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Commentary

Supporting use of thermostable vaccines during public health emergencies: Considerations and recommendations for the future

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1. Introduction

Most vaccines require storage at sufficiently cold temperatures prior to administration. Additionally, some, including certain COVID-19 vaccines, require temperatures as low as −80 °C in a system described as the "ultra-cold chain" (UCC). Cold chain capacity in a country varies by geography, political stability, income-level, and infrastructure, posing significant financial and operational challenges, particularly during health emergencies. Inadequate maintenance and monitoring of the cold chain can contribute to inequitable and suboptimal vaccine potency and access.

There have been efforts to develop and use vaccines less reliant on a robust cold chain between 2 °C and 8 °C, with respect to both storage and last-mile delivery. While a subset, such as cholera and meningococcal A vaccines, exhibit greater thermostability, progress in the development and licensure of thermostable vaccines has been limited. We discuss potential benefits of thermostable vaccines, as well as considerations and recommendations to expand their use.

2. The cold chain poses limitations during health emergencies

Exposures to temperatures outside of authorized ranges have been common during immunization efforts [1,2], due to gaps in cold chain infrastructure and monitoring, particularly in low and middle income countries (LMICs). Investments have aimed to strengthen the global immunization cold chain; however, maintaining, monitoring, and identifying gaps in the cold chain remains logistically complex and costly. Remaining gaps contribute to wastage, reduced coverage, and the potential administration of vaccines exhibiting reduced potency. The problems associated with the cold chain and UCC are exacerbated during pandemics and other emergencies. Mass vaccination with a vaccine that requires UCC is possible but can be incredibly resource intensive, as demonstrated with Ebola vaccines [3]. More recently, over 45 countries requested freezers and resources from UNICEF to establish UCC capacity within weeks to conduct COVID-19 mass vaccination [4].

Immunization efforts during both Ebola epidemics and the COVID-19 pandemic have required use of novel technologies such as mobile Arktek freezers to facilitate UCC implementation, and other costly resources including back-up generators, air conditioners, additional continuous temperature monitoring infrastructure, and increased staffing of storage facilities. COVID-19 response efforts have also highlighted that UCC freezers can have air transport complexities. Efforts to prepare and establish UCC capacity have been further complicated by volatile supply of COVID-19 vaccine dose shipments and ancillary supplies such as dry ice [5], due to factors including demand, export controls, manufacturing constraints, and short-notice donations. High income countries (HICs) also experience challenges with mass vaccination, particularly in

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rural settings or those that lack access to ultracold freezers. In the US, pharmacies and clinics initially had to refill mRNA COVID-19 vaccine storage containers with dry ice regularly, and use all vaccines in a shipment within 2 weeks [6]. These requirements posed logistical challenges for community vaccination and potentially contributed to wastage.

Vaccines exhibiting stability at ambient temperatures would be valuable during emergency mass vaccination. A vaccine that is resilient to both sub-zero temperatures and up to 40 °C during last-mile vaccine delivery can expedite rollout and reduce wastage. WHO and partners have recognized this programmatic need and have supported the development and use of thermostable vaccines. One important example is the controlled temperature chain (CTC) program. The WHO CTC Strategic Roadmap defines programmatic parameters to enable on-label usage of WHO prequalified vaccines for use in qualifying situations to be distributed at temperatures up to 40 °C for a predetermined number of days [7]. Supporting use of CTC has been outlined as a key priority in the recent Vaccine Innovation Prioritization Strategy (VIPS), led by stakeholders including Gavi, WHO, and PATH [8]. WHO also provided logistical guidance on possible use of COVID-19 vaccines under CTC conditions for qualifying vaccines [9]. Despite these efforts, use of thermostable vaccines has been limited for several reasons.

3. Challenges and considerations for developing and using thermostable vaccines

Several factors contribute to lack of use of thermostable vaccines, particularly during emergencies.

