Opportunities in needle-free vaccine formulation

On 31 May 2022, the Future Vaccine Manufacturing Research Hub (the 'Vax-Hub) held an online sandpit workshop to discuss the needle-free administration routes for vaccines, the potential benefits that these might offer, and how the Vax-Hub should prioritise formulation studies in the next phase of their research. The workshop brought together the Vax-Hub team with a range of national and international stakeholders involved in vaccine development, manufacturing, delivery, and policy.

Context

The majority of vaccines are administered as a liquid via injection with a needle and syringe. Whilst this has proven to be an incredibly effective and reliable strategy - COVID-19 vaccines (whose delivery has thus far been limited to intramuscular injection) are estimated to have prevented 19.8 million deaths worldwide in their first year,[1] - there are certain limitations associated with this administration route. Needle stick injuries are a serious occupational hazard for healthcare workers, and vaccines in a liquid form must typically be maintained in a cold chain to prevent degradation, reducing their access to hard-to-reach populations, particularly in low and middle-income countries (LMICs). Improving the thermostability of vaccines and thus avoiding the need for complex cold chain infrastructure was identified as the top priority for innovation by a consultation process run by Gavi on barriers to immunisation as part of their Vaccine Innovation Prioritisation Strategy (VIPS).[2]

Adopting needle-free technologies such as tablets, nasal sprays, and microarray patches could lead to greater-shelf life and better temperature stability vaccines that are easy to administer. These attributes could be particularly impactful for vaccination programmes in LMICs, enabling more people to be vaccinated in remote and challenging settings.

Key points

1. Adopting needle-free technologies such as tablets, inhalers, and microarray patches could lead to greater-shelf life and better temperature stability vaccines that are easy to administer.
2. Although needle-free administration routes are promising, there remain challenges to be overcome in efficacy, regulation, cost and manufacturability
3. To have the largest impact on global supply chains and vaccine availability, a primary goal for vaccine formulation should be achieving better thermostability for storage at ambient temperatures.

The Vax-Hub

The Vax-Hub is a five-year research programme (2018-2023) funded by the UK's Department of Health and Social Care's Official Development Assistance programme, the UK Vaccine Network. The Vax-Hub's mission is to secure supply of essential vaccines to LMICs.

At the time of writing, the team are planning a succession "Vax-Hub 2" in order to continue the important work undertaken by our team throughout the first Hub. Process development studies using single-use technologies as well as next-generation sequencing methods have enabled rapid process development of the ChAdOx-1 viral vector vaccine, more than 2.8 billion doses of which have now been delivered worldwide.

"We are very excited to be a translational spoke within the Vaccine Manufacturing Hub and to collaborate with the team on developing new technologies to improve the expression of our Dengue vaccine, shorten development times and benefit from economic models to achieve low costs."

- PT Biofarma Indonesia

The workshop

The aim of this workshop was to identify the key challenges in vaccine formulation, particularly for needle-free administration routes, and consider how these challenges should be addressed for the Vax-Hub platforms of virus-like particles (VLPs), viral vectors and glycoconjugate vaccines in a future research programme, "Vax-Hub 2". To prepare participants for the ensuing discussions, presentations were provided by:

- The Vax-Hub, who informed participants of recently commenced needle-free formulation research being undertaken in the first Hub, which focused on mucosal administration via the buccal (in the cheek) and sublingual (under the tongue) routes;
- The Coalition for Epidemic Preparedness (CEPI), who shared insights on the ways in which needle-free formulation could affect the development speed and access to vaccines against new pathogens, as well as information on their funding opportunities in this area;[3]
- PATH, who shared insights on the current opportunities and challenges for needle-free vaccination routes, including in pre-clinical development, regulatory approval, scale-up, and manufacturing; and
- Dr Han Fu from the London School of Hygiene and Tropical Medicine who shared highlights of their work into early-stage economic evaluation for future vaccine delivery technologies.

This report summarises the discussions from the three questions put to our participants, namely: what attributes would be desirable for a vaccine to be widely accessible, which administration routes the should the Vax-Hub prioritise, and how cost-effectiveness of different administration routes should be considered. The report also highlights possible formulation research activities for the Hub to take forward in a future research programme.

What would be the attributes of an ideally formulated vaccine and what is holding us back from achieving this?

Thermostability was by far and away the most commonly desired characteristic for a vaccine, which is unsurprising given the emergence and use of mRNA vaccines during the COVID-19 pandemic which must be stored at -80 to -60°C (Pfizer-BioNTech) and -25 to 15°C (Moderna), where the cold chain in most LMICs are geared for the 2 to 8°C temperatures required for most routine vaccines.[4] In addition to more temperature-stable vaccines, participants also considered the following factors in designing an ideal vaccine:

- Transportation and storage. Vaccines would ideally be light, compact and easy to transport and distribute. Visual indicators could be used to indicate whether the vaccine had experienced conditions that would lead to a decrease in potency.
- The mode of administration. A vaccine with high utility would ideally be a single dose, which is painless and easy to administer by a non-medical professional, producing no sharps waste. Some participants felt that self-administered vaccines

would be desirable, especially for use in remote locations or during a pandemic, however, it was also noted that ensuring compliance with self-administered vaccines would be difficult.

