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REVIEW ARTICLE

INTRANASAL (IN) COVID-19 VACCINES - A BREAKTHROUGH

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ABSTRACT

Emerging variants of COVID-19 have threatened the effectiveness of intramuscular (IM) vaccines since that are made to target only the spike protein. Development of Intranasal (IN) vaccination has been proven to provide both the mucosal and systemic immune responses for broader and long lasting protection. Many IN vaccine candidates (virus-vectored vaccines, recombinant subunit vaccines and live attenuated vaccines) are in different phases of clinical trials and in near future many companies would be releasing their vaccines into the drug market. Potential advantages of IN vaccination over IM vaccination makes them ideal to be administered in children and developing populations of the world. This paper focuses on the very recent developments in intranasal vaccination with a spotlight on their safety and efficacy concerns. IN vaccination can prove to be game-changer in handling COVID-19 and potential viral contagious diseases in future.

Key words: *COVID-19, intranasal vaccine, intramuscular vaccine, protection, safety, delivery*

INTRODUCTION

COVID-19 (SARS-CoV-2) has been declared as a devastating pandemic of the 21st century which resulted in millions of deaths worldwide [12]. The development of an effective vaccine against COVID-19 was a challenging task for vaccine makers worldwide. As a result of mass vaccination programs globally and implementation of other public health safety measures, the number of COVID-19 cases have reduced considerably in most parts of the world thereby paving the way for the easing of health restrictions and a gradual return to normal life [7].

A variety of COVID-19 vaccines have been developed by researchers in different countries and have shown a high degree of efficacy with variable protective levels of up to 95% (70–95% range) in vaccinated individuals against COVID-19 [8]. Most of the COVID-19 vaccines in use are administered via intramuscular (IM) injection, eliciting protective humor and cellular immunity [6]. However, existing IM vaccinations are designed to induce only systemic immune response without generating mucosal protection. Therefore, protections offered by IM vaccines may not be sufficient to deal with virus replication and shedding in the upper respiratory tract and so may not stop nasal SARS-CoV-2 infection.

The absence of a local secretory IgA (sIgA) antibody immune response could pose a risk of virus transmission from vaccinated people as they still can be infected and therefore could transmit virus to others. In order to combat this threat, researchers are focusing on the development of intra nasal (IN) vaccines, with their allure for achieving mucosal immunity, complementing and likely bolstering the circulating immunity achieved via intramuscular shots [14].

Mucosal immunity (in brief)

Mucosal immunity is a complex network comprising of various tissues, non-lymphoid cells, lymphocytes, and effector molecules (e.g. cytokines, chemokines, and antibodies) [10]. Conventional vaccine injections are poor inducers of mucosal

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immunity, whereas IN immunization has the capacity to induce strong mucosal immunity to prevent the entry and development of mucosal pathogens. When SARS-CoV-2 enters the nasal cavity, the respiratory epithelial layer becomes the first barrier against viral infection [1]. Then, the innate immunity components (comprising of several diverse immune cells) present in the upper airway mucosa, become the first line of defense. These immune cells can form an integrated system that has the capacity to directly fight against pathogens or induce adaptive mucosal immunity [1]. Mucosal immunization can induce extensive adaptive immune responses, characterized by mucosal secretory IgA (sIgA) antibodies and resident memory T (T_{RM}) cells. T_{RM} cells in the airways and lungs are vital for preventing respiratory virus infection. Upon re-stimulation with viral antigens, T_{RM} cells confer rapid response, which induce the production of inflammatory cytokines and chemokines to mediate tissue antiviral resistance and to recruit auxiliary immune cells respectively. IN vaccination has the capacity to effectively induce the generation of T_{RM} cells, and persistent antigen present in the lungs can promote long-term maintenance of T_{RM} cells [15].

