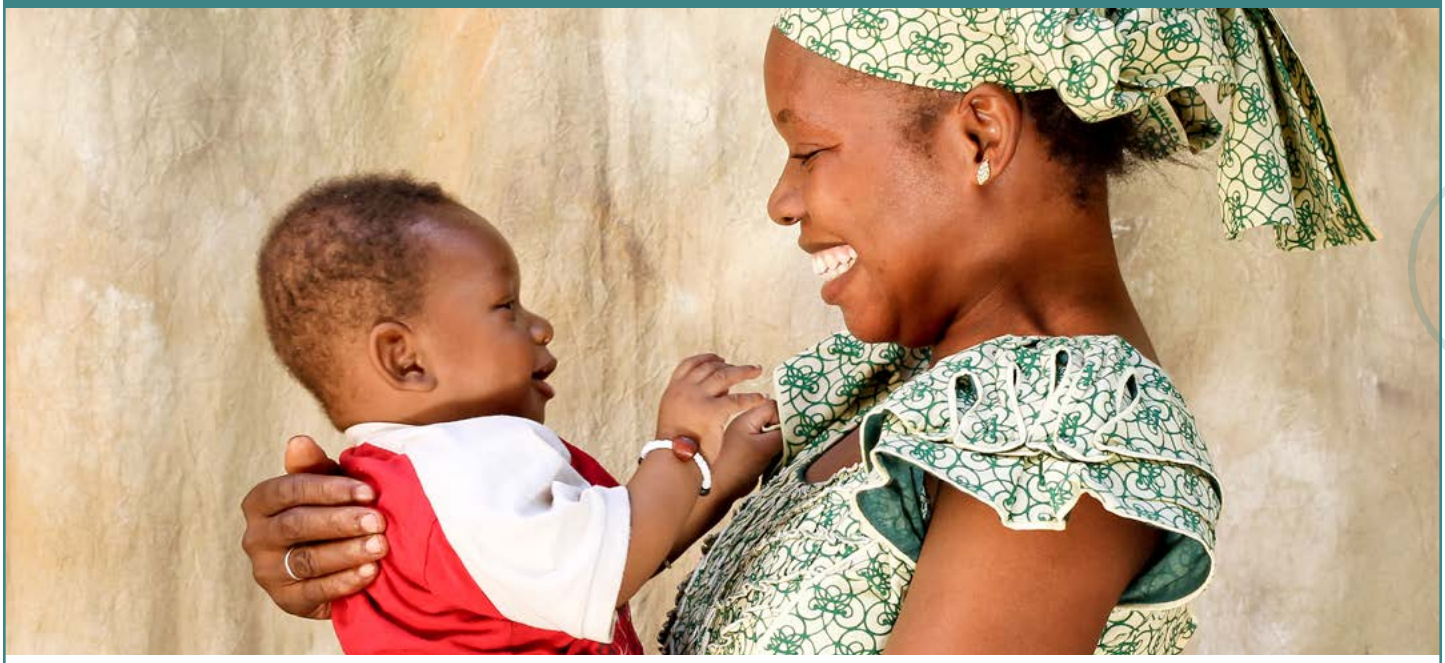
Steering Committee that includes the Bill and Melinda Gates Foundation (BMGF), Gavi, the Global Fund, UNICEF, the United States Agency for International Development (USAID), and the World Bank – is initially focused on the verification of the authenticity of COVID-19 vaccines supplied through the COVAX facility. The system will use GS1-compliant serialized identifiers and 2D matrix barcodes on secondary packaging. While the Repository has limitations, it is being designed to support evolution and complementarity and can have significant impact in detecting SF COVID-19 vaccines.

These tools to detect SF vaccines can be used and combined in post-market surveillance. In passive reporting, events potentially linked to SF vaccines are spontaneously reported by health care providers and patients to regulators who then report to the global data set of GSMS. Active surveillance, which involves sampling products in the supply chain to identify SF products, is more productive than passive reporting, but its resource requirements can constitute a barrier for many countries. The use of a risk-based approach to surveillance can help countries leverage available resources to increase SF vaccine detection capabilities.

The Guidance for Implementing Risk-Based Post-Marketing Quality Surveillance in Low- and Middle-Income Countries document was developed and successfully used by the USAID-funded Promoting the Quality of Medicines (PQM) program (2009-2020), work that has continued and expanded under USAID's current program, PQM+.

