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Commentary

Logistical challenges for potential SARS-CoV-2 vaccine and a call to research institutions, developers and manufacturers

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In the absence of specific treatment or an effective vaccine, the SARS-CoV epidemic was brought to an end through public health tools like isolation, quarantine, physical distancing, and containment measures within eight months in 2003 [1]. Despite similarities between SARS-CoV and SARS-CoV-2 (and with recognition of differences such as trajectories, infectious period, transmissibility, clinical spectrum, and community spread) similar public health measures were only able to slow the spread of COVID-19, suppressing the peak and providing health systems much needed time to scale up for effective response [2]. Much debated herd immunity is far from being an exit strategy for the world since it may result in an intolerable global death toll. Currently, the availability of a safe and effective vaccine against SARS-CoV-2 is considered essential to the pandemic exit strategy with non-pharmaceutical interventions to be continued until the vaccine is made available globally. When a coronavirus vaccine arrives in sufficient quantity, a new marathon will commence for storage, distribution, and vaccination of every person on this planet who needs it.

Research to develop one or more COVID-19 vaccines is proceeding at an unprecedented pace. Globally coordinated efforts began with world researchers and scientists convening at the World Health Organization (WHO) on 11–12 February 2020, to initiate agreement on critical research questions and to define ways to work together to accelerate and fund priority research. Vaccine development efforts are being streamlined by the participation of many countries in efforts to coordinate and standardize key aspects of vaccine research and development, including a Target Product Profile (TPP) defining preferred and critical vaccine characteristics, animal models, assays to evaluate immune response, and designs for late-stage clinical trials [3]. As of 17 June 2020, the WHO draft COVID-19 vaccine candidate landscape indicates 11 candidate vaccines in active phase 1 and/or phase 2 clinical trials underway, and 128 in preclinical evaluation [4].

Vaccine candidates that have reached early-stage clinical evaluation to date include both well-established and novel vaccine platforms: mRNA- and DNA-based vaccines, live-attenuated virus, inactivated virus, replicating and non-replicating viral vectors, protein subunit, and artificial antigen-presenting cells. The current TPP was intentionally designed without restrictive preferred and minimal preferences concerning dosing schedule, need for booster doses, route of administration, formulation, and storage conditions. Critical information on the features of vaccines in early human trials, including storage temperature, is not yet publicly available. While inferences may be made concerning the storage, handling, and administration of traditionally designed products, the range of acceptable characteristics in the TPP allows for products that may be stored or administered in ways unlike any previous vaccine.

Developing, manufacturing, and approving a quality vaccine is not enough to ensure quality throughout the product's lifecycle since vaccines spend considerable periods at country level storage facilities, as well as being transported between warehouses, and all service points regardless whether they are used routinely or in a campaign. To ensure the quality of vaccines, countries require robust storage, transport systems, and well-organized service points staffed with trained workforce for effective vaccine management. To achieve the goal of immunizing the world's population safely with an effective vaccine in the shortest possible time, the vaccine must be prequalified to meet WHO biological standards governing safety and efficacy. Also, two critical factors will optimize and determine the successful conclusion of the goal. First, the presentation of the vaccine product should be simple to prepare and safe to administer with minimum manipulation. Second, country distribution systems should be safe and efficient. Both of these factors require historic amounts of cooperation between the vaccine manufacturers, country immunization programs, and international stakeholders. It should be kept in mind that resource-limited countries have far greater experience than industrialized countries in organizing mass vaccination events throughout the country.

Despite knowing the vaccine platforms, we have no information to date on the time and temperature sensitivity of candidate vaccines, recommended storage and distribution conditions or target presentations (liquid, lyophilized, and doses per vial/ampoule).