Recent progress towards developing intranasal COVID-19 vaccine

IN vaccines have the potential to induce sterilizing immunity against various mucosal pathogens [16]. Antigens are exposed at the initial site of viral attack to induce potent immune responses at local or distant mucosa. Many challenges that are encountered in developing an effective IN vaccine include: (1) delivering the antigens to antigen-presenting cells (APCs) present in the respiratory tract while overcoming nasal clearing, (2) antigen used in the vaccine must remain in the respiratory tract for an adequate amount of time, (3) the antigen must be stable enough to withstand the enzymatic degradation in the mucosal lining [11]. Fortunately, 12 nasal vaccines manufactured by different pharmaceutical giants are in different phases of clinical development (Table 1), but recently in December 2022, world's first IN vaccine 'iNCOVACC' was developed by Bharat Biotech, India, after successfully completing phase I, II and III clinical trials [2].

iNCOVACC (BBV154) - World's first IN vaccine for COVID-19

Bharat Biotech, India has launched world's first IN Vaccine named as **'iNCOVACC'** recently in December 2022. It was developed in partnership with Washington University, St. Louis [2]. This vaccine is a recombinant (ChAd36-SARS-CoV-2-S) replication deficient adenovirus vectored vaccine with a pre-fusion stabilized spike protein. It is specially formulated and can be delivered to an individual in the form of nasal drops. It stimulates a broad immune response – neutralizing IgG, mucosal IgA, and T cell responses at the site of infection (nasal cavity) thereby protecting against disease, infection, and transmission. It is stable in the temperature range of 2-8°C for easy storage, transportation and distribution. It is administered through the nose, as a 2-dose series, 4 weeks apart. A total of 8 drops (0.5 mL per dose), 4 drops are administered into each nostril. It has got approval from the Central Drugs Standard Control Organisation (CDSCO) for restricted use in emergency situations

Table 1. Various intranasal vaccine candidates under different phases of clinical trials

S. No.	Intranasal (IN) Vaccine	Developer/Company
1.	ChAdOx1 nCoV-19	University of Oxford in collaboration with AstraZeneca
2.	*ChAd-SARS-CoV-2-S	Bharat Biotech, India in collaboration with Washington University School of Medicine in St Louis, USA
3.	Ad5-nCoV vaccine	CanSino Biologics Inc. with Beijing Institute of Biotechnology and Jiangsu Province Centers for Disease Control and Prevention, China
4.	AdCOVID	Altimmune, Inc. USA
5.	NasoVAX	Altimmune, Inc. USA
6.	DelNS1-nCoV-RBD LAIV	Beijing Wantai Biological Pharmacy Enterprise with researchers from Xiamen University and Hong Kong University
7.	Mv-014-212	Meissa Vaccines, Inc.
8.	COVI-VAC	CODAGENIX Inc., 3 Bioscience Park Drive, Farmingdale, NY, USA
9.	CROWNase	Illinois Institute of Technology, Chicago, USA
10.	CovOMV	Intravacc, Antonie van Leeuwenhoek laan 9, 3721 MA Bilthoven, Netherlands
11.	CIBG-669	Center for Genetic Engineering and Biotechnology, Cuba
12.	STINGa-liposomes	AuraVax Therapeutics,Ina Mae Rude Entrepreneur Center, USA

*Successfully completed all the clinical trials recently in December 2022 and officially launched

(as a booster dose) in the age group of 18 and above and 6 months after completion of primary schedule of vaccination [9]. The first shipment of vaccines was rolled out by Bharat Biotech to several locations across the country in the first week of February 2023 and will available in government-managed hospitals and drug stores by the end of February 2023.

Delivery devices for intranasal vaccines

Various devices have been developed to deliver IN vaccines ranging from pipette droppers to spray devices [4]. iNCOVACC is based on conventional pipette based delivery method in which vaccines are dropped into the nostrils. The main drawback of this method is that sometimes the drug volume can easily exceed the nasal cavity volume. A variety of spray devices are available in the market due to their affordable cost and clinical efficacy. Metered-dose sprays which are portable, easy to use, self-contained, and safe are most studies by researchers. They can be actuated via hand press, breath, or electrical power. Some examples of vaccines delivered through nasal spray are: FluMist® uses AccuSpray Device (single use pre-filled syringe), vaccination of Shigella antigens with a spray device (Dolphin™) and the Ad5-nCoV vaccine (which is still under phase 3 clinical trial) utilizes the advanced Aerogen Ultra Device [17]. However, there is limited utilization of metered-dose spays as there is high possibility of drug leakage during vaccination which is environment unfriendly. Therefore, all the above factors should be considered while incorporating type of delivery device for vaccine administration.