A case study from Mali, highlighted in Box 3, illustrates application of the risk-based post-marketing quality surveillance (RB-PMS) approach for medicines. The overall risk of poor-quality medical products on the market is assessed by combining the individual risks posed by the product category, geographical location, supply chain considerations, and type of facility (including informal and virtual outlets). This information guides where product sampling takes place. The Medicines Risk Surveillance (MedRS) tool facilitates the planning, design, and development of sampling protocols based on the

Mali implements risk-based post-marketing surveillance to ensure quality of medical products



In Mali, malaria is the leading cause of illness and death, especially for children younger than five, and maternal mortality rates remain among the highest in the world. The need to ensure quality in medicines against malaria is vital. To strengthen Mali's regulatory capabilities, PQM+ is supporting the Laboratoire National de Santé (LNS) and Direction de la Pharmacie et du Médicament (DPM) in efforts to adopt RB-PMS. Although Mali was implementing PMS, medicines sampling was based on convenience rather than science and was expensive, complex, and time-consuming. By contrast, RB-PMS employs a sampling and testing strategy that produces statistically significant results at much lower cost.

A multi-sector technical working group (TWG) was created to oversee implementation. The TWG used the MedRS tool to identify which medicines to sample; to select geographic regions, cities, and facilities; and to determine the number of samples to collect from each site. A total of 262 samples were collected from facilities across four regions with the highest risk (Kayes, Sikasso, Koulikoro, and Segou). The samples underwent as many as three levels of scientific testing: physical/visual inspection, Minilab™ screening, and compendial or confirmatory testing at LNS' medicines quality control laboratory. If samples failed visual inspection, they did not undergo lab screening.

Despite shorter timeframes, fewer regions sampled, and smaller sample numbers, the risk-based approach yielded failure rates similar to those obtained through traditional PMS, demonstrating that RB-PMS is representative, robust, and cost-effective. Sixty-nine percent of sampled medicines were unregistered (i.e., not approved based on evidence of their quality and efficacy) and four percent of samples failed quality control tests, indicating that they were either substandard or counterfeit. The TWG will share its report with the Ministry of Health.

By adopting RB-PMS, Mali is taking important steps to optimize the use of its limited resources and build sustainability into its health programs. This approach has demonstrated its value for medicines, and now, spearheaded by work in Bangladesh, it is being adapted for COVID-19 vaccines.

Box 3. Mali implements risk-based post-marketing surveillance to ensure quality of medical products