3.1. Technical

Vaccine thermostability depends on many elements, including antigen and platform type, presence of adjuvant or additional excipients, amenability to drying and reconstitution, and administration route. Optimizing and assessing thermostability requires time, resources, and expertise. In an emergency context, such assessments are often not prioritized because developers want the vaccine authorized as quickly as possible. However, developing more stable versions of a vaccine does not necessarily delay product use. For example, the mRNA vaccines from Pfizer and Moderna were both authorized for use in the US within a week of each other, despite the Moderna formulation having a less restrictive stability profile. Early trials of the Sputnik V vaccine assessed both liquid and more thermostable lyophilized formulations simultaneously. Nevertheless, the challenges of making thermostable vaccines can be substantial and, at times, prohibitive during emergency mass vaccination.

3.2. Perceptions of value

Stakeholders have assessed the value of thermostable or CTC-labeled vaccines, including in low-income countries, for vaccination campaigns and non-emergency uses that extended beyond administration in traditional health care facilities. Results have been mixed when assessing whether using thermostable vaccines for routine immunizations lowers total program costs of procurement, monitoring, logistics, and delivery, with cost savings in some situations. However, when looking beyond cost savings, thermostable vaccines are found to be a cost-effective way of preventing disease, due particularly to the reduced likelihood people will be given less potent vaccines. More data are needed assessing the operational impacts of using CTC in pandemic response.

Additionally, there have been concerns that staff in routine immunization clinics may experience confusion [10] if only some vaccines are allowed to remain at ambient temperatures. Using more stable vaccines may be less valuable in settings where cold chain needs to be maintained for other stored vaccines, and staff confusion can be mitigated through training. Mixed views on the value of thermostable vaccines have contributed to reduced awareness and limited demand from ministries of health, and consequently reduced prioritization among funders and developers. The emergency use case, however, is a more optimal scenario for CTC because vaccination would at least initially be carried out predominantly as mass vaccination campaigns that would require taking the vaccine out into field settings rather than being integrated operationally into a traditional routine clinic alongside other routine immunizations.

3.3. Prioritization

There is a common belief that cold-chain challenges are limited only to LMICs, and thus optimizing vaccine thermostability is not profitable to pharmaceutical companies predominantly focused on HIC markets. While LMICs generally have substantially more gaps in cold-chain infrastructure, thermostable vaccines can also benefit HICs in alleviating logistical limitations in cold chain infrastructure, and in fostering innovative approaches to community vaccination, particularly during emergencies. For example, thermostable vaccines could be more easily administered through mobile health clinics, door-to-door immunization campaigns, or other outreach activities that can better reach vulnerable populations. Pursuing and prioritizing development of thermostable vaccines can serve the best interests of countries across all income levels.

Although multiple candidates using the mRNA platform have been successful for COVID-19 response, the diversity in COVID-19 vaccine formulations being developed or used demonstrates that there is a diverse range of promising vaccine types that may be more likely to exhibit thermostability, including DNA, inactivated, or protein subunit platforms. Pursuing diverse vaccine candidates for future health emergencies will be beneficial for developing thermostable vaccines. Additionally, as WHO and partners increasingly look toward pursuing diversified vaccine manufacturing capacity to support vaccine access particularly for mRNA platform candidates, strategies should be used to prioritize use of innovations that enable greater thermostability and programmatic suitability in vaccines produced.

4. Recommendations

Future pandemic preparedness efforts should work to support development and use of thermostable vaccines. We recommend the following to achieve this goal:

1. Public health researchers should define and emphasize more potential use cases and best practices for thermostable vaccines. Target product profiles should increasingly incorporate thermostability into parameters, and programmatic guidance should emphasize designing vaccine rollout in ways that maximize its programmatic suitability, acceptability, and uptake in countries.
2. Global health institutions and academic researchers should study the financial and public health value, and optimal programmatic implementation of thermostable vaccines across a wider range of contexts.
3. Funding entities, whether philanthropic organizations or government funders, should support the development and use of thermostable vaccines, particularly for the emergency use case, by committing to pay more or prioritizing funding for ther-

mostable vaccines both for domestic and global use. Vaccine manufacturers should be incentivized to develop thermostable vaccines.
4. Regulatory authorities should build off existing guidance to bolster standard methods for robust and appropriate assessment of vaccine stability in a CTC context.
5. The vaccine development community should support innovation and development of thermostable vaccine platforms. Collaboration among stakeholders should center on approaches to support development of thermostable mRNA and other emerging platforms.

