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INSPIRATIONAL NOTE

# Innovations in vaccine delivery: increasing access, coverage, and equity and lessons learnt from measles and rubella elimination

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## Abstract

Disease eradication and elimination programs drive innovations based on progress toward measurable objectives, evaluations of new strategies and methods, programmatic experiences, and lessons learned from the field. Following progress toward global measles elimination, reducing measles mortality, and increasing introductions of measles and rubella vaccines to national programs, the measles and rubella immunization program has faced setbacks in recent years. Currently available vaccine delivery methods have complicated logistics and drawbacks that create barriers to vaccination; innovations for easier, more efficient, and safer vaccine delivery are needed. Progress can be accelerated by new technologies like microarray patches (MAPs) that are now widely recognized as a potential new tool for enhancing global immunizations efforts. Clinical trials of measles-rubella vaccine MAPs have begun, and several other vaccine MAPs are in the pre-clinical development pathway. MAPs could significantly contribute to *Immunization Agenda 2030* priorities, including reaching zero-dose children; increasing vaccine access, demand, coverage, and equity; and achieving measles and rubella elimination. With strong partnerships between public health agencies and biotechnology companies, translational novel vaccine delivery systems can be developed to help solve public health problems and achieve global health priorities.

**Keywords** Measles · Microneedles · Microarray · Immunizations · Vaccines

**Highlights**

- An improved method for the delivery of measles and rubella vaccines is a long-established need and remains the highest research priority for the measles and rubella immunization program.
- Global efforts to eliminate measles and rubella would be greatly facilitated by the availability of measles-rubella vaccine microarray patches (MAPs) with simplified logistics and improved thermostability, enhancing efforts to increase vaccination coverage and equity, particularly in low and middle-income countries, where children are in greatest need.
- Vaccine MAPs have the potential to significantly contribute to Immunization Agenda 2030 priorities including increasing (1) vaccine access and demand, coverage, and equity with vaccinations across the life-course, and (2) reaching any unvaccinated children to ensure no one gets left behind.
- Strong partnerships between public health agencies and biotechnology companies are needed to develop translational novel vaccine delivery systems to solve public health problems and help achieve global health priorities.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention.

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## The context

A recent study published in the journal *Science* suggests the measles virus emerged as early as the sixth century BCE, making it the oldest human RNA virus genome sequenced thus far and nearly twice as old as previously thought [1]. This revised timeframe of the origin of the measles virus emergence substantially increases the overall toll of human disease, death, and devastation caused by measles throughout human history [2]. Today, after more than 2,600 years, humans remain the only natural host sustaining ongoing measles virus transmission [3, 4].

Clinical measles in the USA was first described in Boston in 1657 [3]. The measles virus (Edmonston-B strain) was

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isolated in 1954 from a measles-infected boy by Thomas C. Peebles while working in John F. Enders' laboratory at Boston Children's Hospital and then propagated in chick embryo cell culture [5]. For vaccine development, the virus was attenuated through multiple passages in chick embryo cells, to the more attenuated Enders (Moraten) strain used in the USA and to the Schwartz measles virus strain used worldwide. Rubella vaccines are based on the live attenuated RA 27/3 strain that was first isolated from an infected fetus in the 1960s and then passed through human diploid cell lines [6]. In the USA, the first measles vaccine was licensed in 1963, and the first rubella vaccines were licensed in 1969; global widespread use started in 1974. Measles-rubella (MR) vaccines are given by subcutaneous injection in a two-dose regimen as recommended by the World Health Organization (WHO). Before the use of MR vaccination, measles infected nearly everyone during childhood, causing 135 million measles cases and 6 million measles deaths globally each year, including 4 million cases and 450 deaths in the USA [7, 8]. Prior to the use of rubella vaccine, an estimated 12.5 million rubella cases including > 30,000 pregnancies affected, and 20,000 infants born with congenital rubella syndrome occurred in the last major outbreak in the USA during 1964–1965. Increasing vaccination coverage in the USA led to the elimination of endemic measles in 2000 and rubella in 2009; however, imported cases into the USA, primarily among unvaccinated US travelers returning home from travel abroad, continue to occur each year [9]. Measles remains a major cause of child mortality globally and rubella the leading cause of birth defects globally, despite both being vaccine preventable and eradicable [10, 11].