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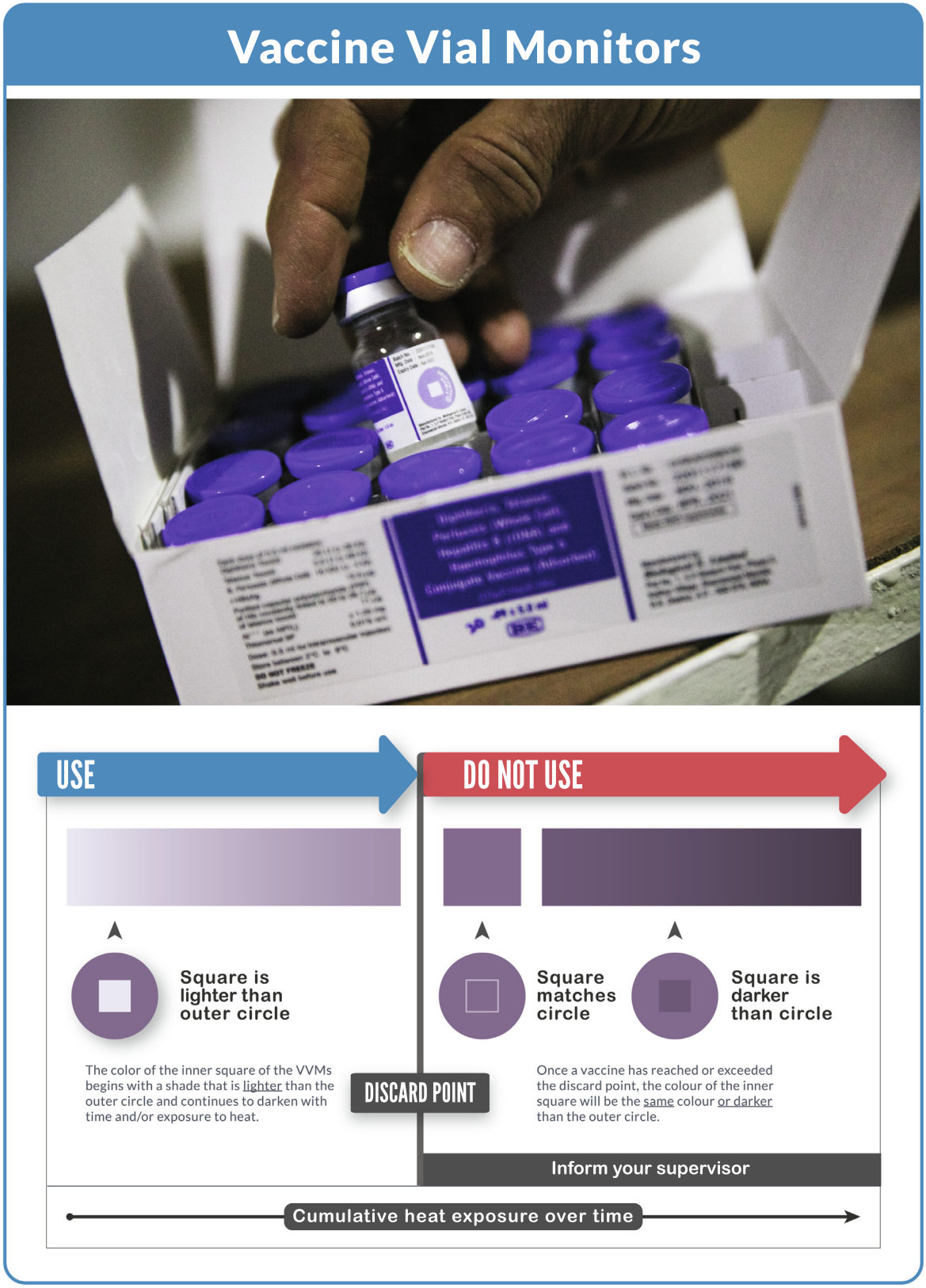

Fig. 1. How VVM works.

These are critical to making necessary preparations for receipt, storage, and distribution by the countries. Despite functionality problems in some countries, the supply chain infrastructure exists but the cool capacity for vaccines in transport and storage is unlikely to be sufficient for a campaign covering the whole population. Countries need to work on different options to either extend the capacity of warehouses to admit the vaccine or bypass one or more levels of storage, which may prolong the delivery journeys,

increasing the transport loads, but reducing vaccine handling. Depending on the temperature requirements, specialized transport boxes might be needed as well as temperature monitoring devices to accompany international transport and in-country distribution. If the potential vaccine has an extreme cold chain requirement (which is the case with the Ebola vaccine), existing systems in countries will not be able to accommodate this demand. Also, licensed vaccines may have different presentations and stability characteristics, further complicating vaccine logistics since more than one source might be needed to meet the demand. Temperatures of storage and transport are recorded at each stage of distribution and for each refrigeration device. In addition, for the health professionals to interpret the cumulative exposure of vaccines to heat and time, Vaccine Vial Monitor (VVM) labels are attached to each vial. These devices provide a simple visual reference to the viability of the vial of vaccine throughout distribution to the point of use (Fig. 1). VVMs warn users not to use vaccines that have been damaged any stage of distribution from manufacture until the vaccine is used [5]. At manufacture of the vaccine, the appropriate VVM label is assigned to the vaccine to match the accelerated stability data at 25 °C and 37 °C [6]. An appropriate VVM attached to the SARS-CoV-2 vaccine permits evaluation of the effect of time and temperature at all levels to ensure quality. Furthermore, VVM will prevent wastage and facilitate outreach to remote populations. Today, a total of 230 vaccine presentations out of 246 WHO prequalified vaccines are shipped with VVM [7].

In addition to accelerated stability studies, manufacturers should also consider generating stability data that is required for licensing vaccines for controlled temperature chain that will be useful to ease logistics and vaccine distribution [8].

To immunize the world's population, the safety of administration will be a key issue. Single-dose vaccine presentations are likely to displace multi-dose, either used conventionally with a syringe or injected by a physically integrated container and needle. However, taken into account the current global shortage of glass vials and the need to expedite filling, multi dose presentations are likely to be considered. Safety also extends to environmental considerations since all these injection devices will generate volumes of waste that need to be disposed of safely. One other logistical issue with COVID vaccine distribution will be the need for security to prevent theft/diversion and training of those handling and administering the vaccines as they may have different characteristics than current vaccines.

Where a Logistic Management Information System is available, they may be used for the management of SARS-CoV-2 mass immunization activities, however, additional efforts are needed to address issues that LMIS cannot solve (e.g. lack of training of service providers, mishandling of multi-dose vials).

The authors call research institutions, developers and manufacturers of SARS-CoV-2 vaccines to make publicly available detailed information of the temperature stability and target product profile (vaccine presentation details) even before clinical trials are completed, so that all potential time-temperature indicator developers have ample time to produce necessary devices/tools, and countries start planning for successful management of vaccine receipt, storage, distribution, and country-wide vaccinations. Authors also recognize the efforts of WHO for establishing a new global coalition to accelerate the development, production and equitable access to new COVID-19 diagnostics, therapeutics and vaccines [9].

Today, there is need for commitments on global unity to make vaccines equitably available everywhere. WHO has a critical role in this and world leaders should join WHO in calling for fair distribution of the SARS-CoV-2 vaccines when available.

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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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