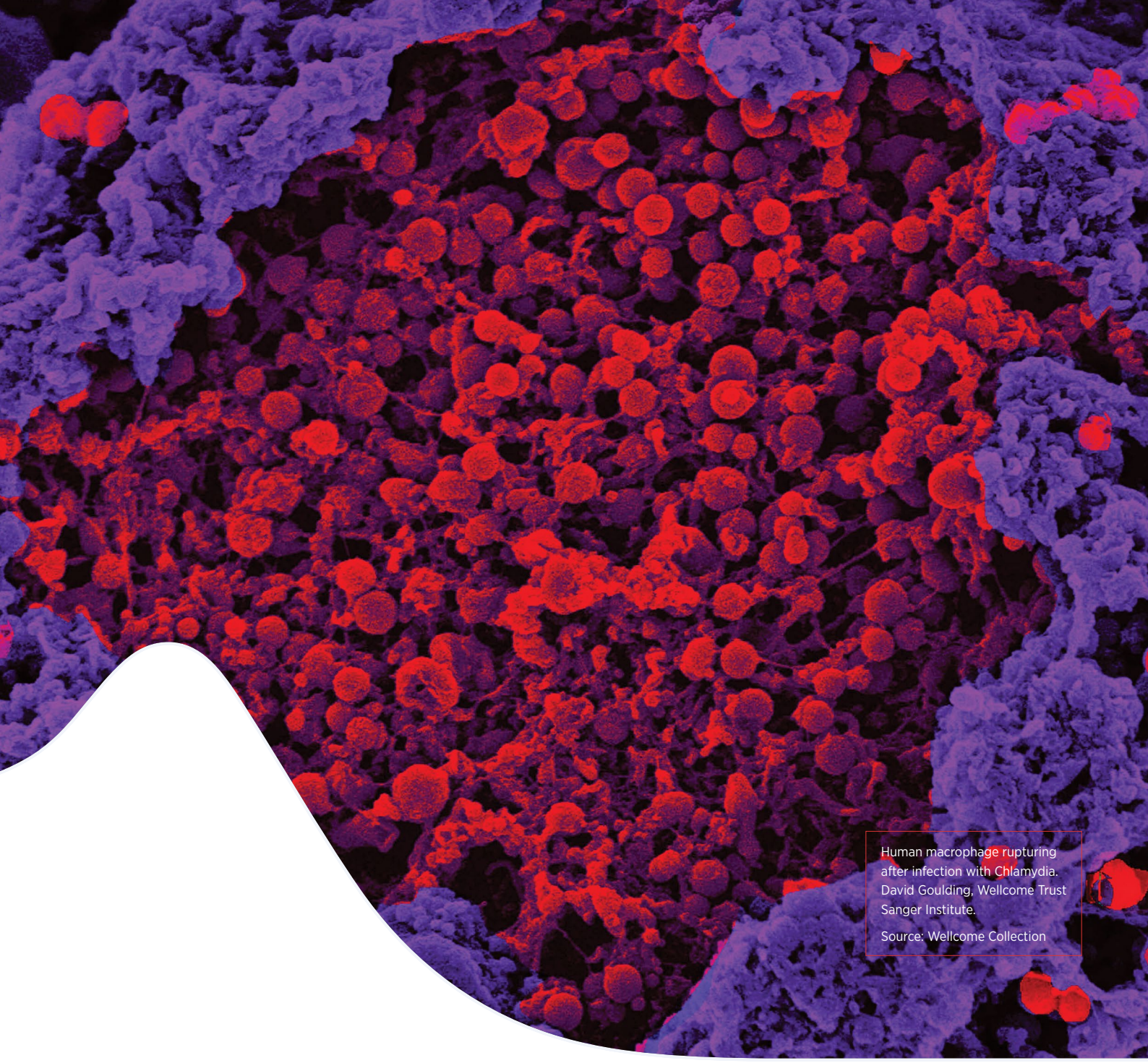

Human macrophage rupturing after infection with Chlamydia. David Goulding, Wellcome Trust Sanger Institute.