During the twentieth century, the development, manufacture, and widespread use of a variety of vaccines brought forth a golden age of immunizations to global public health and opened doors to the possible eradication of some diseases. In 1966, the intensified smallpox eradication program was launched by the World Health Organization (WHO) with major support from the US Centers for Disease Control and Prevention (CDC); after successful implementation of that program, smallpox was declared eradicated in 1980 [12]. Because of this enormous public health achievement, along with overwhelming evidence that mass vaccinations drive down targeted disease incidence and that investments in vaccines bring major societal and economic benefits, the World Health Assembly (WHA) requested WHO to establish the Expanded Programme on Immunization (EPI) in 1974 [13]. During the next few decades, EPI led to increasing vaccination coverage worldwide: In 2020, 87% of children worldwide received at least 1 dose of diphtheria and tetanus toxoids and pertussis-containing vaccine (DTP), and 84% received the routine first dose of measles-containing vaccine (MCV1) [14]. During 2000–2020, the number of countries providing a second dose of measles-containing vaccine (MCV2) nationally through routine immunization services increased from 95 (50%) to 177 (91%) and estimated global MCV2 coverage increased from 18 to 71% [14].

## Effective approaches for improving global vaccination

EPI has evolved and improved based on experience and lessons learned from vaccine-preventable disease eradication and elimination programs that bring valuable focus to the strategic use of disease surveillance and immunization services and inspire innovation to strengthen systems and improve vaccination coverage and equity with all vaccines [15, 16]. Such programs, particularly those for smallpox, polio, measles, and rubella, honed the use of disease surveillance and epidemiology to guide strategic use of vaccines, including mass vaccination campaigns and outbreak response, and led to novel vaccines and delivery for increasing coverage. For example, simplified delivery systems with the use of the bifurcated needle during mass vaccination campaigns and the ring vaccination strategy to contain outbreaks played key roles in the success of smallpox eradication [12, 15]. For polio eradication, evolving programmatic needs led to development of type-specific monovalent and bivalent oral polio vaccines (OPV) with higher efficacy, novel OPV strains with increased genetic stability, and intradermal inactivated polio vaccine (IPV) where only a fraction of the subcutaneous dose is injected into the skin resulting in a lower cost per dose in some settings [16, 17]. Similarly, using a fractional dose of rabies vaccine via the intradermal route proved effective for rabies post-exposure prophylaxis and was approved by WHO in some settings. Measles elimination efforts supported adoption of auto-disabling syringes for improved injection safety and disposal of devices. Targeted disease initiatives set objectives to reach everyone with needed interventions, use disease surveillance to identify and close population immunity gaps, bring innovations for improving delivery of vaccines, and employ special strategies and novel approaches to reach all communities to achieve the high homogeneous population immunity needed to interrupt virus transmission [4, 18, 19].

Increases in global vaccination coverages and reductions in vaccine-preventable diseases were the result of large investments and technical support from donors to countries and implementing partners including WHO and United Nations Children's Fund (UNICEF). The Bill & Melinda Gates Foundation (BMGF) established Gavi, the Vaccine Alliance (Gavi), a public–private global health partnership in 2000 with the goal of increasing access to immunizations and consolidating vaccine purchasing power to support countries and EPI. BMGF also led the Decade of Vaccines initiative that started in 2010 to

extend, by 2020 and beyond, the full benefit of immunizations to all persons. Broad multi-partner disease-specific initiatives like the Global Polio Eradication Initiative (GPEI), established in 1988, and the Measles & Rubella Initiative (M&RI), established in 2001, also directly benefit EPI through advocacy, communications and resource mobilization, and by expanding cold chains, training vaccinators, using data driven vaccination strategies, and driving innovations in vaccine delivery methods.

