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Commentary

Vaccine time–temperature indicators for present and future viral threats

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The extreme vulnerability of our world to rapidly emerging viral threats is most recently evidenced by the new corona virus (COVID-19). Vaccines for this virus are being developed in many places [1], but wide scale vaccine availability will likely not occur before 2021. Many developing countries are especially vulnerable, since they often have neither adequate medical treatment facilities nor a reliable cold chain, which can ensure the delivery of potent vaccines. The purpose of this commentary is to encourage the timely development of quickly and cheaply manufacturable indicators of accumulated thermal exposure (as it affects vaccine potency) for this and future viral threats. This can help ensure the delivery of potent vaccines for people in all countries.

These indicators can determine if a vaccine vial has been in a thermal environment where the vaccine loses potency. They are called time–temperature indicators (or integrators), since they ideally integrate the effects of any history of thermal exposure in the same way that this exposure affects vaccine potency. We believe that time–temperature indicators can importantly assist in the delivery of potent vaccines to parts of the world where a reliable cold chain does not exist, and that many companies and investigators should be enabled to compete (using diverse technologies) for the delivery of the cheapest and most reliable indicators in the available time window.

Our immediate request is that developers of COVID-19 vaccines make publicly available detailed information on the effects of time and temperature on vaccine potency even before human trials are completed, so that all potential time–temperature indicator developers have time to produce reliable indicators. Perhaps the World Health Organization (WHO), a pioneer in the use of time–temperature indicators [2], could develop a website for these results. In fact, this information could be provided on the WHO website that has been developed for COVID-19 vaccines [3]. As a first step, vaccine developers could provide plots of vaccine potency (P) versus time for relevant temperatures above the freezing point of the vaccine. In the simplest cases, these results could be usefully expressed by an Arrhenius equation: $dP/dt = A \exp(-H/RT)$, where A is a constant, H is the effective enthalpy for degradation of vaccine potency, T is the absolute temperature, R is the universal gas constant, and dP/dt is the time dependence of the loss of vaccine potency. For some vaccines, different temperature ranges might provide different fits to this equation. An indicator's response should be conservative – it is better to bear the cost of discarding possibly potent vaccines than to use vaccines having doubtful potency (which means that the highest thereby derived activation energy should be used for an indicator). Since even short time exposures to very high temperatures can rapidly degrade vaccines, this use of a high activation energy for the time–temperature indicator provides an additional safe guard.

Vaccine developers should also make publicly available quantitative results on the decrease of vaccine potency because of inadvertent freezing and multiple freeze–thaw cycles. Vaccines vary between extremes, from those where prolonged high temperature exposures are the major problem (like oral poliomyelitis, measles-mumps-rubella, and hepatitis B vaccines) and those where freezing can be an even greater threat (like hepatitis B and human papilloma virus vaccines). Hence, avoiding refrigeration that could cause accidental vaccine freezing might be the best approach for high thermal stability vaccines, as long as time–temperature indicators are used. Few, if any, yet know where candidates for COVID-19 vaccines are in this range of temperature and freeze sensitivity. This information should be made publicly available for all potential indicator developers (both of time–temperature and freeze indicators). In fact, the availability of this data for long used vaccines could inspire the further development of high-performance low-cost indicators.

Although numerous attractive time–temperature technologies have been developed that might greatly benefit humankind for this and future viral threats [4], only one time–temperature technology has so far been widely deployed for individual vaccine vials [5]. This technology uses the color changes associated with the solid-state polymerization of diacetylene crystals (Fig. 1A). The reaction kinetics of diacetylene polymerization (and corresponding color changes) may be varied, so that they approximately match the degradation characteristics of various vaccines, drugs, human blood, and foodstuffs [5–7].

