PREPARING FOR MASS VACCINATION

In this article, Andy Fry, Founder, and Stephen Blatcher, PhD, Head of Early-Stage MedTech, both of Team Consulting, discuss the need for a mass vaccination device in response to the ongoing covid-19 pandemic. In particular, the authors discuss the benefits and challenges of turning to needle-free injection technology as a solution.

There are currently multiple covid-19 vaccine development programmes running across the world. Hopefully, some of these will shortly be approved for use and will have a major impact on the current pandemic. In parallel, significant investment is being made by governments and non-profit organisations to build adequate capacity for the delivery and administration of such vaccines at both the national and global scale.[1] With potentially hundreds of millions of doses to be administered annually, it is important to think carefully about the platform that will be used for covid-19 vaccine delivery.

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The low cost and ready availability of hypodermic syringes makes them immediately attractive, but the cost burden of needlestick injuries cannot be ignored. Needle-free injection eliminates this risk and, when designed appropriately, enables safe, targeted and reproducible dermal delivery. Furthermore, needle-free delivery is independent of viscosity and hence independent of the flow characteristics of a vaccine. With so many candidate vaccines in development, there is potential to scale needle-free technologies in parallel with ongoing vaccine development programmes, safe in the knowledge that it has maximum potential to reliably deliver whichever vaccine(s) are proven to be effective.

CURRENT STATUS OF COVID-19 VACCINE DEVELOPMENTS

According to a report by The Lancet, there were already 10 SARS-CoV-2 vaccine candidates in clinical trials as of June 2020.[2] These include: mRNA vaccines such as the lipid nanoparticle-encapsulated vaccines mRNA-1273 (Moderna and the US NIH National Institute of Allergy and Infectious Diseases) and BNT162 (BioNTech and Pfizer); DNA vaccines such as INO-4800 (Inovio Pharmaceuticals), the delivery of which is enabled by a brief electrical pulse from the company's hand-held smart device, CELLECTRA, to open small pores in the cell reversibly to allow the plasmids to enter; an unnamed inactivated viral vaccine (Wuhan Institute of Biological Products and Sinopharm); protein subunits such as NVX-CoV2373 (Novavax), which uses Novavax's proprietary nanoparticle technology, Matrix-M; and an adenovirus vaccine, AZD1222 (under development by University of Oxford spinout Vaccitech, and AstraZeneca, with manufacturing support from Catalent's Cell & Gene Therapy division). Operation Warp Speed is underway and many more candidates are now in clinical trials.[3]

The Lancet report suggests that the average development time for a vaccine is 10 years, but the hope is that current life science tools can shorten the process to allow covid-19 vaccines to be delivered in 2020. It highlights that the typical success rate for vaccine development is only 6% and that even an 18-month development programme is considered very aggressive by infection experts. The report also warns that "global appetite for any successful vaccines, if and when they are ready, will bring its own difficulties. Developers are starting to scale up production even now, despite the risk that their favoured candidates will fall short. Distribution, delivery and administration need to be worked out."

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DELIVERY PLATFORMS FOR VACCINE ADMINISTRATION

Many people will have experienced annual influenza vaccinations being administered by intramuscular injection (generally used for adults) or by nasal delivery (generally used for children). These are the most common methods of vaccine administration and a review of covid-19 vaccine trials on ClinicalTrials.gov shows that, for a sample of 17 studies, the following administration methods were cited:

- Intramuscular injection (nine studies)
- Intradermal injection (two studies)
- Subcutaneous injection (two studies)
- Electroporation via the Cellectra 2000 (one study)
- IV infusions (one study)
- Not cited (two studies).

It is clear that parenteral delivery via hypodermic syringe remains the administration method of choice. Although the convenience and cost advantages of hypodermic syringes are undeniable, there is a strong case to be made that a better delivery platform exists to meet the unprecedented demand for rapid global mass vaccination against covid-19.

THE CASE FOR NEEDLE-FREE INJECTION

When appropriately configured, needle-free injection offers compelling advantages over hypodermic syringe delivery as a platform for mass vaccination. These advantages include:

- Dose sparing through intradermal efficiencies
- Reliable intradermal delivery
- Elimination of needlestick and re-use
- Insensitivity to vaccine flow characteristics
- Attractive healthcare economics.

The following sections cover each advantage listed in greater detail.