## Measles and rubella elimination goals and strategic frameworks

In 2001, the M&RI partnership was established with an organizational vision to achieve a world without measles and rubella [20, 21]. The M&RI vision provides an operational raison d'être, aligns investments, and inspires work by countries and partners toward the mission. A global target to eliminate measles and rubella in five of the six WHO regions by 2020 was established in 2012 by the Global Vaccine Action Plan (GVAP) and endorsed by the WHA [22]. In addition to this global goal, countries in all six WHO regions established regional goals for measles elimination, and rubella elimination goals were set in four regions [23]. In August 2020, the 73rd WHA endorsed the *Immunization Agenda 2030: A Global Strategy to Leave No One Behind* (IA2030) [24]. IA2030 reinforces previous commitments, builds on the goals of GVAP and existing disease-specific initiatives, and focuses on health systems strengthening to help achieve these goals. IA2030 emphasizes the need for better delivery systems and uses measles vaccination coverage and measles incidence as indicators to identify communities and age groups that are un- or under-immunized, to focus efforts for strengthening primary healthcare systems and elimination activities [24, 25]. Research and innovation in vaccine delivery is a core strategic priority of IA2030 [24].

Global progress toward measles elimination has faced setbacks in recent years [26], following a period of great success by the M&RI partnership and countries in reducing measles cases and mortality during 2000–2016 [27]. During this period, the global annual number of reported cases decreased from 853,479 to 132,490, and measles incidence declined by 87% from 145 to 19 cases per million population [27]. However, a global resurgence in measles during 2017–2019 led to large outbreaks in countries in the African regions, re-established endemic measles in countries in the Americas and Europe, as well as increased global measles incidence, morbidity, and mortality. In 2019, reported measles cases increased to 869,770, incidence increased to 120 cases per million, and estimated measles deaths were more than 207,500, the largest number since 2006 (Fig. 1). By the end of 2020, 81 (42%) of 194 countries had verified measles