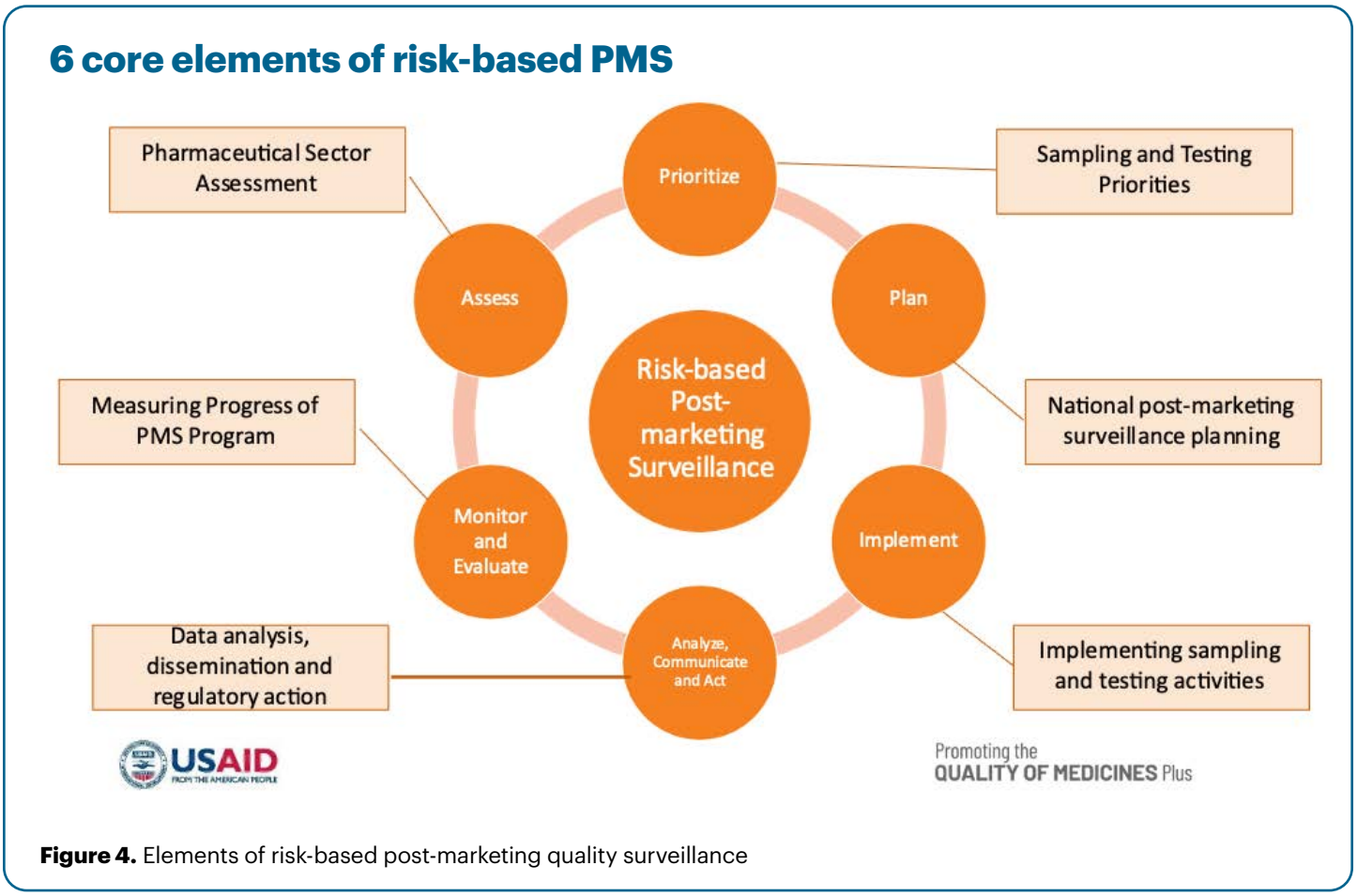


Figure 4. Elements of risk-based post-marketing quality surveillance

assessed risk. Medicines are then assessed following three complementary levels of increasing complexity: visual inspection, field-based screening, and testing quality control laboratories using compendial methods. The root cause for out-of-specification products should subsequently be investigated. Figure 4 depicts the key aspects of developing and implementing a RB-PMS program and its cyclic nature.

RB-PMS has not yet been used for vaccines, but PQM+ is currently supporting a pilot effort to tailor it to COVID-19 vaccines in Bangladesh. One challenge, as noted previously, is that field-based screening methodologies for vaccines are not currently available. Although this unmet need has already been recognized by USP and select academic, regulatory, and industry stakeholders, more attention and resources are required to address this crucial need as rapidly as possible.

Pharmacovigilance (PV) is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related or vaccine-related problem [30]. Timely detection and reporting of adverse events following COVID-19 immunization is the first step. In the context of COVID-19 vaccination, surveillance systems need to be prepared to identify and respond to adverse events following immunization (AEFIs), adverse events of special interest (AESIs), and other safety events including incidents of substandard or falsified vaccines. All AEFIs should be reported using the standard COVID-19 AEFI reporting form. Because several different COVID-19 vaccines may be used in a given country, it is important to record the brand name, manufacturer, and batch/lot numbers of the vaccine and diluent, as relevant, in addition to other relevant information regarding the incident [31].

Since vaccines may or may not be the cause of an AEFI, adverse event reporting should lead to investigations to determine any causal association. Such investigations can include product sampling for quality control testing such as in the case of AEFI clusters where two or more similar event cases have a link such as location, vaccine manufacturer,

batch/lot number, etc. Similarly, confirmed reports of SF products may also trigger further safety reviews. There are clear advantages to being able to link data across safety and quality databases. Such efforts would benefit COVID-19 vaccine safety and quality surveillance, but integration efforts should be systemic rather than product-specific. The African Union's Smart Safety Surveillance (AU-3S) program, launched in 2020 with leadership from the African Union Development Agency (AUDA-NEPAD), provides an example of a systemic approach to the integration of safety and quality surveillance data [32].