Source: Wellcome Collection

Landscape Review of Vaccine-Induced Mucosal Immunity

Framing the evidence, challenges and path forward to harness mucosal immunity for improved protection

2025

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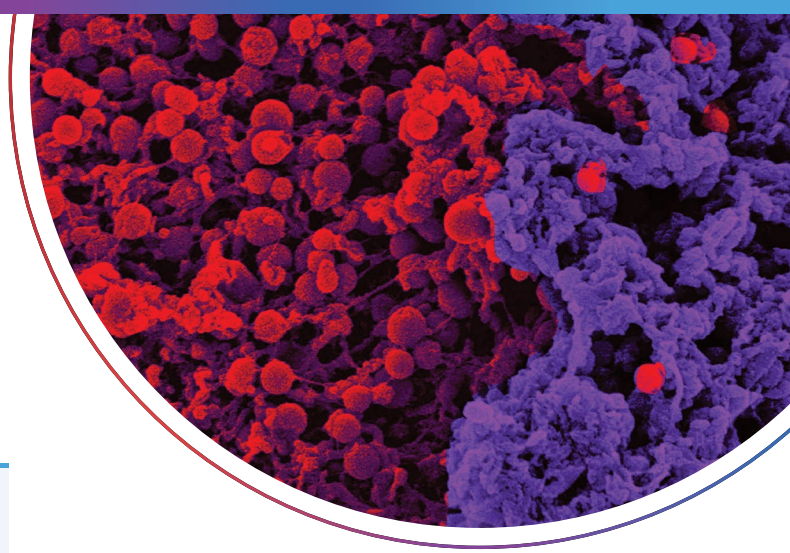

About this Report

Wellcome is a politically and financially independent global charitable foundation that supports science to solve the urgent health challenges facing everyone. Wellcome supports discovery research into life, health and wellbeing, and in 2021, established the Infectious Disease Health Challenge, whose vision is a world in which the impact of infectious diseases is minimised in the most affected communities, creating a healthier future for everyone.

The Novo Nordisk Foundation is an independent Danish enterprise foundation committed to improving people's health and the sustainability of society and the planet. This is achieved through supporting a wide range of projects and initiatives within three main focus areas: Health, Sustainability, and Life Science Ecosystem.

Next Frontier Advisors (NFA) is an independent consulting firm that specialises in helping organisations understand and navigate complex R&D landscapes. With decades of experience across the R&D value chain, NFA is a trusted partner helping clients maximise the impact of vaccines and immunotherapies against major global diseases. NFA is committed to evidence-based decision-making and partners with clients to develop strategies and programs that address medical needs, foster collaboration, and drive sustainable progress toward global health goals.

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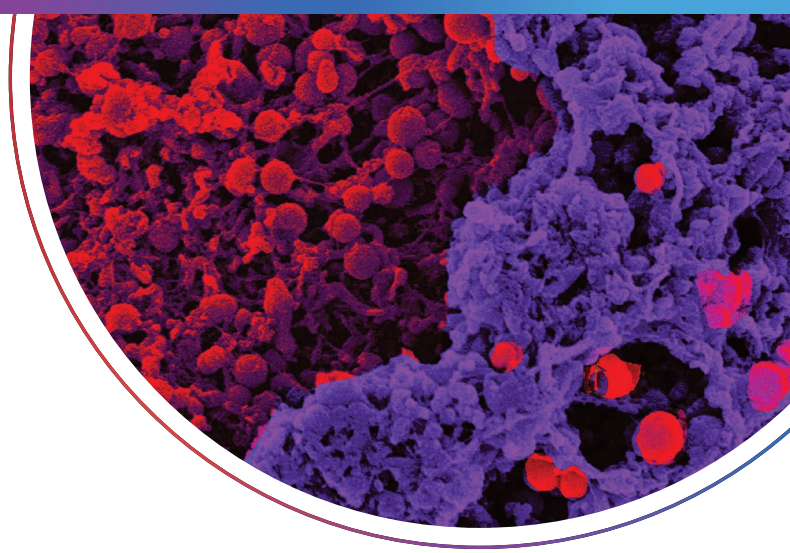

Landscape Review of Vaccine-Induced Mucosal Immunity

Framing the evidence, challenges and path forward to harness mucosal immunity for improved protection