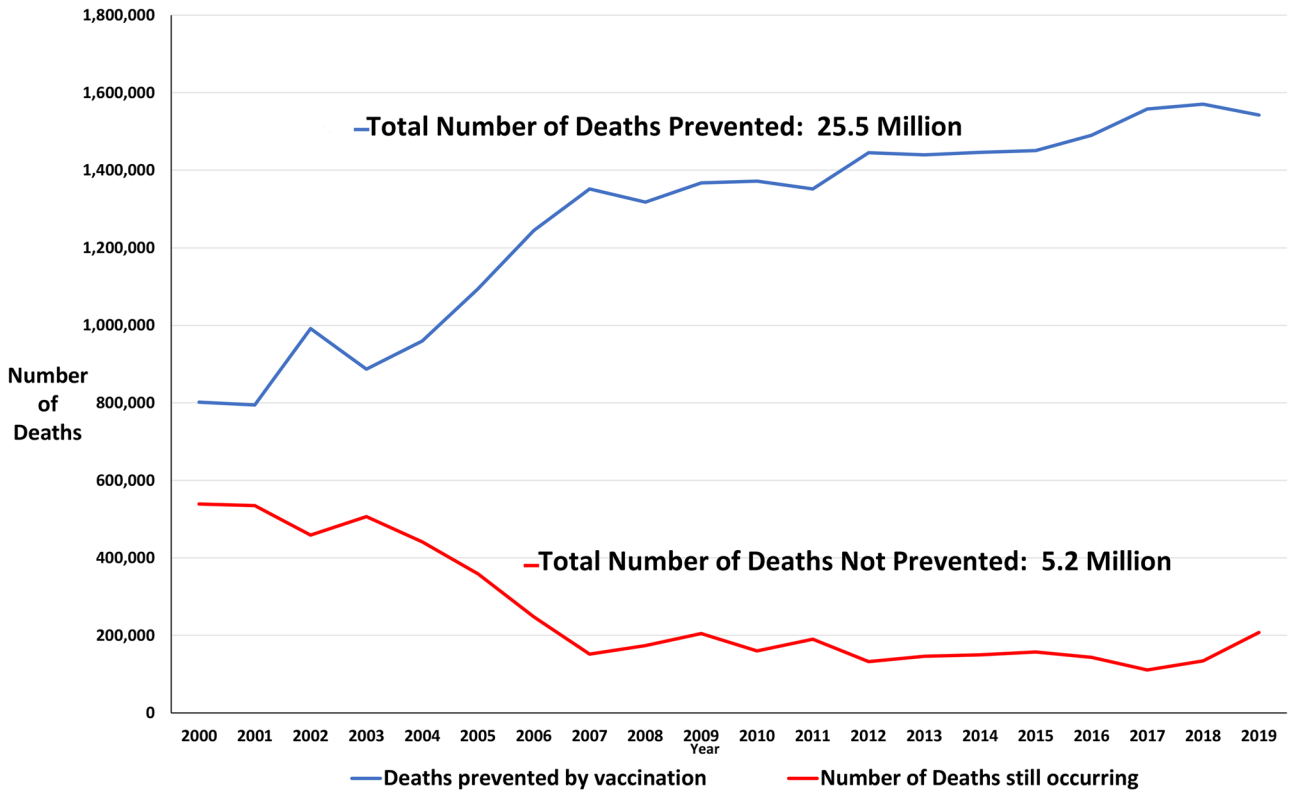


**Fig. 1** Number of Estimated Measles Deaths Prevented by Vaccination Globally and Those Not Prevented, 2000–2019 [23]

elimination [9]; however, measles deaths persist, with annual estimates oscillating around 100,000 since 2013 [28]. These deaths are preventable and unacceptable, highlighting failures in systems to reach all children with immunizations.

To ensure further progress, increased community demand and access to vaccinations, stronger partnerships for strengthening health systems, improved delivery methods, and further investments in innovations that can overcome access barriers to vaccinations are needed [9]. The Mid-term Review of the Global Measles and Rubella Elimination Strategic Plan 2012–2020 concluded that developing new technologies and a better use of data to achieve measles and rubella elimination were necessary to accelerate progress, conclusions that informed the new Measles and Rubella Strategic Framework 2021–2030 [29]. Both the IA2030 and the new Measles and Rubella Strategic Framework strongly emphasize the need for investing in research and innovation for vaccine delivery and elimination efforts [30]. The highest research priorities for measles and rubella elimination consistently include developing new and innovative tools for increasing vaccination coverage; improved delivery methods for MR vaccines remain a long-established and the highest research priority for the program [11, 31–35].

## Limitations for measles and rubella vaccination

Although MR vaccines are safe, highly effective, and well-established within EPI, their delivery poses significant logistical challenges for handling and maintenance of strict continuous cold chain requirements that create missed opportunities for vaccinations (Table 1). Currently available MR vaccines must be given by trained health care workers only, using a specific reconstitution diluent and hypodermic needle and syringe for subcutaneous injection. Although the lyophilized powder vaccine is stable when refrigerated at 2–8 ºC, it becomes very heat- and light-sensitive after it is reconstituted with the diluent before use. Once the vial is opened and the vaccine is reconstituted, the vial and vaccine must be discarded after 6 h, whether the doses were used or not. Vaccinators, particularly in resource-limited settings and low volume clinics, are reluctant to open multi-dose vials when only a few children are present, for fear of vaccine wastage. Also, in some settings, vaccinators near the end of vaccination sessions are sometimes reluctant to open another vial for the remaining few unvaccinated children. This leads to unofficial practices of "batching children" by asking mothers to leave and come back with their child the next day, or next week, or next month when the MR vaccine might be available again. It also leads to MR vaccination sessions not always being available daily, but rather weekly or monthly in some settings.

These practices, especially in settings where caregivers have difficulties bringing their children to the vaccination site, can drive down demand, delay vaccinations, cause invalid doses given too early, or worse, tempt vaccinators to use vaccine from a vial that has been opened for longer than 6 h and is no longer potent or is potentially contaminated and harmful. Multiple injections during the same clinic visit can be a deterrent to vaccine uptake due to pain, emotional distress, and needle phobia, leading to lower vaccination demand and acceptance. Mass vaccination campaigns, including outbreak response, can be challenging in some settings due to a shortage of trained medical personnel to handle and deliver the vaccines that require careful reconstitution, safe injection techniques, and sharps disposal. Human errors during vaccine reconstitution and lack of adherence to strict vaccine storage and handling requirements have led to severe adverse events, including anaphylaxis and death, that are tragic and can erode trust in vaccines [36]. Accidental needle-sticks and needle reuse as well as mishandling of syringes and needles can result in sharps injuries and inadvertent transmission of bloodborne pathogens and disease.

