



## An Innovative Review Study on Using Pulmonary Vaccination in COVID 19 Pandemic

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### ABSTRACT

The current state of pulmonary vaccine delivery will be discussed in this review. The prospects for lung immunization using dry powder generation technologies and specialized medicinal formulations are discussed. In terms of vaccine durability and antigenicity, dry powder vaccine generation technologies may be advantageous. The non-invasive, reasonably safe, and low-cost nature of pulmonary delivery could help the public health vaccination significantly. The vaccines, which are all given intramuscularly, produce systemic antibodies in the blood but not antibodies in the pulmonary mucosal lining. Inhalation vaccines provide a number of potential benefits over injectable vaccines, including ease of delivery, and even self-administration. To create a dry powder inhalation formulation that is breathable and mediates robust transfection in the lung, a safe and effective mRNA delivery vector as well as a suitable particle engineering approach is needed.

**Keywords:** Pulmonary vaccine delivery, mucosal antibodies, mRNA, pulmonary lining, Dry powder inhalation.

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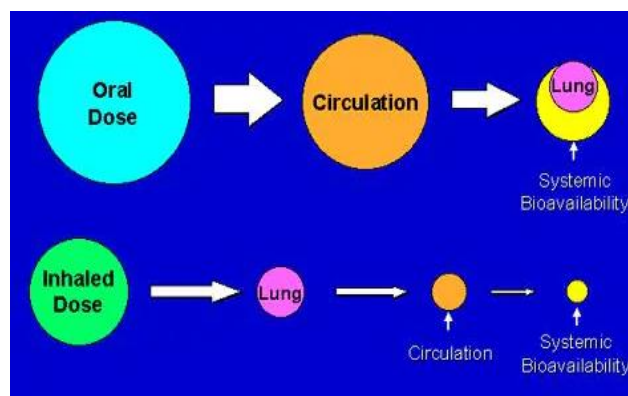


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### INTRODUCTION

Vaccination is the most efficient technique for preventing diseases. The most reliable routes for vaccination are intramuscular, intradermal, subcutaneous, oral, and intranasal<sup>1</sup>. As above, mentioned routes are mostly preferred over intranasal leading to less frequent use of pulmonary delivery. In pulmonary and other immunocompromised conditions such as HIV, AIDS, and patients with cancer, autoimmune disorders receiving immunosuppressive agents have reduced immune response, in these conditions use of pulmonary delivery shows a quick and effective immune response<sup>2,3</sup>. Inhalation is also a possible way of vaccine administration against airborne diseases such as covid 19, tuberculosis, and other pulmonary diseases. Pulmonary delivery is used as a site-specific alternative to systemic vaccination. Through this type of vaccination, the immune response starts within the pulmonary system exhibiting both local and systemic immunological responses. Vaccination against the coronavirus that causes severe acute respiratory syndrome 2 (SARSCoV2) is a critical step in eliminating the present global pandemic. However, in coronavirus disease 2019 (Covid19) vaccination studies, certain highly vulnerable groups in the public were not recruited in sufficient numbers<sup>4,5</sup>. As a result, as science

progresses, the recommendations for vaccination these specific populations against Covid19 will change. Using current research information, this focused overview gives the most recent recommendations and considerations for these particular populations. In the case of respiratory diseases, pulmonary delivery has the advantage of delivering the vaccine directly to the pathogen's point of entry, where it can generate a local immune response<sup>4</sup>. (figure 1).



**Figure 1:** The difference between oral vaccine delivery and inhaled vaccine delivery

### Pulmonary Vaccination

Pulmonary vaccination refers to inhaling a vaccine through the airway. For the treatment of numerous respiratory disorders such as pneumonia chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis, and others, inhalation is the preferred mode of administration<sup>6</sup>. Because the surface area of the human lungs is enormous and the epithelium is extremely permeable, an inhaled dose can quickly reach it<sup>7</sup>. The pulmonary route is considered a targeted lung delivery