Summary of Proposed Strategies and Interventions for Detection

Strategies	Interventions		Addresses Substandard, Falsified, or Both	Possible Timeframe for Implementation and Impact: Short (2021) or Medium/Longer (2022+)
① **Develop and/or increase use of tools which can be widely deployed**	Visual Tools	Develop and make available visual inspection guides	Falsified	Short (2021)
		Include VVMs on vaccine primary packaging as supported by stability data	Both	Short (2021) may be possible with intensified effort
② **Develop traceability systems**	Traceability Systems	Develop and enable widespread use of the Global Trust Repository	Falsified	Medium/Longer (2022+)
③ **Strengthen quality surveillance systems that make use of passive, active (RB-PMS), and integrated safety-quality approaches**		Develop national traceability systems	Falsified (& potential to reduce administration errors)	Medium/Longer (2022+)
④ **Enhance regional and other network laboratory capacity to support lot release and post-market surveillance**	Physical and Chemical Testing	Develop and make available field-based screening tests	Both	Short (2021) may be possible with intensified effort
		Develop vaccine-specific identity assays for independent testing	Both	Short (2021) may be possible with intensified effort

Table 3. Summary of Proposed Strategies and Interventions for Detection

Respond

Once SF products are detected, efficient mechanisms to enable alerts for health workers and the public, as well as recalls, are vital. Traceability systems, discussed in the previous section, can play a key role in facilitating identification and recall of SF products.

As mentioned in the section on prevention, WHO's GSMS provides an approach to collecting and analyzing data on incidents, issuing alerts, and linking these to efforts to drive improvements. This is initiated through reports of suspected SF medical products submitted by the public, health care professionals, industry, supply chain operators, customs, police, procurers and nongovernmental organizations to the NRA of a country, which is responsible for assessing and responding to these reports. An NRA Focal Point searches and reports to WHO's GSMS (noting that industry is also able to report directly to GSMS), which in turn issues alerts as appropriate and provides immediate short-term support to deal with the incident if requested. WHO also issues targeted market surveillance lists to regulators through this mechanism. Data collected by GSMS permit the deep analysis of vulnerabilities and needs at national, regional, and global levels and can drive policy change and systemic improvements in regulatory strengthening (with a focus on market surveillance, laboratory testing, inspection and enforcement), legal frameworks, judicial procedures, and coordination across stakeholders [3].

Further strengthening and use of this mechanism, with emphasis on maximizing breadth (all stakeholders, including the public, are aware of how to report incidents), enhancing speed (reduction of administrative barriers; updating of database), extending visibility of alerts and data (across a full range of implicated stakeholders beyond regulators), and acting to reduce exposed vulnerabilities can drive more effective responses to SF incidents.

The identification and prosecution of criminals who work across global supply chains and use the internet poses many challenges. Low rates of prosecution further encourage nefarious behavior. Enhanced global, regional, and national cooperation across a broad set of stakeholders (such as law enforcement, customs, regulatory agencies, and industry) has already demonstrated value [33] and is more likely to be effective than countries acting on their own.

Coordination can be strengthened through explicit mechanisms developed at national and regional levels which bring together diverse stakeholders to share information and manage a concerted response. A public-private stakeholder group developed in Romania involving the Public Ministry, the Internal Affairs Ministry, the National Tax Administration Agency, the National Medicines and Medical Devices Agency, the Romanian Intelligence Service, the National Veterinary and Sanitary Authority for Food Safety, the Romanian Association of International Medicines Manufacturers, and the Romanian Generic Medicines Manufacturers Association provides an example of this type of approach [34].

Summary of Proposed Strategies and Interventions for Response

Strategies	Interventions	Addresses Substandard, Falsified, or Both	Possible Timeframe for Implementation and Impact: Short (2021) or Medium/ Longer (2022+)
Strengthen breadth, speed, and visibility of SF incident reporting	Support continued enhancements to WHO's GSMS mechanism	Both	Short (2021) may be possible with intensified effort
Develop and ensure wide availability of procedures and tools to help health care workers manage increased complexity	Improve information sharing and action through national and regional stakeholder groups	Falsified	Short (2021) may be possible with intensified effort

Table 4. Summary of Proposed Strategies and Interventions for Response

None of this is easy, but the COVID-19 pandemic has taught us that with focused will, resources, and efforts we can challenge our limitations and assumptions about what is possible.

