What's Next for Respiratory Virus Vaccines?

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Current Landscape of Respiratory Virus Vaccines

Inactivated vaccine

- Based on chemically and/or physically inactivated virus grown in cell culture
- Advantages: stable, no risk of reversion, cost-effective, relatively easy to manufacture
- Ex: *Influenza IIVc, aIIV, IIV-HD[2,3]

Recombinant subunit vaccine

- Composed of assembled nanoparticles coated with purified or recombinant viral antigens; often formulated with adjuvants
- Advantages: no risk of infection or reversion, fewer side effects, easy antigen modification
- Ex: SARS-CoV-2 Nuvaxovid® (Novavax);[4] RSV Abrysvo® (Pfizer)[5] and Arexvy® (GSK)[6]

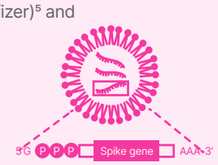
Live attenuated vaccine

- Uses a weakened version (with limited replication extent) of the living virus
- Advantages: preserves native antigen and mimics natural infection, induces long-term immunity, no adjuvants required
- Ex: Influenza Fluenz® (AstraZeneca)[2]

Viral vector vaccine

- Adapts existing successful and safe modified viral vectors to express viral proteins
- Advantages: induces strong cellular and humoral immunity, preserves native antigen, mimics natural infection
- Ex: **SARS-CoV-2 Vaxzevria™ (Oxford/AstraZeneca)[7]

RNA vaccine



- Uses mRNA packed in lipid nanoparticles
- Advantages: safe and well-tolerated, highly adaptable to new pathogens, native antigen expression
- Ex: RSV: mResvia® (Moderna);[8] SARS-CoV-2 Spikevax® (Moderna)[4] and Comirnaty® (BioNTech/Pfizer)

Adapted from Al-Jighefee et al.[1] *Move from quadrivalent to trivalent formulation for 2025–2026 season[2,3] **EMA marketing authorisation was withdrawn in May 2024[7]

Future Directions in Mucosal Vaccine Development

Improving delivery systems to enhance vaccine bioavailability

- Adenoviral vectors are thermostable and can transduce a broad range of cells in the mucosa[10]
- Lipid nanoparticles have emerged as promising vehicles for mRNA delivery[15]
- Chitosan, a biocamptible polymer, can act as both a delivery vehicle and immunostimulatory molecule[10,15]

Developing more effective mucosal vaccine adjuvants

- TLR agonists are potent immune adjuvants: TLR4 agonists activate APCs and innate immune cells, favouring strong Th1-associated humoral responses; TLR5-specific flagellin activates both the innate and adaptive immune system[10,15]
- However, selection of adjuvants with a low inflammatory profile is critical to avoid safety concerns

Long-term boosting of innate immune responses through "trained immunity"

- BCG, oral polio, and measles vaccines, as well as PRR ligands LPS, flagellin, and β-glucans, have shown evidence of cross-protection against mucosal pathogens, but more studies are needed to confirm safety profiles[10,14]

Understanding the association of mucosal immune markers with clinical outcomes

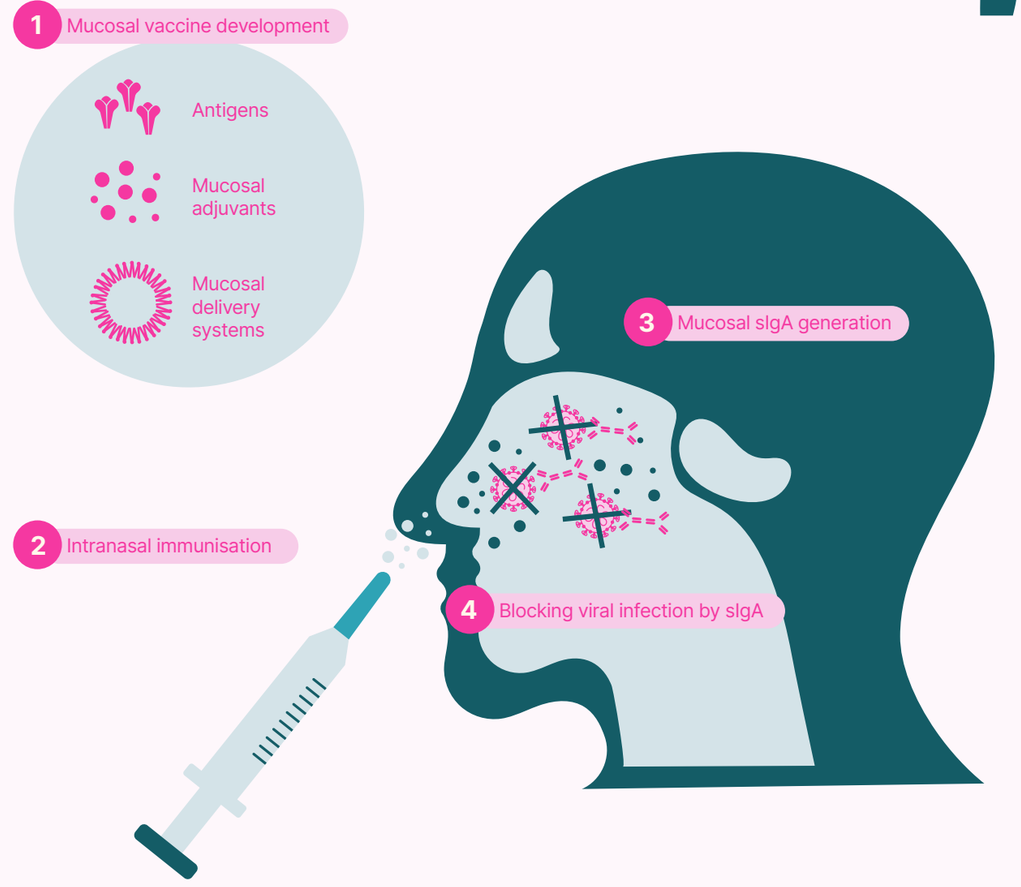
- New technologies like CHIM, single-cell RNA-seq, antigen-specific T-cell proliferation assays, and highly sensitive mucosal antibody assays are advancing the field of mucosal immunology[9,14]