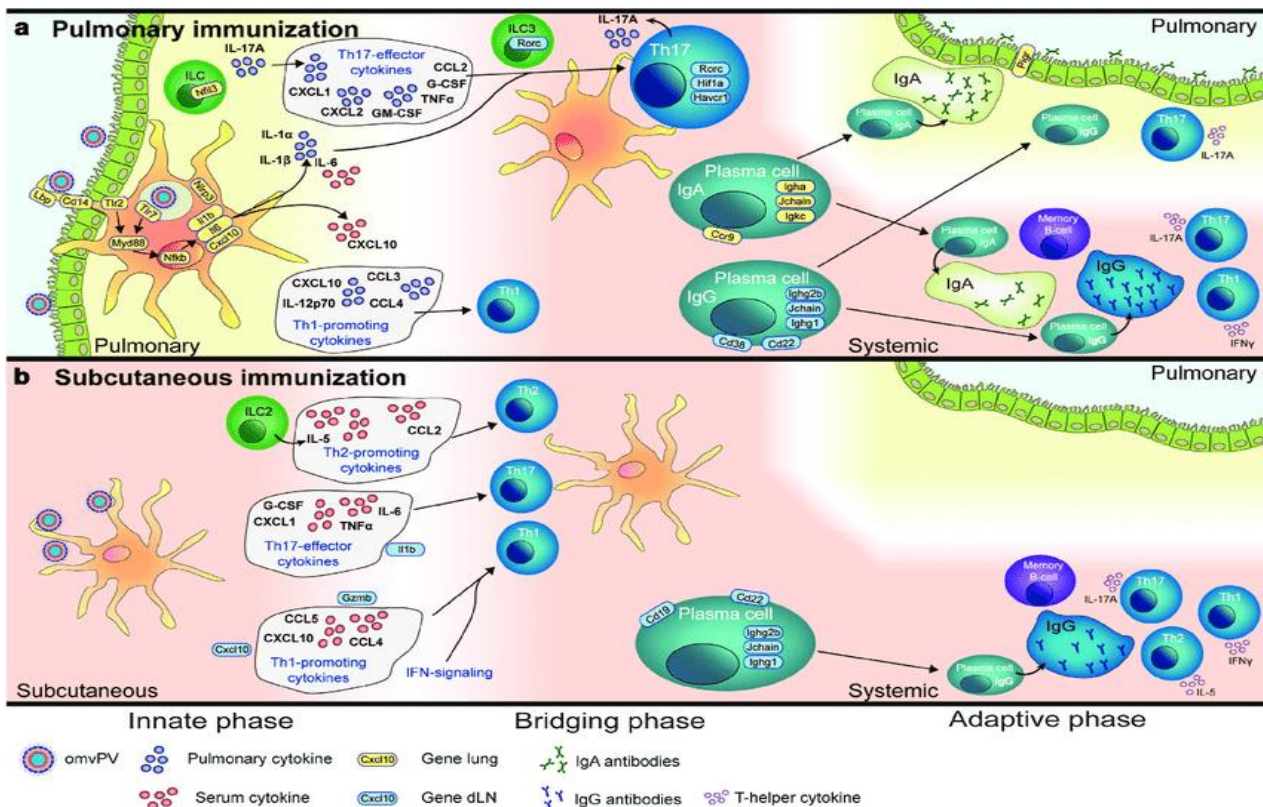


because it allows a medicine to be given directly to its site of action, resulting in a faster beginning of action with smaller dosages and higher concentrations supplied locally to the illness site in the lungs. Additionally, reducing systemic bioavailability minimizes the risk of severe systemic toxicities and prevents first-pass metabolism in the liver<sup>8,9</sup>.

**MECHANISM OF IMMUNOLOGICAL RESPONSE IN PULMONARY DELIVERY**

The conducting and transitional airways, as well as the lung parenchyma, can be split into two components from a physiological standpoint. A dense mucus layer of dendritic cells (DCs) surrounds the conducting airways, allowing infections or vaccinations to be trapped. The lamina propria can create local antibodies beneath the surface. Epithelial cells cover the lung parenchyma, which also contains antigen-presenting cells (APCs) such as DCs and

alveolar macrophages. The DC's move to draining lymph nodes after antigen absorption, when antigens are given to naive T lymphocytes<sup>10</sup>. These T cells have the ability to become memory or effector T cells. T cells can assist B cells in the systemic germinal centers via efferent lymphatics, resulting in the generation of systemic antibodies<sup>11</sup>. In addition to the systemic immune response, it is considered that pulmonary vaccine administration induces local immunity more effectively than standard immunization<sup>4</sup>. Antigens can be picked up by these macrophages or DCs when they enter the lungs. The bronchoalveolar lymphoid tissue induces local immunity, which is given by secreted IgA (sIgA) (BALT). It protects the infection site and sIgA is thought to be more cross-protective against diverse pathogen subtypes<sup>4,12</sup> (figure 2). However, little is known about BALT's role in immunological memory and cellular immunity to date.