Driving action

The proliferation of SF COVID-19 vaccines and the threat they pose to public health will grow as more vaccines are introduced globally. This paper posits that the proliferation of SF vaccines and the harmful consequences for individuals and public health can be mitigated. It is possible to effectively address this issue through the use of a multi-pronged approach combining the proposed interventions to prevent, detect, and respond. All of these interventions have an important role in preventing SF vaccines.

Responsibility for implementing these efforts varies. The interventions proposed to strengthen the prevention of SF products are largely implementable in the short-term and are primarily the responsibility of countries. However, the ability of countries to do so effectively during the current crisis will vary, and several countries may benefit from financial and technical support.

Many of the interventions to detect SF vaccines – the use of VVMs, development of a Global Trust Repository, field-based screening methods, and strengthening of regional laboratories – rely on global and regional stakeholders to drive the progress. The ultimate implementation and use of the strategies proposed, such as enhanced surveillance, depend on the political will of countries, but can benefit from external support.

Response interventions strongly benefit from efforts to develop efficient mechanisms to link diverse stakeholders (manufacturers, distributors, customs agents, local regulators, law enforcement, logistics personnel, and health workers) and facilitate the flow and use of information across these to drive action.

None of this is easy, but the COVID-19 pandemic has taught us that with focused will, resources, and efforts we can challenge our limitations and assumptions about what is possible. It is time to apply these lessons to combat SF COVID-19 vaccines.

Acknowledgements:

USP expresses its gratitude to the following, who provided valuable information or commentary: the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), the Incidents and Substandard/Falsified Medical Products Team within the Regulation and Prequalification Department at the World Health Organization, and Zebra Technologies. Select tools and examples shared in this paper emanate from USAID-funded PQM and PQM+ programs implemented by USP.

Resources:

Resource	URL
USP Global Public Policy Position: Combatting Substandard and Falsified Medicines	https://www.usp.org/sites/default/files/usp/document/about/public-policy/combatting-substandard-and-falsified-medicines-policy-position.pdf
Accelerating the Rollout of COVID-19 Vaccines: A How-to Guide for National Regulatory Authorities in Low- and Middle-Income Countries	https://www.usp.org/global-public-health/accelerating-covid-19-rollout
Educational content at USP Education site	https://uspharmacopeia.csod.com/LMS/catalog/Welcome.aspx?tab_page_id=-67&tab_id=20000495
USP-NF Chapter <1079> Risks and Mitigation Strategies for the Storage and Transportation of Finished Drug Products	https://online.uspnf.com/uspnf/current-document/1_GUID-5EE764A5-0531-405E-9475-5D0D11E0921C_5_en-US?source=emailLink
COVID-19 Vaccine Handling Toolkit (with Visual Inspection Guide)	https://www.usp.org/covid-19/vaccine-handling-toolkit
COVID-19 Vaccine Quality Assessment Toolkits (including Vaccine Compendial Assay Toolkit)	https://www.usp.org/covid-19/quality-attributes-toolkits
Guidance for Implementing Risk-Based Post-Marketing Quality Surveillance in Low- and Middle-income Countries	https://www.usp-pqm.org/sites/default/files/pqms/article/risk-based-post-marketing-surveillance-feb-2018.pdf
Medicines Risk Surveillance Tool	https://medrsv2.com/