Dose Sparing Through Intradermal Efficiencies

Intradermal injection is a shallow injection of a substance into the dermis, which can be easily and reliably achieved with needle-free technology, as detailed in the next section. The dermis and epidermis of human skin are rich in antigen-presenting cells. As such, focusing the delivery of vaccines to these layers – rather than to muscle or subcutaneous tissue – should be more efficient, inducing protective immune responses with smaller amounts of vaccine antigen.

The potential benefit of dose efficiency through intradermal delivery has long been recognised,[4] with the WHO bulletin presciently stating that dose sparing might also "stretch" the availability of vaccines in cases where supply is limited by manufacturing capacity. This is probably most relevant for pandemic influenza vaccines where global production capacity limits access to a vaccine at the start of a pandemic. In 2009, the H1N1 vaccine was not available in most low-income countries until eight months after the WHO's declaration of the influenza pandemic.

Currently, no country in the world has access to a covid-19 vaccine and hence developing a delivery system that allows efficient vaccine dosing is a key early consideration.

Reliable Intradermal Delivery

The traditional procedure for intradermal delivery is needle-based injection via the Mantoux procedure, which involves injecting at an angle of administration of 5–15° (i.e. almost holding the syringe against the skin). With the bevel of the needle pointing upwards, the needle is inserted approximately 3 mm into the skin and the injection performed while watching for a small wheal or blister to appear. This procedure is most commonly used in BCG tuberculosis vaccinations.

The degree of needle control necessary in the Mantoux procedure requires careful delivery by the clinician and a high level of co-operation from the patient to ensure reliable intradermal delivery. In needle-free delivery, the substance being injected acts as the needle and hence, by controlling the dose volume and skin contact pressure, it is possible to achieve intradermal delivery easily and reliably.

One simple approach is the addition of a simple ring around the nozzle of a needle-free injector. This causes a dome of skin to reliably engage the nozzle of the injector, and also allows space for the skin to lift up into the characteristic blister or wheal that is generated by successful intradermal delivery. Figure 1 shows successful intradermal delivery achieved by a DosePro® (Zogenix, Emeryville, CA, US) needle-free device modified with a simple polycarbonate intradermal spacer component.

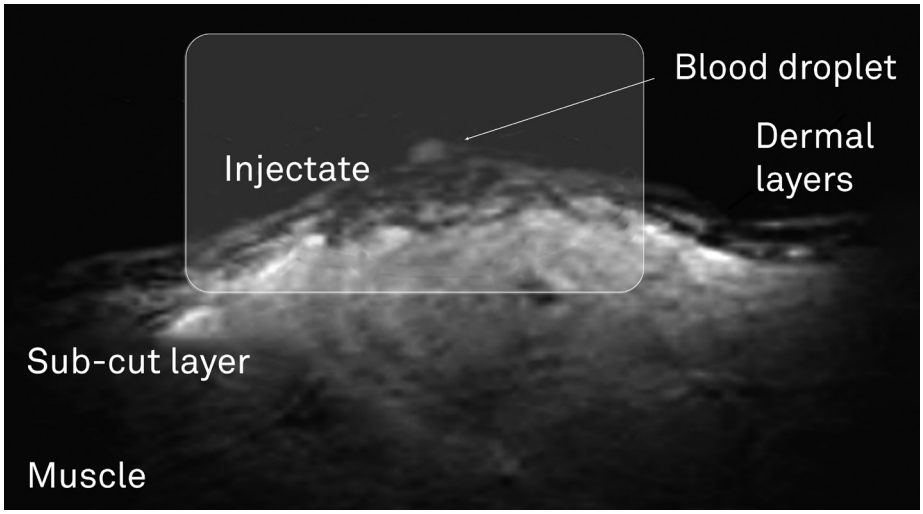


Figure 1: Successful intradermal delivery achieved by a DosePro needle-free device modified with a simple polycarbonate intradermal spacer component.

Elimination of Needlestick and Re-Use

A well-recognised advantage of needle-free delivery is the avoidance of needlestick injuries and the associated healthcare and societal costs that arise from them. Furthermore, disposable vaccine capsules provide single-use advantages, such as that any body fluids picked up from contact with a patient's intradermal blister will not be transferred to the next patient.

