HHS Public Access

Author manuscript

Trans R Soc Trop Med Hyg. Author manuscript; available in PMC 2023 June 02.

Published in final edited form as:

Trans R Soc Trop Med Hyg. 2017 February 01; 111(2): 41–42. doi:10.1093/trstmh/trx018.

Time for an immunisation paradigm shift

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Keywords

Eradication; Immunisation; Measles; Microarray patch; Rubella; Syringes; Vaccination

We are approaching a tipping point in measles history where the world community must decide on whether to pursue a global eradication goal. Considerable progress has been made to reduce this deadly scourge globally; increasing vaccination coverage is estimated to have saved 4.2 million lives during 2012–2014 alone.[1] However, tragically, nearly a fifth of every global birth cohort misses out on measles vaccination, and measles remains a major cause of childhood mortality.[2] Although every WHO region has a goal to eliminate measles on or before 2020, a recent midterm review of the Global Measles and Rubella Strategic Plan reported progress was not on track.[1]

The Region of the Americas eliminated measles using the currently available heat-sensitive, lyophilised measles-containing vaccine and needle-and-syringe delivery instrument for subcutaneous injection.[3] Technically, measles eradication should be feasible globally with these same tools. Given high transmissibility of measles virus, to achieve elimination, health services must reach ≥95% of children with vaccine, including the socio-economically marginalised, geographically remote, and mobile and politically disenfranchised. Sadly, this high coverage is not achieved, and doing more of the same without innovation will continue leaving vulnerable children unprotected. This reality was recognised at the 2016 Global Vaccine and Immunization Research Forum, where new vaccine delivery tools were deemed ‘critical’ and a ‘potential game-changer’ in measles elimination efforts.[4]

The design of our current ‘delivery instruments’ is generally attributed to Scottish surgeon Alexander Wood, who combined a hollow steel needle with a syringe into a hypodermic instrument for injecting morphine in 1853. However, the concept goes back 200 years earlier when Blaise Pascal, a French mathematician, physicist and inventor, applied

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Authors’ contributions: DND and JLG wrote the paper and read and agreed the final version. DND is guarantor of the paper

Competing interests: None declared.

Disclaimer: The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry.

his understanding of barometric pressure to design a syringe that strikingly resembles instruments used today. The first mass-produced disposable glass syringe and needle was marketed in 1954. In 1956, a New Zealand pharmacist, Colin Murdoch, patented disposable plastic syringes to replace glass syringes. The recognition of blood borne pathogen infections, particularly HIV, and the potential for transmission by needle and syringe reuse prompted Australian plastic surgeon, Colin Moore, to design a non-reusable syringe in 2000. Use of non-reusable syringes in the global Expanded Programme on Immunisation has been the only remarkable change to the fundamental design of vaccine delivery instruments since the programme was launched in 1974.

While the high protective efficacy of properly handled measles vaccines and currently available delivery instruments are lauded, they have inherent shortcomings. Although lyophilised powder vaccine is stable when refrigerated at 2–8°C, once reconstituted, it is exquisitely heat and light sensitive, with exposure resulting in rapid reduction in potency; therefore, reconstituted vaccine must be discarded within 6 hours. The need for constant refrigeration is a major challenge to immunisation programmes in many developing countries. Logistics and storage volume challenges are compounded by the need for additional reconstitution needles and syringes for mixing diluent and vaccine. Add to this the reality that multi-dose vials, commonly used to reduce cost, lead to missed opportunities for timely vaccination due to reluctance of immunisers to open a vial for a small number of children, and the need for a new vaccine formulation and new delivery techniques becomes obvious.

Due to the injectable nature of measles vaccine, skilled health workers, predominantly nurses, are the gatekeepers to vaccination, and strict injection safety and sharps disposal precautions must be followed.[5] Reuse of syringes and needles can result in transmission of bloodborne pathogens, and mishandling of needles can result in sharps injuries. Improper injection techniques are accompanied by a greater risk of adverse events, pain and negative community perceptions; and needle phobia and injection pain can deter vaccination acceptance. Injectable measles vaccine is also liable to human error during reconstitution with incorrect diluents and potentially tragic consequences.[6]

Enter Mark Prausnitz, a chemical engineer, and his team at Georgia Tech who have developed a microarray patch containing 100 microscopic vaccine-embedded water-soluble polymer cones, each approximately the width of a human hair with a sharp tip about the size of a cell, that simply dissolve into the skin within minutes after patch application. They deliver vaccine through the skin without reaching the sensory nerve cells responsible for pain and can be easily administered by minimally trained personnel or possibly self-administered. The microarray patches maintain potency after storage at elevated temperature, demonstrating improved thermostability compared with standard lyophilised vaccine, with full potency for almost 4 months at 25°C, and less than 10-fold decrease in potency after almost 4 months at 40°C.[7] Microarray patches eliminate the risk of sharps injuries, since microarrays dissolve and no sharps remain, and bio-waste disposal requirements are markedly reduced.

But would a vaccination strategy using microarray patches actually provide immunological protection against measles, would it be acceptable to the public and is it affordable?

The immunological response to microarray patches containing the standard dose of measles vaccine (~1000 $TCID_{50}$) was compared with subcutaneous injection in rhesus macaques. Both groups generated protective and equivalent measles neutralising antibody titres.[7] In a recent trial of influenza vaccination, the safety and immunogenicity profiles were similar between microarray patch and intramuscular injection groups (Rouphael et al. Personal communication. 2017). Based on promising results, additional human clinical trials are planned to confirm immunological non-inferiority.

In the context of seasonal influenza vaccination, 51% of people who usually accepted vaccination stated a mild or marked preference to receive vaccine through a microarray patch rather than conventional intramuscular injection; and among those who would normally not be vaccinated, 38% would accept vaccination if provided by microarray patch.[8] A recent phase 1 clinical trial of influenza vaccination showed that microarray patches were strongly preferred (>70%) compared to intramuscular injection (Rouphael et al. Personal communication. 2017).

Recent work suggests microarray patch vaccination could cost less than subcutaneous injection,[9] and a separate analysis concluded that microarray patch vaccination would be cost effective in seasonal influenza vaccination.[10] Accurate costeffectiveness calculations will need to wait for vaccine effectiveness studies in humans.

Change is always met by obstacles. Donors and regulators could facilitate progress by seeking expedited product development pathways to licensure.[11] Multinational vaccine producers might be concerned if microarray patches are viewed as disruptive or having prohibitive start-up costs to re-tool production lines. To allay these concerns, vaccine producers could participate in product development partnerships with public stakeholders to develop business plans for initial investments in manufacturing infrastructure, market shaping and careful demand forecasting to de-risk the process and reassure investors of returns.

The availability of microarray patches could offer a renaissance moment in the global effort to eliminate measles and reach unreached children with life-saving and disability preventing vaccines. By improving thermostability, removing the need for vaccine reconstitution before administration and eliminating needle stick injuries associated with measles vaccination, potent vaccine on microneedle patches could be a game changer for equitable access to measles vaccination for all children globally.

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