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PERSPECTIVES

Inundative, Dry-Powder, Inhaled Measles Vaccination to Prevent Deaths of Young Children in War-torn Regions

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Children living in war-torn and geographically remote regions often die from measles due to undervaccination. Protective community immunity could be safely improved through the comprehensive use of small, inexpensive, easy-to-use, dry-powder aerosolized measles vaccination inhalers. Influential local community members could be engaged to provide risk counseling and inform their peers of measles risks to inspire vaccine uptake. Vaccination by inhaled live attenuated measles vaccine has been shown to be safe and protective among several million research subjects and omits (1) needles, syringes, glass vials, and specialized disposal systems; (2) deadly vaccine reconstitution errors; (3) cold chain technology to protect temperature-sensitive vaccine; (4) vaccine wastage associated with suboptimal use of multidose vials; (5) trained vaccinators; (6) food, housing, and transportation costs associated with centralized vaccination campaigns; and (7) risk of violence to vaccinators and associated staff. All elements for inhaler-based measles vaccination are readily available. Dry-powder measles vaccine inhalers can be assembled and distributed to save lives.

Keywords. dry-powder inhalation; measles; medicine in conflict zones; self-vaccination; vaccination.

Measles undervaccination, compounded by malnutrition, contributes to the deaths of children in war-torn regions. Well-intentioned, emergency mass vaccination responses in areas experiencing violent conflict continue to be suboptimal and, in exceptionally rare instances, dangerous. During a 2017 vaccination campaign to protect children in Sudan from measles, 15 children died of sepsis because of inappropriate syringe reuse and insufficient refrigeration of vaccines [1, 2]. In Syria in 2014, a measles vaccination campaign inadvertently killed fifteen Syrian children after they received a measles vaccine that was reconstituted using muscle relaxants instead of sterile water diluent [3]. Atracurium ampules had been incorrectly included in vaccination packs assembled in one district vaccine center and then distributed to four separate vaccination teams. Five years later, atracurium was again mistakenly used as measles vaccine diluent in Samoa in 2019, directly killing 2 children, reflexively leading to halted measles vaccinations followed by an overwhelming measles outbreak resulting in the deaths of 83 young children due to undervaccination [4].

Billions of individuals have been safely vaccinated against measles using needles and syringes. However, widespread mistrust of vaccinations and public health teams directly resulted from each of these avoidable reconstitution, storage, and handling mistakes. On a personal level, multiple earnest healthcare providers who failed to catch their inadvertent error must now live with the fact that their attentional lapse directly killed children. Public health systems should not continue to place staff in a position where unintentional negligence can severely injure or kill vaccine recipients. Ultimately, the existing needle and syringe vaccination delivery system should comprehensively shift to the use of newer, safer measles vaccine delivery approaches.

Inhaled measles vaccinations are safe, protective, and well-established. In the 1980s, Albert Sabin helped develop an aerosolized, needle-free, inexpensive, safe measles vaccine for mass vaccination campaigns [5]. Almost 4 million children in Mexico received wet-mist, aerosolized measles vaccinations and 92% achieved protective seroconversion [6]. In an age-restricted trial that evaluated nebulized wet-mist vaccine inhaled by children between 9 and 12 months of age, 85.4% seroconverted [7]. Promisingly, when delivered as a second dose to older children and adults, inhaled measles vaccine achieved higher and more durable levels of protection compared with subcutaneously administered vaccines [8, 9].

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Live attenuated measles vaccinations delivered by wet-mist nebulizer in centralized campaigns safely provide durable measles protection, though they are associated with considerable logistical challenges. Inhaled, dry-powder measles vaccines would be far easier to implement in war-torn regions. Inhalation particle engineering advances employing carbon dioxide–assisted nebulization and spray drying have delivered a high-yield process for measles vaccine dry powder achieving the World Health Organization standard for thermostability [10, 11]. Live attenuated Edmonston-Zagreb virus can be formulated as a temperature-stable dry powder using myo-inositol as a stabilizer instead of sorbitol. Spray drying using carbon dioxide–assisted nebulization has been shown to produce 3- to 5-μm vaccine particles reliably, ensuring optimal size for deep lung delivery [12, 13].