In a recent covid-19 webinar from PATH[5] (Seattle, WA, US) it was predicted that, in developing countries, the disruption in services from covid-19 isolation would knock progress in treating HIV, TB and malaria back by five years. Vaccination programmes for vulnerable groups will be a high priority in these countries. A needle-free injector with single-use, dose-efficient vaccine capsules offers the potential for safer, more reliable and lower-cost vaccination programmes in these vulnerable patient groups.

Insensitivity to Vaccine Flow Characteristics

A further advantage of needle-free injection is that the intradermal delivery performance is independent of the flow characteristics of the substance being delivered. As shown in Figure 2, for a conventional hypodermic syringe and needle, flow rate is characterised by the Hagen-Poiseuille equation, where:

- Q = flow rate
- D = needle bore
- L = needle length
- P = drive pressure
- μ = dynamic viscosity.

However, for a needle-free injector, as shown in Figure 3, delivery is through an orifice. Here, the flow is characterised by the Bernoulli equation, where:

- Q = flow rate
- D = orifice bore
- P = drive pressure
- ρ = density
- Cf = flow coefficient (0.95 for a practical round edged orifice).

The only fluid property which appears in the Hagen-Poiseille equation is μ, dynamic viscosity. The only fluid property which appears in the Bernoulli equation is ρ, density. For a conventional needle and syringe, it can be seen from the Hagen-Poiseuille equation that for any increase in viscosity, μ, an increase in pressure (i.e. an increase in the syringe plunger force) will be required to maintain the same flow rate.

However, when considering a needle-free injector, there is no viscosity term and, for the range of fluids of interest, the only property which affects the flow rate is density, ρ. Since most fluids of interest as injectables have approximately the same density, the pressure to deliver at a given flow rate, and hence the plunger force, will remain unchanged. This unique property makes it viable to scale the technology in parallel to ongoing vaccine development programmes, safe in the knowledge that it will tolerate different vaccine viscosities and hence should be capable of reliably delivering whichever vaccines are proven to be most effective.

Attractive Healthcare Economics

Needle-free injection relies upon a very high jet velocity; therefore, the pressure and operating force is much higher. Hence, all needle-free technologies rely upon a stored energy source, rather than unaided manual operation. Although this adds expense to the unit device cost (the unit cost of standard hypodermic syringes will always be cheaper), the potential benefits of reliable, safe, dose-efficient, needle-free delivery systems remain compelling from a healthcare economics perspective.

As highlighted previously, the ability to eliminate needlestick injuries is a significant economic benefit. The annual cost of treating needlestick injuries in hospital workers alone is as high as US$591 million (£458 million) in the US, $302 million (£234 million) in Japan and $900,000 (£698,000) in the UK.[6] These represent developed countries with the highest levels of training and resources available. covid-19 is a global pandemic, therefore the cost burden of needlestick injuries is likely to be far higher.

Based on work by Team Consulting, it is feasible to develop mass vaccination needle-free injectors where the cost of re-use is limited to a prefilled single-shot vaccine cartridge. One concept involves vaccines being dispensed from the low-volume single-shot, non-reusable capsule using a robust, high duty cycle, multi-use actuator device.

The Sumavel (sumatriptan) DosePro is a factory-filled, single-use needle-free injection product, which was approved in the US, UK and Germany for needle-free delivery of sumatriptan for migraine relief. Figure 4 shows a self-powered variant based on a system developed and proven in clinical trials in the early 2000s by Team Consulting – alongside a leading veterinary medicine company – for vaccination of farm animals. It is powered by a small reservoir of butane/propane fuel, similar in size to a cigarette lighter. The farm animal version was much like a power drill in size and appearance, but a scaled-down human-use version

Needle and syringe

$$Q = \frac{\pi D^4 P}{128 \mu L}$$

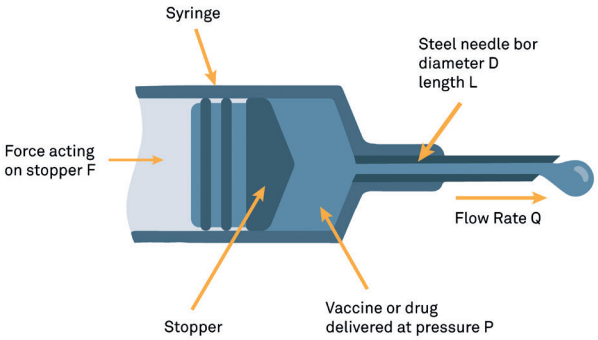


Figure 2: For a conventional hypodermic syringe and needle, flow rate is characterised by the Hagen-Poiseuille equation.