## Delivery strategies for measles and rubella vaccination

In 1997, after experiencing challenges to measles elimination efforts due to the logistical constraints of using currently available MR vaccines, a comprehensive review was published by Cutts et al. that summarized previous studies of measles vaccine serological responses after intradermal, conjunctival, oral, aerosol, and intranasal administration [37]. The review was informed by a wealth of programmatic field experience and lessons learned. Using injectable vaccines during mass campaigns was found to be logistically challenging and resource-intensive compared with using oral vaccines such as OPV that can be simply administered by non-skilled volunteers. Also, the use of needle and syringe for MR vaccine delivery increased cost and requirements for safe disposal and introduced the risk for needlestick injuries and inadvertent transmission of pathogens during campaigns and in routine immunization clinics. The review concluded that further clinical trials should be conducted to evaluate comparative responses to aerosolized, intranasal, and subcutaneous vaccine [37]. Early efforts focused on development of an aerosolized measles vaccine; however, inhalation devices that had to fit over the nose and mouth created practical logistical challenges for administration in young infants and ultimately a phase 3 clinical trial in 2010 found suboptimal immunogenicity [38]. There is still a need for an alternative vaccine delivery system that simplifies logistics and provides non-inferior immunogenicity compared with the current methods. Today, the most promising alternative

**Table 1** Key advantages of measles-rubella microarray patches (MR MAPs) over the currently available measles-rubella (MR) vaccine

| Product characteristic | Constraints of currently available MR vaccine | Key advantages of MR MAPs |
|---|---|---|
| Thermostability | To avoid loss of potency, must be kept in continuous cold chain in the dark at 2–8 ºC; -20 °C for long-term storage a temperature. If stored in a dark place at 2–8 ºC, then shelf life is 24 months from date of last satisfactory potency test | Superior vaccine potency stability and amenable to controlled temperature chain (CTC). Shelf life > 24 months at 2–8 °C, particularly useful for stockpiling. Meeting CTC standards will tolerate at least 40 ºC for a minimum of 3 days (2 months preferred) prior to use |
| | Once reconstituted with the diluent, becomes very heat and light sensitive, and the vial and vaccine **must be discarded after 6 h**, whether the doses were used or not, resulting in vaccine spoilage | Less dependent on cold chain equipment and logistics, extending the reach of routine immunization services and facilitating mass vaccination campaigns, including house-to-house strategies |
| | These strict cold chain requirements lead to missed opportunities for vaccination, particularly in low volume clinics, nomadic and urban poor communities, hard-to-reach areas, and resource-limited settings | |
| Presentation and handling | Supplied as a lyophilized powder vaccine in glass vials that needs reconstitution. Currently only 5- and 10-dose vials are available through the United Nations Children's Fund (UNICEF) supply division | Provided in an integrated (vaccine and patch combination) single-dose, single-use (disposable) format that minimizes wastage and reduces missed opportunities for vaccination |
| | Manufacturers provide a necessary specially designed diluent in a separate vial that must be used to reconstitute the vaccine using a mixing needle and syringe | No reconstitution needed |
| | | No diluent needed |
| | An adequate supply of diluent, devices, needles and syringes, and safety boxes and materials for safe sharps disposal are required | No vials, devices, needles, syringes, safety boxes, or materials for sharps disposal |
| | Diluent must not be frozen but should be kept cool. Water for injection must not be used for this purpose. Using an incorrect diluent may result in damage to the vaccine. Using incorrect diluents due to error has resulted in serious adverse events including deaths | Risks related to reconstitution with wrong, or incorrect use of diluents will be eliminated, and risks related to other types of operational errors should be reduced |
| Administration | Administered by subcutaneous injection using needle and syringe that requires well-trained medical personnel. An adequate workforce of well-trained medical personnel is a limiting factor for mass vaccination in some resource-limited settings | Ideally suited for vaccine delivery through routine sessions, mass campaigns, and outbreak response due to ease of use and simplified logistics |
| | | Will facilitate efforts to increase demand and access to vaccines, and coverage by reaching everyone, particularly in settings with weak health systems and hard-to-reach communities |
| | The pain associated with the injection can be a deterrent for vaccine acceptance | |
| Sharps waste and disposal | After administration, the trained medical personnel must safely dispose of used needles and syringes as sharps and biohazard waste. Safe disposal of the used diluent vials, mixing syringes, and needles is required. Disposal of bulk medical waste is a significant burden, particularly in resource-limited settings | Will be acceptable as biohazardous waste and not considered sharps waste. No sharps handling or waste, and overall lower volume with minimal environmental impact of waste disposal |
| | | No needle sticks, no re-use of needles or syringes, or inadvertent transmission of bloodborne pathogens |
| Package size | Cold chain storage volume per dose is 2.11 cubic centimeters ($cm^3$) for 10-dose vials and 3.14 $cm^3$ for diluent. Very difficult to determine visually how many doses are left in multi-dose vial after reconstitution | Much smaller and lighter, saving on cold chain space and shipping costs; can easily visualize the number of remaining doses |
| Immunogenicity | Seroconversion = 89.6% (interquartile range [IQR] 82–95) when vaccinated at 8–9 months of age; 92.2% (IQR 59–100) at 9–10 months; and 99% (IQR 95.7–100) at 11–12 months | A non-inferiority margin to be determined a priori for phase 3 clinical trial in consultation with regulatory agencies and program implementing partners. Potential dose-sparing and fractional dose with intradermal delivery |