Potential advantages of IN vaccines

Various researchers around the world have documented certain benefits of intranasal vaccinations over intramuscular (IM) immunization [3, 13] (Figure 1).

- A single dose of IN vaccine may induce substantial amount of neutralizing antibodies that can combat viral infection in both the upper and lower respiratory tracts.

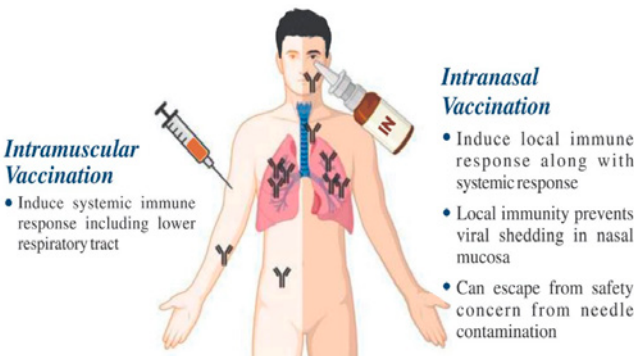

Figure 1. Schematic representation of intranasal and intramuscular vaccine administration

- Mucosal surfaces of the lungs and upper airways which are common sites for invasion by the SARS-CoV-2, are safeguarded by mucosal immunity. It can prove to be an effective approach to minimize viral shedding and spread.
- These can be more appealing than IM administration with regard to lower dosage.
- There is no need for trained health care professional to deliver IN dosage owing to ease of administration.
- As nasal vaccinations can be administered in the form of a nasal spray or nasal drops, and being non-invasive and needle-free, it is a better option for immunization in infants and children.
- In near future, these vaccines would even be stable at room temperature, making them easier to store and transport and potentially improving the vaccine coverage in remote areas, especially at the village level. Moreover this is advantageous for carrying out immunization programs, particularly in developing nations.
- It provides a more cost-effective and convenient approach to administering vaccinations during disease outbreaks.

Possible shortcomings of IN vaccination

There are some possible shortcomings which could be associated with IN vaccinations which again depend upon the type of vaccine and manufacturer. These are addressed below [5]:

Sterilizing immunity: Though intranasal vaccines induce both IgA and IgG antibodies, providing 'sterilizing immunity' in the upper respiratory tract, but it is observed with some IN vaccine candidates that systemic IgG antibody response in the lower respiratory tract is not as potent as in the upper airways.

Ineffective long-lasting immunity: Sticky mucous which acts as a first line of defence and presents a barrier for pathogens in the respiratory system, may interfere with vaccine access and immune activation. This can hamper long lasting immunity and faster waning of immunity.

Administration in infants and children: Though this route seems to be more suited for vaccine administration in infants and adults, however it is a common observation that children tend to sneeze right after administration in case of intra nasal flu vaccines. This can be risky considering the virulence of COVID-19. Moreover, smooth administration can be hampered during seasonal allergies.

Safety-related concerns: These vaccines employ live attenuated virus, therefore there is a rare risk for reverting to a replicating form (virus regaining its ability to cause disease in a person). Although extremely rare, this phenomenon has also been observed previously in the oral polio vaccine. Safety

of live attenuated vaccines can only be proved after considerable period of time.

CONCLUSION

Since the nasal mucosa acts as the first-line barrier to SARS-CoV-2 entrance before dissemination into the lungs, development of effective and reliable intranasal vaccine would be crucial at this time and adds a second line of defence immediately at the infection site. India has already launched its first Covid-19 IN vaccine and hopefully in near future many more vaccines would be available after successfully completing all the clinical trials in different countries. IN vaccines certainly have many advantages over their IM counterpart and therefore it can act as an alternative route of vaccine delivery for both prophylaxis as well as therapy. It would prove to be beneficial is several developing countries where vaccination is still a major concern. However, it is necessary to develop potential delivery systems that can efficiently deliver the intact forms of antigens towards target cells. Furthermore, safety and efficacy of IN vaccines have to be evaluated thoroughly before we incorporate them in worldwide vaccination programs.

Conflict of interest

The authors declare no conflict of interest.

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