References

1. World Health Organization. Seventieth World Health Assembly update. May 29, 2017. WHO. https://www.who.int/news/item/29-05-2017-seventieth-world-health-assembly-update-29-may-2017. Accessed July 30, 2021.
2. OECD/EUIPO. Trade in counterfeit pharmaceutical products. Paris: OECD Publishing. 2020. https://doi.org/10.1787/a7c7e054-en. Accessed July 30, 2021.
3. World Health Organization. WHO Global Surveillance and Monitoring System for substandard and falsified medical products. 2017. WHO. https://www.who.int/medicines/regulation/ssffc/publications/GSMSreport_EN.pdf?ua=1. Accessed July 30, 2021.
4. Taylor P. More fake Pfizer/BioNTech COVID shots found, this time in Poland. April 21, 2021. Securing Industry. https://www.securingindustry.com/pharmaceuticals/fake-pfizer-biontech-covid-19-shots-found-this-time-in-poland/s40/a13343/#.YOcrHnBYZPZ. Accessed July 30, 2021.
5. BBC. Coronavirus: Pfizer confirms fake versions of vaccine in Poland and Mexico. April 22, 2021. BBC News. https://www.bbc.com/news/world-56844149. Accessed July 30, 2021.
6. Healthworld.com. Over 2,000 in Mumbai duped in fake vaccine drives, says govt. June 25, 2021. The Economic Times. https://health.economictimes.indiatimes.com/news/industry/over-2000-in-mumbai-duped-in-fake-vaccine-drives-says-govt/83828413. Accessed July 30, 2021.
7. Agence-France Presse. Hundreds of Ugandans paid for fake coronavirus jabs in vaccination scam: health officials. The Coronavirus Pandemic. July 22, 2021. South China Morning Post. https://www.scmp.com/news/world/africa/article/3142018/hundreds-ugandans-paid-fake-coronavirus-jabs-vaccination-scam. Accessed July 30, 2021.
8. Bhalla N. 'Vaccine grabbing' seen fueling risk of fake COVID-19 jabs in Africa. April 9, 2021. Reuters. https://www.reuters.com/article/us-health-coronavirus-vaccine-africa-idUSKBN2BW231. Accessed July 30, 2021.
9. Reuters Staff. South Africa sells AstraZeneca COVID-19 vaccines to other African countries. March 21, 2021. Reuters. https://www.reuters.com/article/us-health-coronavirus-safrica-vaccine/south-africa-sells-astrazeneca-covid-19-vaccines-to-other-african-countries-idUSKBN2BD0K4. Accessed. July 30, 2021.
10. Jerving S. DRC to return 1.3M COVAX vaccine doses before expiry. April 29, 2021. Devex. https://www.devex.com/news/drc-to-return-1-3m-covax-vaccine-doses-before-expiry-99792. Accessed July 30, 2021.
11. Higgins-Dunn N. Johnson & Johnson told to throw out 60M COVID-19 shots made at troubled Emergent site: report. June 11, 2021. Fierce Pharma. https://www.fiercepharma.com/pharma/johnson-johnson-told-to-throw-out-60m-covid-19-shots-made-at-troubled-emergent-site-report. Accessed July 30, 2021.
12. Cordell J, Sauer P. WHO finds production infringements at Sputnik V manufacturer. June 28, 2021. The Moscow Times. https://www.themoscowtimes.com/2021/06/23/who-finds-production-infringements-at-sputnik-v-manufacturer-a74310. Accessed July 30, 2021.
13. World Health Organization. Bar-codes, QR codes and Vaccine Vial Monitors in the context of COVID-19 vaccines. October 30, 2020. WHO. https://www.who.int/publications/m/item/bar-codes-qr-codes-and-vaccine-vial-monitors-in-the-context-of-covid-19-vaccines. Accessed July 30, 2021.
14. Kwok Y. Indonesia will revaccinate 'millions' of children after fake vaccines come to light. June 28, 2016. Time. https://time.com/4385064/indonesia-children-vaccination-scandal-vaccine-health/. Accessed July 30, 2021.
15. Gander K. Saline injected instead of COVID vaccine in South Carolina. June 29, 2021. Newsweek. https://www.newsweek.com/saline-injected-instead-covid-vaccine-south-carolina-1605087. Accessed July 30, 2021.
16. Ozawa S, Evans D, Bessias S, Haynie DG, Yemeke TT, Laing SK, Herrington JE. Prevalence and estimated economic burden of substandard and falsified medicines in low- and middle-income countries: A systematic review and meta-analysis. JAMA Netw Open. 2018;1(4):e181662. doi:10.1001/jamanetworkopen.2018.1662. Accessed July 30, 2021.
17. Pan American Health Organization and World Health Organization. Recommendations on regulatory processes and aspects related to the introduction of vaccines during the COVID-19 pandemic and other emergencies. July 16, 2021. PAHO/WHO. https://iris.paho.org/handle/10665.2/54516. Accessed July 30, 2021.
18. World Health Organization. How to manage COVID-19 vaccines without VVM at vaccination service points? June 3, 2021. WHO. https://www.who.int/publications/m/item/how-to-manage-covid-19-vaccines-withoutvvm-at-vaccination-service-points. Accessed July 30, 2021.
19. World Health Organization. COVID-19 vaccination: supply and logistics guidance. February 15, 2021. WHO. February 15, 2021. https://www.who.int/publications/i/item/who-2019-ncov-vaccine-deployment-logistics-2021-1. Accessed July 30, 2021.
20. World Health Organization. Guidelines for Safe Disposal of Unwanted Pharmaceuticals in and after Emergencies. 1999. WHO. https://www.who.int/water_sanitation_health/medicalwaste/unwantpharm.pdf. Accessed July 30, 2021.