Table adapted from the World Health Organization Measles-Rubella Microarray Patch Working Group defined target product profile published in 2019 as a guide for MR vaccine patch developers [48]; additional characteristics and costs expected to be at least similar in MR-MAPs

delivery method for vaccination is subcutaneous delivery using small adhesive patches that insert an array of hundreds to thousands of micro-projections with vaccine into the skin when applied; these are generally referred to as microneedle patches or microarray patches (MAPs) [39].

## Micro-array patches (MAPs): a leading technology for global vaccination

The huge advantages of MAPs compared with current methods for vaccination are now widely recognized by all immunization partners [40–42]. MAPs offer thermostability that would untether the vaccine from the strict continuous cold chain requirements and extend vaccination services to rural communities and hard-to-reach areas (Table). That huge advantage, along with completely removing the need for needle and syringe subcutaneous injection, makes MAPs a complete game-changer for increasing vaccination coverage and elimination efforts. The lack of sharps waste, reduced cold chain requirements, and simplified logistics allowing for administration by community volunteers will greatly facilitate routine outreach services and mass vaccination campaigns with house-to-house vaccination that are periodically needed in areas where systems fail to routinely reach everyone. MAPs have been in development by many academic and biotech laboratories for more than two decades, and there have been at least 31 published randomized controlled trials including two phase 3 clinical trials (parathyroid hormone for osteoporosis and zolmitriptan for acute migraine) evaluating MAPs for drug delivery [43]. However, only a few candidate vaccine MAPs have entered human clinical studies [39].

The recent alignment of priorities and investments among immunization partners for innovations is truly inspiring and could lead to the further development, licensure, and global use of this important new tool that enhances global public health work to save lives [44]. In 2015, the BMGF sponsored a meeting in Geneva that brought together immunization partners, patch developers, regulators, and large pharmaceutical companies to further understand the critical pathway from preclinical development and clinical trials to licensure and manufacturing. In 2016, after reviewing pre-clinical assessment results and potential impact on increasing access to vaccinations and reducing missed opportunities for vaccination, the WHO SAGE recommended that the most expeditious clinical development and regulatory pathway to licensure of MR MAPs be determined and that barriers to the development, licensure, and use of MAPs for MR vaccine delivery be identified and addressed urgently [45]. CDC has supported development of this vaccination technology through ongoing public–private partnerships for more than a decade, initially for IPV, measles vaccine, and measles-rubella vaccine, and later for several additional vaccines.

