Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

Intradermal immunization—a dose-sparing strategy to combat global shortages of severe acute respiratory syndrome coronavirus 2 vaccines?

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Background

Shortages in vaccine supplies are a major health problem of global concern, particularly during epidemics and pandemics, such as the coronavirus disease 2019 (COVID-19) pandemic. At the time of writing, merely 13.0% of the world's population had been fully immunized against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), leaving 6.9 billion people worldwide still unprotected [1]. Therefore, dose-sparing approaches such as intradermal (ID) vaccination should be considered in mass immunizations. Numerous studies over the past decades showed that for several vaccines (e.g. rabies, influenza, and hepatitis B) doses can be reduced by using ID immunization as an alternative to intramuscular (IM) and subcutaneous (SC) immunization, without the loss of vaccine immunogenicity and efficacy, thereby augmenting vaccine supply utilization [2]. The target layer for ID immunization is the papillary dermis, which is rich in antigen-presenting cells (APCs) (namely Langerhans cells and dendritic cells). The APCs capture antigens deposited in the dermis and migrate through lymphatic vessels to lymph nodes. Here, APCs present the antigens to T and B cells, triggering activation. Because of the abundance of APCs in the dermis, stimulating adaptive immune responses, reduced doses of antigen can be used when applied intradermally [3].

Summary of evidence

Over the past decades, many clinical trials have been published comparing fractional dose ID immunization with standard routes of immunization. A recent systematic review and meta-analysis provided an overview of the literature, including 156 studies comparing fractional ID to IM/SC immunization covering 12 vaccines [2]. For ID influenza, rabies and hepatitis B vaccines, non-inferiority of immunogenicity was demonstrated when administering 20%–60% of antigen compared with standard routes of immunization. For inactivated polio and measles vaccines, it remained uncertain if doses could be reduced by the use of ID administration, as the results of these studies varied. Clinical trials on other vaccines (i.e. hepatitis A, diphtheria–tetanus–pertussis, human papillomavirus, Japanese encephalitis, meningococcal disease, varicella zoster and yellow fever vaccines) yielded promising results, but are both scarce and limited with regard to numbers of participants.

Combatting vaccine shortages

Mainly during outbreaks, when there is an increased demand for vaccines, serious shortages have occurred in the past. Vaccine

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shortages and stock-outs are a serious public health issue, affecting prevention and control programmes of infectious diseases, and can lead to critical reduction in population coverage. Although there are limits to fractionating standard IM or SC vaccine doses [4], dose-sparing strategies such as ID immunisation can help to battle vaccine shortages. To date, WHO have approved ID administration of three marketed vaccines: rabies vaccine, inactivated poliovirus vaccines and tuberculosis vaccine, using the live attenuated Bacillus Calmette–Gúerin strain of *Mycobacterium bovis* [5,6]. Since then, ID rabies immunization has been introduced to combat vaccine shortages at a national level by resource-constrained countries such as India, Thailand and the Philippines [7].

Overcoming obstacles

Although the dose-sparing potential for certain vaccines has clearly been established, still some barriers need to be overcome, and more data are needed, so that evidence can be turned into action. First, there are technical challenges that vaccinators may encounter. Intradermal vaccination is a more complex vaccination technique, which requires training. Though, training can be very effective and time-efficient, especially with the assistance of novel ID application devices [3]. Additionally, there might be reservations about the accuracy of ID application of antigen. However, this is easily verified by the appearance of a wheal of >5 mm in diameter, which indicates the correct administration of 0.1 mL of vaccine solution [3]. Another concern of ID delivery is the higher rate of local reactions at the injection site, including redness, swelling and itching. Systemic adverse events, on the other hand, are not more common after ID delivery, but are comparable to IM/SC immunization [2].

Another major bottleneck for implementing ID administration into routine care lies with regulatory issues. When a fractional dose of an existing vaccine is applied intradermally, it is often off-label use, as the vaccine is intended for IM/SC use [3,7]. Therefore, national authorities should provide clear guidelines on which vaccines can be delivered intradermally, and under what requirements. An alternative option would be to obtain marketing approval for the new ID vaccine formulation and presentation. However, the commercial incentive for manufacturers of existing IM/SC vaccines is probably not strong enough, as the expenses of reformulating, producing new dosing and packaging formats and applying for marketing authorization are high. A far more cost-effective method would be to add a fractional-dose ID arm to early-stage novel vaccine development trajectories. Fractionally dosed ID vaccines could be marketed for more competitive prices, as expenses for a smaller amount of antigen are lower. From a public health perspective, safe and effective dose-sparing regimens would be a logical choice anyway, but investing in fractional-dose ID vaccines up front might also be profitable for pharmaceutical companies.