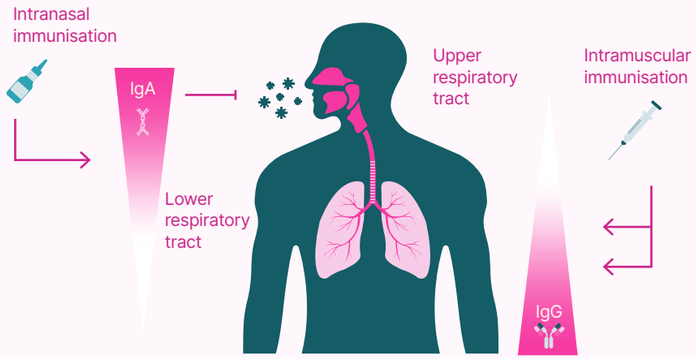
Considering public health implications with vaccine acceptance as a priority

- Administration routes and vaccine schedules need to be optimised, with a focus on at-risk populations[14,16]

Next-Generation Vaccines: Towards Mucosal Immunity

- Very few mucosal vaccines for respiratory viral infections have been approved (Fluenz®, the only nasal influenza vaccine, is approved in children aged 2–18 years)[2]
- Most respiratory virus vaccines are given intramuscularly, protecting against severe lower airway disease but not necessarily against upper airway viral replication and transmission[9]
- Preclinical evidence has shown that mucosal vaccines can induce superior protection by eliciting a robust mucosal immune response, but this has proven difficult in humans[11]





Advantages:

(1) Production of secretory IgA in mucosa-associated lymphoid tissues blocks viral spread from upper respiratory tract[9,10]

(2) IgG and IgM antibodies in the nasal mucosa can neutralise virions and activate complement[12]

(3) Tissue-resident memory B and T cells offer long-term immunity at mucosal sites and a rapid response to reinfection[9,10]

(4) The mucosa also sheds pathogens, so mucosal immunity would prevent transmission in case infection gets established[10,11]

(5) Induction of mucosal immunity at one site may protect other mucosal sites, also producing robust systemic immunity[10]

(6) Mucosal vaccines offer needle-free administration, potentially improving vaccine uptake and accessibility in underserved regions[10]

Mucosal vaccine
Virus
sIgA

Key challenges:

- Tolerance to foreign antigens by the mucosal innate immune system, essential for avoiding inflammatory responses to harmless antigens, hampers the efficacy of mucosal vaccines[10,13]
- Vaccine delivery via the mucosal route is impeded by dilution in mucosal secretions, enzymatic degradation, and the epithelial barrier[13]
- A better understanding of immune correlates of protection is needed to inform selection of mucosal vaccine platforms, adjuvants, and immune markers that should be measured in clinical trials[9,14]
- Efficient routes of mucosal vaccine delivery to the lower respiratory tract are still under investigation (e.g., oral vs intranasal vs intratracheal)[9,11]

Abbreviations
aIIV: adjuvanted inactivated influenza vaccine, APC: antigen-presenting cell, BCG: Bacillus Calmette-Guérin, CHIM: controlled human infection model, DC: dendritic cell, IIV-HD: high-dose inactivated influenza vaccine, LAIV: live attenuated influenza vaccine, LPS: lipopolysaccharide, NK: natural killer, PRR: pathogen recognition receptor, RBD: receptor-binding domain, TLR: toll-like receptor.

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