Readily available, dry-powder, fill and finish manufacturing lines can produce standardized doses in blister packages for inclusion in inexpensive, disposable, tamper-resistant, dry-powder inhalers for use by individuals aged ≥5 years who are able to cooperate and coordinate inhalation from a mouthpiece. Familiar Diskus or Inhub inhalers enabling 60 vaccine doses could be readily employed. In a more cost-constrained setting, the reusable Papillon inhaler might be a simple, appropriate choice consisting of 2 reusable plastic components and single-use vaccine blisters.

For younger children, the dry-powder vaccine could be mechanically dispersed into a readily available holding chamber and inhaled through normal tidal breathing. However, it is acknowledged that added development would be required to realize dry-powder vaccinations for infants as no inhaler device is currently commercially available [14].

Regardless of which inhaler technology is selected, a cost-effectiveness analysis suggests that meaningful cost savings over needle and syringe delivery would be realized overall [15]. In low- and middle-income countries, measles vaccines purchased in bulk cost approximately US$0.20 per immunization [16]. Using inexpensive spray drying technology, costs should be comparable when the vaccine is placed as individual doses in the aluminum blister pack–finished format instead of lyophilized in a multidose vial format. Notably, considerable cost savings are anticipated as expenses associated with centralized campaigns would be omitted.

Shifting to inundative, dry-powder, inhaled measles vaccination requiring minimal trained supervision could also meaningfully reduce hazards to the many individuals who staff vaccination campaigns both in war-torn regions and locations where mistrust of vaccines has resulted in violence toward vaccinators. Tragically over the last decade, 95 polio vaccinators have been killed in Afghanistan and Pakistan [17–19]. Importantly, risks to medical staff are increasing globally. From 2016 to 2020, 1524 healthcare workers were injured, 401 were kidnapped, and 681 were killed [20].

Change is challenging. Having injected measles vaccine by needle and syringe for over 60 years, the delivery approach seems utterly sacrosanct. However, war-torn settings demand an added simplicity of use and thus represent a relevant and appropriate setting to implement dry-powder, inhaled measles vaccine delivery. The crisis of life-threatening undervaccination associated with the regional collapse of public health systems demands urgent intervention. Redoubling efforts to conduct conventional vaccination campaigns in these regions should not be our reflexive answer because it is encumbered by the very real risks of reconstitution errors and increasing risks of harm to vaccinators. The unfolding measles risk to young children in war-torn regions requires the courage to try something new.

It is envisioned that vaccine inhalers would be widely distributed and amply available to minimize scarcity or hoarding behaviors. Health agencies administering the project would cultivate assistance from military and/or paramilitary groups to help distribute vaccine inhalers in particularly hazardous conditions. As with all live-attenuated vaccinations, those who are pregnant, planning a pregnancy, or meaningfully immunosuppressed individuals would be guided to avoid self-vaccination. Given the emergency circumstances and diminished measles herd immunity, *all* individuals who are able to inhale from a dry-powder inhaler would be encouraged to self-vaccinate, regardless of prior measles vaccination history. Providing inundative community vaccination provides the greatest chance of meeting the 95% seropositivity threshold that is believed to be associated with arresting measles outbreaks.

Emergency use of dry-powder measles vaccine inhalers in war-torn regions would necessitate shifting vaccination supervision responsibilities to influential local community members identified based on their commitment to safely encouraging appropriate vaccine use and avoiding inadvertant vaccination of immunosuppressed individuals. For this reason, it is exceptionally important that simple pictorial instructions accompany the inhalers to help drive safe, effective, dispersed vaccination efforts across broad territories. It would follow that typical written documentation practices linking each vaccination delivered to a specific individual may be less practical under emergency circumstances. Conceivably, the entrusted local community member could simply photograph each vaccine recipient holding the unique batch-specific QR (quick response) code on the inhaler to enable linkage of product to the individual to enable tracking of any adverse events, should they occur. This simple documentation could be uploaded to a secure server routinely employing satellite cellphone links. It is acknowledged that innovative record-keeping technology would be highly desirable to bring the self-vaccination vision to practice in crisis circumstances.

In the broadest terms, success would be measured by lowered infection and death

rates of measles in outbreak regions. It is conceivable to sample communities for measles seropositivity before and after inundative vaccination to determine overall uptake and to better guide future implementation efforts. If all necessary elements enabling dry-powder, inhaled measles vaccinations are readily available, what stops us from distributing vaccine inhalers and providing simple use instructions to influential local community members to prevent child measles deaths in Afghanistan, Syria, Yemen, and Ukraine?

Notes

Patient consent. This Perspective does not use any original patient data.

Potential conflicts of interest. All authors: No reported conflicts.

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