These presently used vaccine vial monitors (VVMs) are inexpensively made by printing a diacetylene ink on vaccine labels. They

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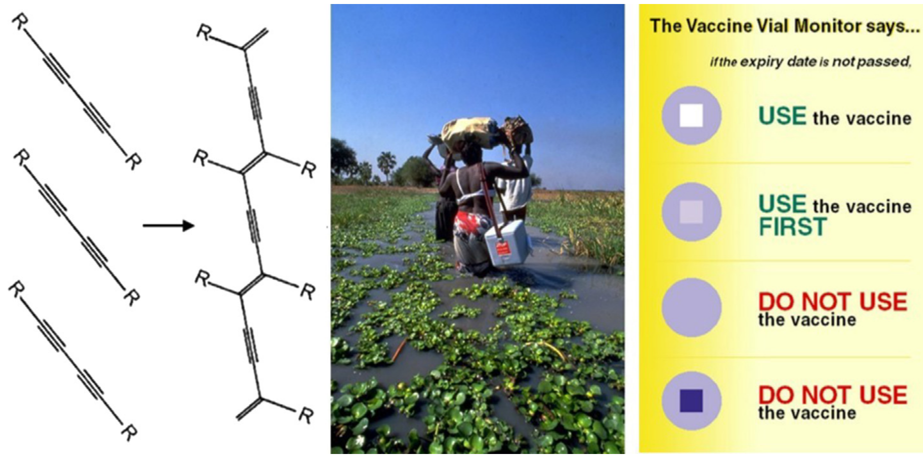

Fig. 1. (*Left*) The solid-state thermal polymerization of a colorless diacetylene indicator material to produce a highly colored polydiacetylene. (*Middle*) Vaccines, in the blue cooler, being carried to a remote village. (*Right*) A strategy for indicator deployment, which is presently used for the diacetylene VVMs, and could be used for alternative devices of many types. The central square is the printed indicator ink. If this central square matches or is darker than the background, the labeled vaccine should not be used. The middle and right panels are from the WHO and PATH, respectively.

are printed in the activated state, which means that rolls of these indicators are refrigerated at −24 °C prior-to and during shipment to the vaccine manufacturer for application on individual vaccine vials. While this strategy contributes to total indicator cost (about 6 US cents per VVM indicator manufactured by Temptime Corporation), it also eliminates the possibility of faulty actuation of the indicator. The cost of pre-application refrigeration could potentially be eliminated if a reliable method for activation was developed for any appropriate inexpensive technology.

Other than experts and a few individuals in countries receiving vaccines from United Nations procurement agencies, few know about the existence and need for these VVMs. Over 8 billion of these inexpensive diacetylene time–temperature indicators have been used on vaccine vials [5]. On the tenth anniversary of their use (2007), PATH (Program for Appropriate Technology in Health) estimated [8] "that over the next ten years, VVMs will allow health care workers to recognize and replace 368 million doses of inactive vaccines and deliver an additional 1.5 billion doses in remote settings - actions that could save more than 140,000 lives and reduce morbidity for countless others.".

Now is the time for developers of COVID-19 vaccines to start working with those interested in developing inexpensive vaccine vial indicators, so that people everywhere can receive potent vaccine. A host of time–temperature indicator technologies, many of which have been developed for the food industry, are available for possible use for vaccines [9].

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.

References

[1] Cohen J. Vaccine designers take first shots at COVID-19. Science 2020;368:14–6.
[2] World Health Organization. Controlled temperature chain (CTC). https://www.who.int/immunization/programmes_systems/supply_chain/ctc/en/ [accessed on 8 Sept 2020].
[3] World Health Organization. WHO target product profiles for COVID-19 vaccines. https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines/ [accessed on 8 Sept 2020].
[4] World Health Organization. Specifications and verification protocols for PQS/E006 temperature monitoring devices. https://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/categorylist.aspx?cat_type=device [accessed on 8 Sept 2020].
[5] Kartoğlu ÜH. The book of VVM: Yesterday-today-and-tomorrow. (Electronic versions are available free at http://kartoglu.ch/vvm/.) Published 2020.
[6] Baughman RH. Solid-state synthesis of large polymer single crystals. J Polym Sci, Polym Phys Ed 1974;12:1511–35.
[7] Patel GN, Preziosi AF, Baughman RH. Time-temperature history indicators. US 3,999,946; 1976.
[8] World Health Organization and PATH. https://www.who.int/immunization/programmes_systems/supply_chain/optimize/vaccine_vial_monitors_faqs.pdf?ua=1%20%20 [accessed on 8 Sept 2020].
[9] Manjunath SJ. Time temperature indicators for monitoring environment parameters during transport and storage of perishables: A review. Environ Conserv J 2018;19(3):101–6.