**Figure 2:** Difference between mechanisms of pulmonary and subcutaneous immunization

**TECHNIQUES UTILISED IN THE PRODUCTION OF VACCINES**

**Spray drying technique**

The atomized solution is subsequently dried in a dedicated chamber with preheated drying gas to remove water moisture from the system, resulting in dry particles<sup>8</sup>. Because mechanical high-energy input is avoided in this method, it is also ideal for thermolabile materials such as proteins and peptides. Spray-drying, moreover, can result in a homogeneous particle shape<sup>13,14,15</sup>.

**Evaporation of a double emulsion and a solvent**

This approach entails creating an oil/water emulsion and then removing the oil phase via evaporation. The organic solvent diffuses from the polymer phase to the aqueous phase before being evaporated, resulting in drug-loaded polymeric nanoparticles. Biodegradable polymers have been thoroughly studied as carriers for respiratory solid medication nanoparticles using this approach.

### Technology for supercritical fluids

The controlled crystallization of pharmaceuticals from dispersion in supercritical fluids, such as carbon dioxide, is the key aspect of this technique<sup>16</sup>. This approach has been utilized to make microparticles, nanoparticles, liposomes, and inclusion complexes in the pharmaceutical industry. This technology is utilized to make protein and peptide-based particulate pulmonary drug delivery systems, as well as to improve the formulation properties of specific drug candidates<sup>16,17</sup>.

### Replication of particles in nonwetting templates

Dr. Joseph DeSimone and his team created Particle replication in non-wetting templates (PRINT), a top-down particle production process<sup>18</sup>. This technology allows for the loading of small organic medicines, proteins, peptides, oligonucleotides, siRNA contrast agents, radiotracers, and fluorophores into uniform-sized organic micro- and nanoparticles with total control of size, shape, and surface functionality<sup>18,19,20</sup>.

### Method of solvent precipitation

By using opposing liquid jets, this process involves sonocrystallization and micro-precipitation. Direct controlled crystallization could be used to make crystalline medication particles with a limited size distribution<sup>21</sup>. Antisolvents can be used to rapidly precipitate inhalable particles from aqueous solutions. Ultrasonic radiation has recently been used to manage precipitation. The sono-crystallization process was used to make a variety of antiasthmatic medicines.

### Method of spray-freeze drying

In the early 1990s, this approach was investigated for use in the pharmaceutical industry. It's a cutting-edge particle engineering technique that combines spray drying with freeze-drying<sup>15</sup>. Spraying the medication solution into liquid nitrogen as a freezing medium, then lyophilization is how it's done<sup>22</sup>. At sub-ambient temperatures, this approach creates light and porous particles with a high fine particle percentage, increased aerosol performance, and nearly 100% yield<sup>23</sup>. plasmid DNA<sup>24</sup> are examples of thermolabile protein and peptide compounds that can be packaged into dry powder inhalation products. However, this is a costly procedure that is limited to only the most expensive drugs<sup>15</sup>

### VACCINE FORMULATION STRATEGIES USING NANOMATERIALS

Antigens and adjuvants can be delivered simultaneously in a single particulate carrier using nanoparticle delivery techniques<sup>25</sup>. Nanoparticles have unique properties that influence their immunogenicities, such as small particle size, high loading efficiency, surface charge, and bio-adhesiveness, which promote mucosal permeability and provide appropriate protection against gut fluid<sup>26</sup>. Nanocarriers also have the ability to stimulate the immune system. Nanoparticles can be designed to encapsulate

vaccine components on or within their surface, allowing them to be effectively given to antigen-presenting cells<sup>10</sup>.

### Nanoliposomes

Nanoliposomes are lipid vesicles that are nanoscale in size. Liposomes have been studied extensively for their potential to transport antigens that are both lipophilic and hydrophilic. The phospholipids encase hydrophilic antigens, while the interior core encases lipophilic antigens<sup>27</sup>. Nanoliposomes also allow for a longer release time and targeted immune cell absorption. They have the ability to penetrate mucus and can be utilized for active targeting<sup>28</sup>. The use of nanoparticulate technologies to improve medication or vaccine delivery by IN drug administration is being investigated<sup>29</sup>.

### Nano-emulsions

Nano-emulsions are emulsions that have droplets that are approximately 20–200 nano-meters in size. A wide range of therapeutic compounds have been tried in combination with this nano-system for nasal delivery, and now these studies have proved it as a viable carrier/adjuvant for nasal formulations<sup>30</sup>. It has been proven that nano-emulsion-based vaccinations are not physically or chemically changed after being actuated with nasal spray devices and preserve their effectiveness<sup>31</sup>. NanoEmulsions have been used for influenza IN delivery in a variety of studies. A vaccine and a recombinant anthrax vaccine have been developed<sup>30</sup>.