Needle free

$$Q = \frac{\pi D^2 Cf}{4} \sqrt{\frac{P}{2\rho}}$$

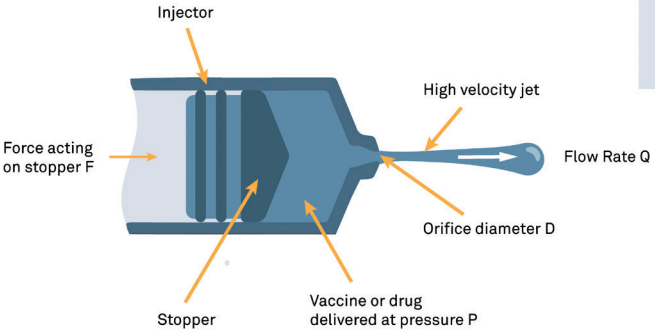
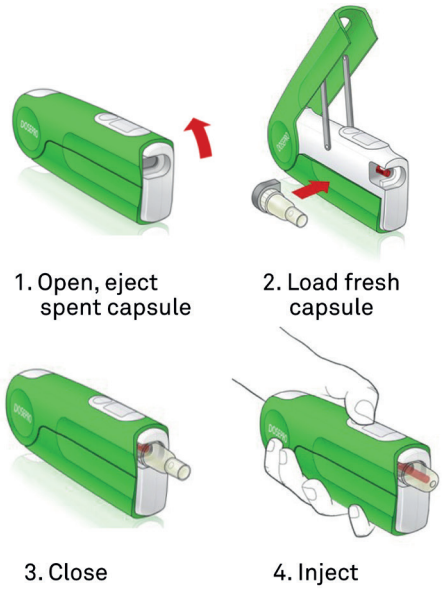


Figure 3: For a needle-free injector, delivery is through an orifice and the flow rate is characterised by the Bernoulli equation.

> "Based on work by Team Consulting, it is feasible to develop mass vaccination needle-free injectors where the cost of re-use is limited to a prefilled single-shot vaccine cartridge."



- Light (0.5 Kg), compact device, minimal user effort (<15 N)
- Controlled, repeatable, silent needle-free injection
- Prefilled capsule, contents integrity protected throughout
- Safety interlocked mechanism ensures correct sequence
- On-board power for up to 3,000 injections

Figure 4: Mass vaccination device (with on-board fuel tank).

was built and tested. The images show the operational sequence of the system with cartridges (capsules) configured for subcutaneous injection.

An alternative approach is a mass vaccination system powered by pressurised nitrogen (Figure 5). The nitrogen-powered concept is simpler to use than the self-contained butane/propane fuelled device, but is dependent on the availability of a compressed nitrogen supply (typically a standard cylinder).

The self-contained nature of the butane/propane fuelled device – though requiring more user effort to prime the system – may be preferred in areas with limited infrastructure/logistics. The nitrogen-powered systems may be more widely accepted in developed countries.

CHALLENGES AND RISK

Clearly the decision to adopt needle-free technology is a significant one and not without risk. In addition to the development and scaling risks (applicable to any new medical technology) there is also the question of whether all vaccines will actually be suited to the efficiencies of intradermal delivery.

In terms of technical development and scaling, Team Consulting, in its 30+ years, has investigated needle-free platforms and seen encouraging clinical results, as well as approvals obtained. With sufficient investment it is very feasible to scale the technology to be ready to deliver novel vaccines at large scale. The key challenge will be the availability of large-scale filling systems and the supply of a custom vaccine cartridge. It is very likely that existing available filling systems will all be configured for filling "standard" prefillable syringes or vials. It will take at least 18 months and significant investment to set up the high-volume manufacturing and filling capacity for needle-free capsules, but this is still commensurate with the 18 months that vaccine experts consider it will likely take for a covid-19 vaccine to be developed.[2]

In terms of vaccine efficacy under intradermal administration, the WHO bulletin from 2011[4] states that "Live-attenuated vaccines have been successfully delivered intradermally and should be good candidates providing that appropriate formulations can be developed. Reduced doses of inactivated whole-virion vaccines have also shown satisfactory immunogenicity when delivered intradermally. Inactivated whole virion influenza vaccines might also be suitable because they have intrinsic immune-stimulating sequences, which might avoid the need for addition adjuvants". With timely investment, a low-volume needle-free system could be developed more quickly for researchers to use in vaccine trials, allowing vaccine efficacy under intradermal needle-free delivery to be demonstrated from the outset.