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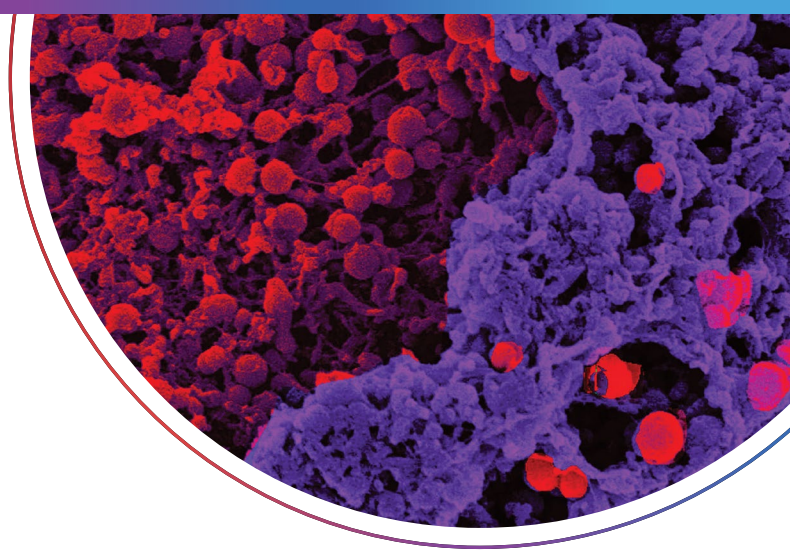
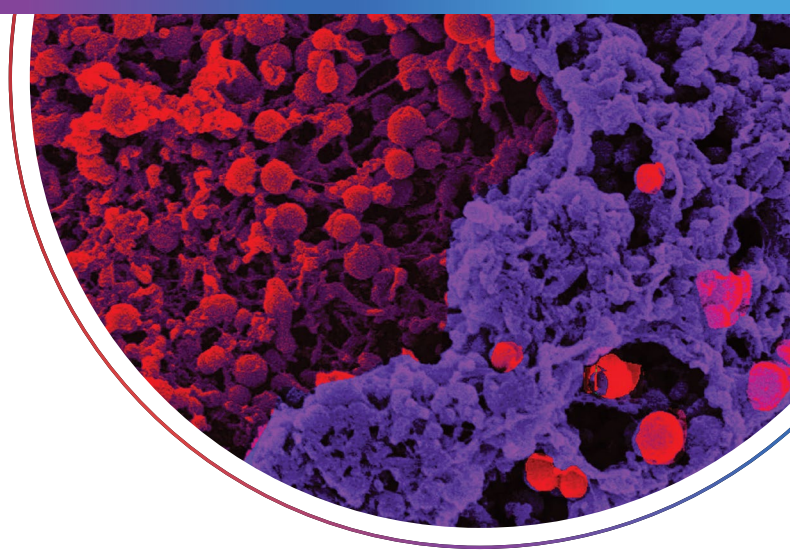


Glossary

ADP	Adenosine Diphosphate
AH	Aluminium Hydroxide
AP	Aluminium Phosphate
BCR	B Cell Receptor
CHIM	Controlled Human Infection Model
CoP	Correlate of Protection
COVID-19	Coronavirus Disease 2019
DNA	Deoxyribonucleic Acid
EED	Environmental Enteric Dysfunction
EMA	European Medicines Agency
FDA	Food and Drug Administration
GALT	Gut-Associated Lymphoid Tissue
GAS	Group A Streptococcus
GBS	Group B Streptococcus
GI	Gastrointestinal
GU	Genitourinary
HI	Hemagglutination-Inhibition
HBGA	Histo-Blood Group Antigen
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
ID	Intradermal
IIV	Inactivated Influenza Vaccine
ILC	Innate Lymphoid Cell
IM	Intramuscular
IN	Intranasal
iNTS	Invasive Non-Typhoidal Salmonella
IPV	Inactivated Polio Vaccine
KOL	Key Opinion Leader
LAIV	Live Attenuated Influenza Vaccine
LMIC	Low- and Middle-Income Country
MAIT	Mucosal-Associated Invariant T cells
MALT	Mucosa-Associated Lymphoid Tissue cells
MAP	Microarray Patch
mRNA	Messenger Ribonucleic Acid
NTS	Non-Typhoidal Salmonella
OPKA	Opsonophagocytic Killing Assay
OPV	Oral Polio Vaccine
OSP	O-Specific Polysaccharide
PCV	Pneumococcal Conjugate Vaccine
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RA	Recommendation Area
RNA	Ribonucleic Acid
SBA	Serum Bactericidal Assay
SC	Subcutaneous
sIgA	Secretory Immunoglobulin A
sIgG	Secretory Immunoglobulin G
ss-RNA	Single-stranded RNA
TB	Tuberculosis
TLR	Toll-Like Receptor
TCR	T Cell Receptor
TRM	Tissue-Resident Memory (cells)
VLP	Virus-Like Particle
WHO	World Health Organisation