Intradermal SARS-CoV-2 vaccines

The promising perspectives of ID immunization should be extrapolated to SARS-CoV-2 vaccines. Various vaccines against SARS-CoV-2, based on different platforms, are currently in use or are undergoing clinical trials; including inactivated, live-attenuated, recombinant protein, vectored, RNA and DNA vaccines. Vaccine types against different pathogens that have demonstrated a dose-sparing potential in the past include inactivated (e.g. influenza, rabies), live attenuated (e.g. yellow fever) and recombinant protein (e.g. hepatitis B) vaccines [2]. However, clinical trials including ID arms are needed to determine for which SARS-CoV-2 vaccines dose-sparing by ID immunization could be an option.

Recently, two clinical trials have initiated assessing the safety and immunogenicity of fractionally dosed ID compared with standard IM delivery of registered SARS-CoV-2 vaccines [8,9]. The first ongoing study is a Dutch randomized clinical trial on healthy adults comparing the immunogenicity of ID delivery of two fractional doses of 10 μg and 20 μg of mRNA-1273 vaccine (Moderna®) with that of two doses of 20 μg and 100 μg (standard dose) through IM delivery [8]. In a recent press release, the investigators stated that the phase I/II study showed promising results, and a phase III study would start soon [10]. Another clinical trial that recently started and that is taking place in Belgium, is investigating adapted vaccine schedules and routes, including fractional dose ID delivery of 6 μg (one-fifth of the standard dose) of BNT162b2 (Comirnaty®) and 0.1 mL (one-fifth of the standard dose) of ChAdOx1 (Vaxzevria®), and comparing those with standard route and doses [9]. Depending on the results of these trials, we prompt policy-makers to consider the introduction of ID regimens of these registered SARS-CoV-2 vaccines to lower costs and significantly increase vaccine supplies. Especially in low-income settings, the paucity of SARS-CoV-2 vaccines is a most pressing issue, and dose-sparing solutions are warranted. According to recent estimates by researchers from the Duke Global Health Innovation Centre, the world's population is expected to be vaccinated against SARS-CoV-2 in 2023, which is still two years from now [11]. However, if ID immunization with one-fifth of the standard vaccine dose is effective, then this period could hypothetically be shortened to only six months. Given the urgency of this matter, we indeed advocate for considering investigating fractional-dose ID arms as early as the dose-finding studies, which have determined optimal dosing of standard applications for novel and re-engineered SARS-CoV-2 vaccines.

Intradermal mRNA vaccines

A relatively new class of vaccines are the mRNA vaccines. Over the past decade, mRNA vaccines have been increasingly recognized as a promising tool for both preventing infectious diseases and as cancer immunotherapy. However, it was not until the COVID-19 pandemic that the first two mRNA vaccines were approved for human use, namely the mRNA-1273 vaccine (Moderna®) and BNT162b2 vaccine (Comirnaty®). After administration, the mRNA, encoding a target antigen, is internalized by host cells. Subsequently, ribosomes in the cytoplasm translate the mRNA, resulting in the production of the target protein. This antigen will be presented to immune cells, mounting an adaptive immune response against the target protein. As the dermis is rich in APCs, it is the ideal site for delivery of mRNA encoding the antigenic protein. Therefore, the ID delivery route is widely used for mRNA cancer vaccines [12]. Recently, there has been a huge amount of investment in mRNA vaccine companies developing both mRNA cancer vaccines and mRNA vaccines against infectious diseases [11]. We therefore expect more mRNA vaccines to become registered and marketed over the next couple of years. We prompt vaccine developers of novel mRNA vaccines against infectious agents that are still at an early stage to include fractional-dose ID arms, as shortages in vaccine supplies are an ongoing major health problem contributing to the prolonged duration of the current COVID-19 pandemic.

Transparency declaration

All authors declare no conflict of interest. None received.

Contribution

MPG conceived this commentary. JLS wrote the first draft, with input from all authors. All authors have contributed to, and endorsed the final version of the manuscript.

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