- The cost and ease of manufacture. Ideally, the cost of goods would be low, and the manufacturing process simple and transferrable to LMICs for local manufacture.
- Some participants raised that further innovation was required for effective adjuvants, particularly for mucosal delivery.

Which vaccine administration routes should the Vax-Hub prioritise and do you see any gaps in our current plans?

Whilst many needle-free vaccines are in a solid formation (e.g. tablets, microarray patches etc.) and hence tend to be thermostable, some participants felt that thermostability and shelf-life should be prioritised over the actual administration route as this would reduce the amount of waste, with fewer overages required. Greater thermostability would resolve many of the access issues in LMICs where the cold chain remains a barrier in some regions. On needle-free formulations, the following insights were shared:

- There remain questions around different needle-free administration routes, largely due to their technological immaturity. Innovation in excipients (a constituent of a medicine other than the active substance, added in the formulation for a specific purpose) , adjuvants (an ingredient used in some vaccines that helps create a stronger immune response in people receiving the vaccine), manufacturing processes including enhancing ease and scalability is required, along with considerations on determining suitable animal models to demonstrate efficacy. Additionally, new regulatory pathways would be required for these novel products and so working with regulators at an early stage of product development would be vital. Novel correlates of protection will be required, after identification and development of suitable immunoassays. Participants did feel however that the potential benefits would outweigh these challenges and the enhanced vaccine profiles could make needle-free products suitable for hard-to-reach populations, for stockpiling and during outbreak scenarios.
- Some participants felt that there would be opportunities to “platform” vaccine formulation along with vaccine design. Using a plug-and-play as is pursued in the Vax-Hub would allow rapid developments for a wide range of existing and emerging pathogens.
- Understanding user-acceptability and patient preferences for new administration routes would be important: for example, would taste masking be required for orally administered vaccines? Additionally, suitability for LMIC use should be paramount.

Participant list by organisation

The workshop brought together 15 participants from the following organisations:

- BiologicalE
- Cardiff University
- Coalition for Epidemic Preparedness Innovations (CEPI)
- The Department for Business, Energy and Industrial Strategy (Vaccine Taskforce)
- The London School for Hygiene and Tropical Medicine
- PATH
- Unicef
- Vax-Hub
- World Health Organization (WHO)
- Wellcome

A number of different routes are being investigated for administration of needle-free vaccines, including nasal sprays, buccal (in the cheek), sublingual (under the tongue), and dermal, for example microarray patches, a key technology in Gavi’s Vaccine Innovation Prioritisation Strategy

References

1. Imperial College, "Vaccinations may have prevented almost 20 million COVID-19 deaths worldwide". www.imperial.ac.uk/news/237591/vaccinations-have-prevented-almost-20-million/ (accessed 18 July 2022)
2. Gavi, The Vaccine Innovation Prioritisation Strategy (VIPS). www.gavi.org/our-alliance/market-shaping/vaccine-innovation-prioritisation-strategy (accessed 18 July 2022)
3. CEPI, Call for Proposals: Innovative technologies to improve vaccine thermostability. cepi.net/wp-content/uploads/2022/01/CfP-thermostability_Jan2022_CallText.pdf (accessed on 18 July 2022)
4. McKinsey, Port to patient: Improving country cold chains for COVID-19 vaccines, www.mckinsey.com/industries/public-and-social-sector/our-insights/port-to-patient-improving-country-cold-chains-for-covid-19-vaccines (accessed 18 July 2022)

How much of a factor should cost-effectiveness be when developing needle-free vaccine administration technologies?

Participants were asked to consider the cost-effectiveness of alternative vaccine delivery routes, and whilst some felt that proving efficacy should be the primary goal when developing new technologies, others felt that the cost of goods (COGs) should be embedded in the target product profile (TPP) to ensure that these are kept low. There were also questions around the extent to which the development pipeline would contribute to the price of a new type of product. Other key points that were raised included:

- The need to take into account acceptability and vaccine hesitancy when planning product portfolios.
- To keep costs down, low-cost starting materials and manufacturing methods should be targeted.
- Integration of economic modelling into Vax-Hub's work on needle-free formulation would assist with decision-making. For example, would the goal of the new products be to be adjacent to standard needle and syringe vaccines thereby giving access to a new population, or would they be intended to replace them all together.

Conclusion and next steps

Whilst needle-free vaccine administration of vaccines promises to give access to hard-to-reach populations around the world, there remain challenges to be overcome in efficacy, regulation, cost and manufacturability. To have the largest impact on global supply chains and vaccine availability, a primary goal should be to achieve more thermostable vaccine products. Organisations such as the Vax-Hub can make important contributions in this regard on innovation, however any technological efforts should be combined with understanding the target populations and acceptability of new vaccine types, as well as the costs, planning for this early in the development phase. The Vax-Hub will use the ideas generated in this workshop to inform the activities in their research proposal for a Vax-Hub 2 to continue and build on activities from the first research cycle. This proposal is being developed in Spring/Summer 2022.

Our research

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To find out more, please visit: https://www.ucl.ac.uk/biochemical-engineering/research/research-and-training-centres/vax-hub

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