In 2018, the Gavi Secretariat, WHO, BMGF, UNICEF, and PATH established the Vaccine Innovation Prioritisation Strategy (VIPS) Alliance to develop a framework to evaluate, prioritize, and drive forward vaccine product innovations [46]. VIPS conducted a process to identify and prioritize the top three vaccine product innovations with the greatest potential to achieve vaccination coverage equity and improve immunization systems. VIPS identified [1] MAPs, [2] heat-stable formulations for controlled temperature chain, and [3] barcoding on primary containers as the top three priorities [46]. They concluded that MAPs were the highest priority as they are potentially "transformational" innovations that could overcome immunization barriers identified by low- and middle-income countries [46]. In 2019, PATH established a Center of Excellence for Microarray Patch Technology as a four-year initiative to mobilize efforts to accelerate the development of MAPs to meet global public health needs and a Regulatory Working Group to identify target product profiles and standards for regulatory filings and assess MAPs manufacturing methods [47].

Also in 2018, the WHO Immunization Practices Advisory Committee formed the Measles-Rubella MAP Working Group [48] that developed a defined target product profile as a guide for MR vaccine patch developers [49]. In 2016, BMGF issued a solicitation for proposals to develop MR MAPs and awarded grants to the Georgia Tech–CDC–Micron Biomedical collaboration, to Vaxxas, and to Vaxess Technologies. The first two of these groups have moved ahead and started first-in-human phase 1 clinical trials with preliminary results expected in 2022. The Micron Biomedical MR patch is currently in a phase 1/2 clinical trial underway at the Medical Research Council in The Gambia. Other MAPs for IPV, human papilloma virus, rabies, rotavirus, and hepatitis B vaccines tetanus toxoid, Bacille Calmette-Guérin, diphtheria, and anthrax are in preclinical development [39, 49–52]. With recognition that vaccine MAPs would be a powerful tool for pandemic preparedness and response, two successful phase 1 clinical trials of seasonal influenza MAP vaccines were completed, one by Micron Biomedical and one by Vaxxas [50, 53]. A SARS-CoV-2 MAP is in pre-clinical development, and MAPs for other new vaccines for potential emerging pathogens are being considered. For translational innovations to succeed, partnerships between technology developers and public health program implementers should start early in the development pathway. This will ensure that products are fit-for-purpose, investment cases are clear, and advocacy reaches the right places to make the critical pathway to product licensure efficient and without delay.

These promising translational innovations highlight the power of partnerships, including early close collaboration

between novel drug delivery technology developers and public health program implementers and leaders; the importance of having clear goals and an established organizational vision statement; and the need for steadfast pursuit of that vision, especially during times when experiencing setbacks. Ongoing global efforts to eliminate measles and rubella would be greatly facilitated by the availability of MR MAPs, enhancing efforts to increase vaccination coverage and equity, particularly in settings where children are in greatest need. MAPs have the potential to enhance all immunizations strategies, not only the house-to-house campaigns in hard-to-reach areas and outbreak response, but also in routine clinics for ongoing immunization services delivery. MAPs have the potential to significantly contribute to IA2030 priorities including increasing vaccine access and demand, coverage, and equity with vaccinations across the life-course, and reaching zero-dose children to ensure that no one gets left behind [21, 24, 46]. The successful use of MR MAPs also could kick open the door for other vaccine MAPs that are in the development pipeline. There is plenty more work to be done including careful evaluation of safety and immunogenicity of MR MAPs. If proven to be safe and effective, then large investments and commitments will be needed for manufacturing plants for mass production to establish a predictable and sustainable global supply. These hurdles to realizing a potentially transformational innovation can be cleared with strong partnerships between vaccine delivery technology developers, public health agencies, and donors to work on important global health problems and find solutions like the promising MR MAPs that could propel efforts toward achieving measles and rubella elimination goals. These partnerships for improved vaccine delivery are essential for efforts to ensure everyone, everywhere, at every age, fully benefits from vaccinations for good health and well-being [21, 24, 46].

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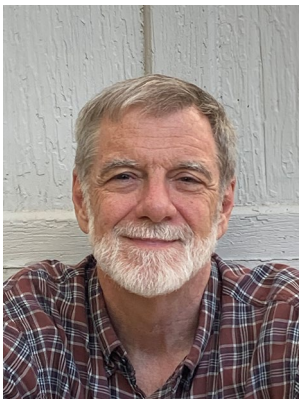

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