### Polymeric nanoparticles

pH-sensitive nanoparticles, specific ligand attached nanoparticles, and mucoadhesive nanoparticles are the three types of polymeric nanoparticles used for mucosal delivery. The type of polymer utilized influences the vaccine's physicochemical and drug release qualities. Poly Lactic co glycolic acid (PLGA), Polylactic acid (PLA), and Polyanhydrides are the most commonly utilized polymers in vaccine administration<sup>32,33</sup>. These nanoparticles are constrained by their low loading efficiency, difficulties scaling up, high production costs, and quick burst release.

### Bio-adhesive delivery system

To improve mucosal vaccine delivery, the use of bio-adhesive delivery systems offers numerous advantages, including protection from degradation, increasing concentration of antigen in the vicinity of mucosal tissue for better absorption, extending their residence time, and/or targeting them to sites of antigen uptake<sup>34</sup>.

### Virus-like particles

Viruses are naturally occurring nanomaterials because their size is in the nanometre range. VLP's are multiprotein that naturally self-assemble to imitate the 3D conformational structure of a true virus but lack the viral genome, rendering them non-pathogenic and requiring neither inactivation nor attenuation<sup>35</sup>. VLPs are easily detected by the immune system because they are identical to genuine viruses. These nanoparticles are non-toxic, immunogenic, and adjuvant in nature. VLP has the ability to encapsulate DNA, providing

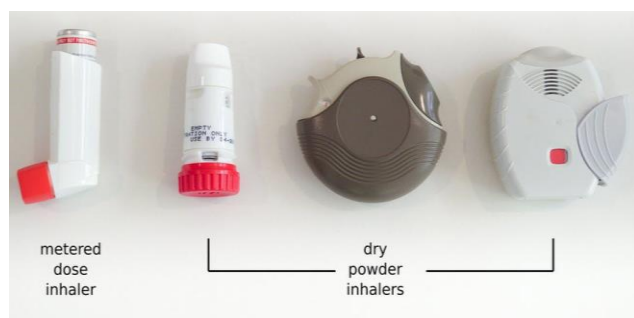


enough protection against DNA vaccine breakdown<sup>36</sup>. Despite being potential possibilities, VLPs have limitations. VLPs confront challenges such as impurity contamination and batch-to-batch variance in the manufacture of identically sized particles.

## DEVICES

The delivery device used in pulmonary administration is critical to the system's performance. Great strides have been made in the creation of innovative technologies in recent years. Devices, on the other hand, have received far less attention than powder formulations<sup>37</sup>. If the medicine is to be delivered to a certain section of the lungs, the device chosen must be capable of producing and delivering particles/droplets with a specific aerodynamic diameter. Nebulizers, metered-dose inhalers, and dry powder inhalers are the most frequent respiratory delivery devices<sup>38</sup>. (figure 3).

**Dry powder inhalation:** It is a non-invasive type of method, that improves patient safety and vaccine compliance, decreases the cost of manufacturing, handling. It also saves time, effort and increases the speed of delivery. As pulmonary delivery is needle-free which eliminates cross-contamination<sup>4,39</sup>. As most of the vaccines are in liquid formulation cold chain storage conditions become mandated. In conditions of not maintaining principles of storage guidelines, there will be a chance of vaccine degradation and expiry<sup>39</sup>. This can be avoided by manufacturing dry powder form in nasal delivery. Inhaled dry powder formulation of mRNA is particularly attractive as it has superior stability and dry powder inhaler is relatively easy to use. A safe and effective mRNA delivery vector, as well as a suitable particle engineering method, are required to produce a dry powder formulation that is respirable and mediates robust transfection in the lung<sup>40</sup>. After a single intratracheal injection, the PEG12KL4/mRNA complexes showed no signs of inflammatory response or toxicity. PEG12KL4 is a good mRNA transfection agent for pulmonary delivery in general. This might be the first study to successfully demonstrate the creation of inhalable dry powder mRNA formulations with *in vivo* transfection effectiveness, demonstrating PEG12KL4 peptide's considerable potential as an mRNA delivery vector option for clinical applications<sup>41</sup>. DPI is used for expulsion of vaccine through a nostril. By this method, an accurate dose reaches the lungs<sup>39,42</sup>.