Executive Summary



Executive Summary

Pathogens that enter the body via mucosal surfaces are responsible for significant global morbidity, mortality, economic burden, and pandemic risk. While there are highly efficacious vaccines for some of these pathogens, others offer limited protection, particularly within high-risk populations. For many other pathogens, effective vaccines remain elusive.

Mucosal immunity is a fundamental component of the immune system and the body's first line of defence at sites of pathogen entry. Vaccines that induce mucosal immune responses in addition to systemic immunity may offer important advantages, including improved protection at the site of infection, reduced transmission, and potentially longer durability. Mucosally delivered vaccines may also provide practical benefits, including needle-free delivery, easier administration, and improved access in resource-limited settings.

The Wellcome Trust and the Novo Nordisk Foundation commissioned this landscape to assess the current state of the field, identify promising areas for innovation and collaboration, and define priorities to accelerate the development of human vaccines to induce mucosal immunity. Extensive literature reviews and input from key opinion leaders revealed a broad consensus on the principle that inducing mucosal immunity should improve vaccine effectiveness and, thereby, enhance global health outcomes.

However, consensus is not the same as evidence.

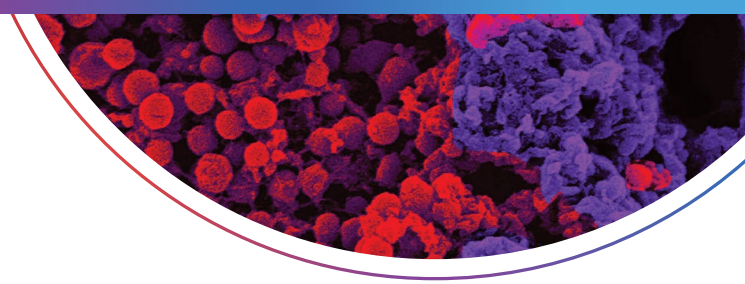
There is limited direct evidence in humans of the relative role of mucosal immunity in protection against natural infection. Additionally, few studies offer clear evidence that vaccine-induced mucosal responses are necessary or advantageous for protection. This evidence gap, along with technical and systemic barriers, has slowed progress and discouraged investment.

Generating clinical proof that vaccine-induced mucosal immune responses improve protection would mark a turning point in the vaccine field, enabling prioritisation, increased investment, and regulatory clarity, all of which would help accelerate progress.

Pathogens included in this landscape review:

- ***Respiratory:*** Group A streptococcus (GAS), influenza virus, measles virus, *Mycobacterium tuberculosis* (TB), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; COVID-19), *Streptococcus pneumoniae.*
- ***Enteric:*** *Vibrio cholerae*, rotavirus, typhoidal Salmonella, nontyphoidal Salmonella (NTS), *Shigella* spp.
- ***Genitourinary:*** *Chlamydia trachomatis,* group B streptococcus (GBS), herpes simplex virus (HSV), human immunodeficiency virus (HIV), human papillomavirus (HPV), *Neisseria gonorrhoeae* (NG).

Pathogens were selected based on a combination of criteria, including alignment with WHO's prioritisation, interest of the respective foundations, and the potential to contribute meaningful insights into this landscape review.



High-Level Findings by Tissue Tract

The examples below highlight tract-specific patterns, scientific barriers, and areas of active innovation drawn from a substantial body of research that has advanced understanding to date and can inform future strategies.