5. Conclusions

Maintaining and monitoring the vaccine cold chain during emergency mass vaccination presents challenges for all countries, particularly LMICs. The failure to maintain cold chain, particularly UCC, can lead to significant logistical hurdles, wastage, and suboptimal coverage. Development and use of thermostable vaccines has been complicated by technical challenges, programmatic considerations, and lack of prioritization from key stakeholders. Thermostability of vaccines should be clearly defined, and vaccine developers should be incentivized to consider thermostability and programmatic suitability early in the development process.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Hanson CM, George AM, Sawadogo A, Schreiber B. Is freezing in the vaccine cold chain an ongoing issue? A literature review. Vaccine 2017;35 (17):2127–33. https://doi.org/10.1016/j.vaccine.2016.09.070. , https://pubmed.ncbi.nlm.nih.gov/28364920/.
[2] Yauba S, Joelle S, Jude N, et al. Temperature monitoring in the vaccine cold chain in Cameroon. J Vaccines Vaccin 2017;9(1). , https://www.researchgate.net/publication/323315027_Temperature_Monitoring_in_the_Vaccine_Cold_Chain_in_Cameroon.
[3] Carter RJ, Idriss A, Widdowson M-A, Samai M, Schrag SJ, Legardy-Williams JK, et al. Implementing a multisite clinical trial in the midst of an Ebola outbreak: lessons learned from the Sierra Leone trial to introduce a vaccine against Ebola. J Infect Dis 2018;217(suppl_1):S16–23. https://doi.org/10.1093/infdis/jix657. , https://academic.oup.com/jid/article/217/suppl_1/S16/4999143.
[4] Unicef. The historic push to provide ultra-cold chain freezers around the world. Published September 20, 2021. Accessed October 17, 2021. https://www.unicef.org/supply/stories/historic-push-provide-ultra-cold-chain-freezers-around-world.
[5] Jerving S. How dry ice shortages can complicate Pfizer vaccine deliveries. Devex. Published June 17, 2021. Accessed November 02, 2021. https://www.devex.com/news/sponsored/how-dry-ice-shortages-can-complicate-pfizer-vaccine-deliveries-100162.
[6] Kaiser J. Temperature concerns could slow the rollout of new coronavirus vaccines. Science. Published November 16, 2020. Accessed October 9, 2021. https://www.science.org/content/article/temperature-concerns-could-slow-rollout-new-coronavirus-vaccines.
[7] World Health Organization. Controlled Temperature Chain: Strategic Roadmap for Priority Vaccines 2017–2020. Published 2017. Accessed October 9, 2021. https://www.who.int/immunization/programmes_systems/supply_chain/ctc_strategic_roadmap_priority_vaccines.pdf?ua=1.
[8] Gavi, the Vaccine Alliance. Overview of the VIPS Prioritisation Process and Outcomes. Accessed November 02, 2021. https://www.gavi.org/sites/default/files/about/market-shaping/Overview%20of%20the%20VIPS%20Prioritisation%20Process%20and%20Outcomes_July%202020.pdf.
[9] World Health Organization. COVID-19 vaccination: supply and logistics guidance. Published February 12, 2021. Accessed October 9, 2021. https://apps.who.int/iris/bitstream/handle/10665/339561/WHO-2019-nCoV-vaccine_deployment-logistics-2021.1-eng.pdf?sequence=1&isAllowed=y.
[10] Kristensen DD, Lorenson T, Bartholomew K, Villadiego S. Can thermostable vaccines help address cold-chain challenges? Results from stakeholder interviews in six low- and middle-income countries. Vaccine 2016;34 (7):899–904. https://doi.org/10.1016/j.vaccine.2016.01.001. , https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4744085/.