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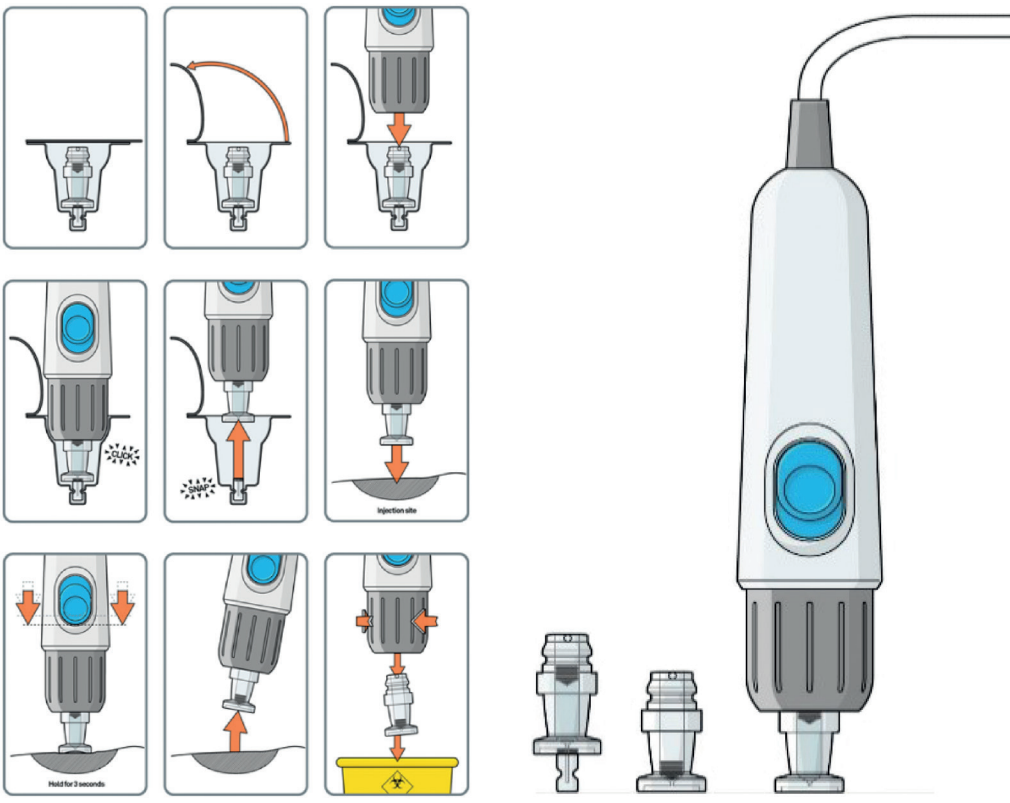

Figure 5: Compressed nitrogen powered vaccination system.

CONCLUSION

Governments, international agencies and technology companies are already investing significant sums of money into vaccine development programmes and associated delivery systems. With sufficient co-ordination across stakeholders, a reliable, needle-free, dose-efficient vaccine delivery system is a very viable concept that should be considered for mass vaccination of covid-19.

ABOUT THE COMPANY

Team Consulting is a medical device design and development consultancy based in Cambridge, UK. For 30 years Team has worked closely with its clients at leading pharmaceutical and device companies, applying its expertise in design, human factors, science and engineering to deliver successful devices from concept through to industrialisation and commercial launch. Everyone at Team is driven by the same desire, to make things better by working in collaboration with clients and each other.

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ABOUT THE AUTHORS

Andy Fry has played a leading role in developing Team Consulting's drug delivery business, both in development of client and partner relationships and in technology development. He has helped both multinational and start-up companies identify and develop the right parenteral delivery system for their drugs.

Dr Stephen Blatcher joined Team Consulting's commercial team in 2019 to help expand the company's work in the MedTech space. With a particular focus on high-risk devices, his strategic business skills and background in engineering and biotechnology give him an aptitude for both managing technical projects and developing business opportunities.