21. World Health Organization. The WHO Member State Mechanism on Substandard and Falsified Medical Products. June 24, 2020. WHO. https://www.who.int/publications/i/item/WHO-MVP-EMP-SAV-2019.04. Accessed July 30, 2021.

22. World Health Organization. WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems. WHO. https://www.who.int/tools/global-benchmarking-tools. Accessed July 30, 2021.

23. World Health Organization. Regulation and Prequalification. WHO. https://www.who.int/teams/regulation-prequalification/regulation-and-safety/laboratory-networks-and-services/regulatory-harmonization/who-nnb. Accessed July 30, 2021.

24. Kato A, Fujita K, Ochiai M, Naito S, Konda T. Study on the procedure for lot release of vaccines in Japan. Jpn J Infect Dis. 2019;72(3):133-141. https://doi.org/10.7883/yoken.JJID.2018.446. Accessed July 30, 2021.

25. World Health Organization. TRS 1033 - 55th report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, Annex 10. March 25, 2021. WHO. https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations. Accessed July 30, 2021.

26. World Health Organization. Guidelines for independent lot release of vaccines by regulatory authorities. June 4, 2012. WHO. https://www.who.int/biologicals/Guidelines_Lot_Release_DB_4_JUNE_2012.pdf. Accessed July 30, 2021.

27. Joi P. China's Sinopharm COVID-19 vaccine first to carry a smart label to monitor heat-damage. May 14, 2021. Gavi. https://www.gavi.org/vaccineswork/chinas-sinopharm-covid-19-vaccine-first-carry-smart-label-monitor-heat-damage. Accessed July 30, 2021.

28. World Health Organization. Policy paper on traceability of medical products. March 18, 2021. WHO. https://www.who.int/publications/i/item/policy-paper-on-traceability-of-medical-products. Accessed July 30, 2021.

29. Center for Vaccine Ethics and Policy. (2021, July 25). RFPS – Development of a Global Trust Repository, Solution, Implementation, and Operation Services. Retrieved from Vaccines and Global Health: Ethics and Policy: https://centerforvaccineethicsandpolicy.net/2021/07/25/rfps-development-of-a-global-trust-repository-solution-implementation-and-operation-services/

30. World Health Organization. What is pharmacovigilance? 2021. WHO. https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance Accessed July 30, 2021.

31. World Health Organization. Covid-19 vaccines: safety surveillance manual. WHO. December 22, 2020. WHO. https://www.who.int/publications/i/item/10665338400. Accessed July 30, 2021.

32. African Union Development Agency-NEPAD. A case for including substandard and falsified (SF) medical products in the African Union Smart Safety Surveillance (AU-3S) System. April 30, 2021. AUDA-NEPAD. https://www.nepad.org/news/case-including-substandard-and-falsified-sf-medical-products-african-union-smart-safety. Accessed July 30, 2021.

33. Interpol. Fake COVID vaccine distribution network dismantled after INTERPOL alert. March 3, 2021. INTERPOL. https://www.interpol.int/en/News-and-Events/News/2021/Fake-COVID-vaccine-distribution-network-dismantled-after-INTERPOL-alert. Accessed July 30, 2021.

34. United Nations Interregional Crime and Justice Research Institute. Building an effective cooperation mechanism against falsified medicines: the establishment of a public-private stakeholders group in Romania. March 18, 2014. United Nations. http://files.unicri.it/news/article/2014-03-08_falsified_medicines_cooperation_. Accessed July 30, 2021.