**Figure 3:** Types of inhalers

## VACCINE IMMUNIZATION IN IMMUNOCOMPROMISED AND AUTOIMMUNE CONDITIONS

Immunosuppressive therapy patients are particularly vulnerable to Covid19-related morbidity and mortality<sup>43</sup>. Although it should be a top priority for healthcare practitioners and governments to vaccinate these communities, they have been largely omitted from vaccination trials<sup>2</sup>. The main rationale for these exclusions is that immunosuppressive medications can impede vaccine-induced humoral and cellular immunological responses, making it impossible to assess the vaccine's immune system efficiency<sup>2,44</sup>. The number of studies on the safety and efficacy of vaccines in immunocompromised patients is limited, resulting in insufficient guidelines and data on vaccine administration in these patients<sup>45</sup>. Because of their underlying malignancy, cytotoxic chemotherapy, radiation, other existing comorbidities, and advanced age, cancer patients are particularly sensitive to unfavourable outcomes from mild and severe Covid19 infections<sup>46</sup>. Several case studies have shown how difficult it is to generate adequate immune protection in cancer patients against certain infectious antigens that cause infectious diseases, implying that developing an effective vaccine against SARS-CoV-2 for immunocompromised cancer patients will be difficult as well<sup>47,48</sup>. The lower-than-expected immune system response in cancer patients is considered to be due to anti-CD20 or cytotoxic medications, making mRNA vaccines less effective in these individuals<sup>49</sup>. Lower CD4/CD8 ratios, T-cell exhaustion, or persistent inflammation related to HIV infection despite effective antiretroviral therapy are thought to be mediated by lower CD4/CD8 ratios, T-cell exhaustion<sup>50</sup>. Reduced immunogenicity to SARS-CoV-2 mRNA vaccine has been shown in various immunocompromising circumstances, including solid organ transplantation, with data developing for further disorders<sup>51</sup>. When patients living with HIV were included in the analysis, efficacy dropped from 60% (95 percent CI 20–80) to 49% (6–73), according to researchers from the Novavax COVID-19 vaccine study's South African locations<sup>51,52</sup>. Similarly, autoimmune illnesses have a poor immunological response to the covid 19 vaccine. Nonetheless, in face of evidence, their safety and efficacy should be examined first and foremost<sup>53</sup>.

## REASONS FOR CHOOSING PULMONARY DELIVERY TECHNIQUE OVER OTHER TECHNIQUES FOR VACCINATION

An aspect to be considered in pulmonary vaccination is mucosal epithelium have high permeability, high perfusion rate, and low enzyme activity, having a number of immunocompetent cells, a larger surface area of 70-100 m<sup>2</sup>.<sup>4</sup> As pulmonary mucosal immune cells are triggered firstly to foreign particles. Inhalation vaccination results in high levels of antigen-specific IgA antibodies and tissue-resident memory T cells (Trms) in the respiratory tract<sup>54</sup>. Invading germs are immunological exclusion, complexing, and neutralization by secretory IgA antibodies, which cover the lung mucosa and protect the lungs<sup>55</sup>. Furthermore, pulmonary formulations have better stability

during product transport and handling, reducing injection site pain and needle contamination risk<sup>56</sup>, which are crucial considerations and manage cautiously, particularly for immunosuppressed patients who are vulnerable to minor contamination from vaccine needles due to their weakened innate immune reaction system or hyper-response<sup>57</sup>. When a parenteral COVID 19 vaccine is approved by the FDA, a change in administration method demands new clinical studies. Because these studies are so costly, governments and philanthropic funding are the most practical ways to fund the development and testing of inhaled COVID 19 vaccines<sup>47,57</sup>. To determine overall cost savings and benefits in illness management, pharmaco-economics cost-benefit modeling of introducing inhaled COVID 19 vaccination can be explored. The capacity of these nano-based vaccination formulations to lessen adverse effects and improve vaccine candidate efficacy is predicated on the nano-materials distinctive ability to induce strong immunomodulatory activities. This could be extremely important, notably in those who have altered immune responses, such as people with cancer, and could be a key tool in producing vaccines that are not only safe yet very successful in cancer patients and other immunocompromised people<sup>47</sup>.

## CONCLUSION

Innovative inhaled medications for lung disorders, as well as many other infectious and non-infectious diseases, have been created for decades and continue to increase exponentially. In comparison to intramuscular and subcutaneous immunization, pulmonary vaccination is significantly superior in respiratory disease. Inhalation delivery of anti-SARS-CoV-2 medicines and vaccines is a potential, non-invasive route of administration with distinct advantages such as the rapid onset of action, targeted vaccine delivery, reduced systemic circulatory vaccine dose, less systemic toxicities. Many liquid formulation vaccines decayed during the Covid-19 pandemic due to a lack of cold chain storage conditions, this can be avoided by producing vaccines in dry powder form

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