Respiratory Tract

- **Heavy burden; ongoing gaps:** Respiratory infections remain a leading cause of global morbidity and mortality. While several systemic vaccines have reduced the severity of disease, many do not prevent infection or transmission, highlighting the potential for mucosal strategies, including those for pandemic preparedness.
- **Complex mucosal immunology:** The respiratory tract features distinct upper and lower compartments, each with specialised immune structures. No validated mucosal correlates of protection have yet been identified.
- **Emerging tools and platforms:** Licensed intranasal vaccines for influenza and COVID-19 show that airway-targeted delivery is possible. Sampling tools and CHIMs offer platforms for generating mechanistic insights and accelerating vaccine development.
- **Safety and formulation challenges persist:** Formulations must overcome mucosal barriers while maintaining tolerability and local immune engagement. Because the airway is highly sensitive to inflammation, safety considerations are a priority.

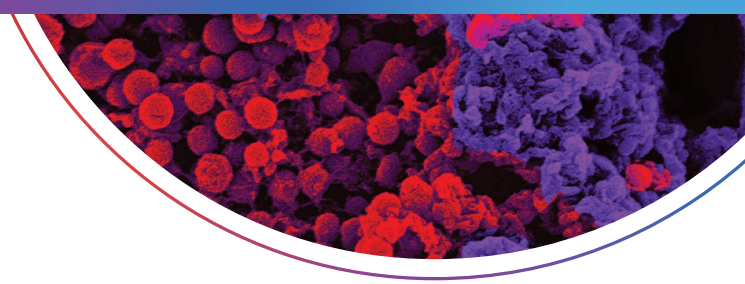
Gastrointestinal (GI) Tract

- **Experience to build on:** There are decades of experience delivering vaccines to the relevant mucosa by oral delivery.
- **Variable efficacy remains a challenge:** Oral vaccines consistently show reduced performance in low- and middle-income countries (LMICs), due to complex factors including microbiota, enteropathy, and early-life immune imprinting.
- **Sampling is invasive; surrogates are underdeveloped:** Gut biopsies offer direct data but are not scalable. Blood-based proxies and stool-based IgA show promise but require further validation.
- **Correlates still undefined:** Even for licensed oral vaccines, universally accepted mucosal immune correlates are lacking, limiting rational design and iterative development.

Genitourinary (GU) Tract

- **High burden, thin pipeline:** GU pathogens impose substantial global health burdens, yet HPV remains the only GU pathogen with a licensed vaccine; most others lack candidates in late-stage development.
- **Immunological complexity and variation:** The GU tract is shaped by sex-specific anatomy, hormonal cycles, inflammation, and a dynamic microbiome. These features influence both susceptibility to infection and vaccine responsiveness, making it difficult to generalise findings across populations.
- **Sampling challenges:** Sampling can be invasive or socially sensitive, and measurement tools are still underdeveloped, particularly in men.
- **Some success, growing promise:** Novel approaches, such as prime-pull strategies, mucosal boosting, and cross-site induction, are being explored. Work is underway to establish and qualify assays and baseline immunology in the female GU tract.

Together, these tract-specific findings underscore the need for enhanced tools and foundational understanding, along with tailored vaccine strategies that account for anatomical and pathogen-specific nuances.



Challenges

While clinical proof is lacking, substantial research across the major anatomical tracts has helped identify several persistent scientific and structural challenges that must be addressed:

Complex biology. Mucosal surfaces are not a single immunological compartment. Immune architecture varies and is shaped by distinct microbial environments, tissue structures, and immune cell distributions, making it difficult to extrapolate from one mucosal site to another and even harder to generalise across vaccine platforms or pathogens.

Diverse pathogens. The immune requirements for protection differ across pathogens, and the relative contributions of mucosal versus systemic immunity remain poorly defined.

Sampling challenges. Mucosal tissues are challenging to access, and optimal sampling methods are often invasive, variable in yield, or unsuitable for large-scale trials, thereby complicating analysis.

Lack of standardized measurement tools. There is no gold standard for assessing mucosal immune responses. Assays are often adapted from systemic studies, lack validation, and vary in sensitivity and reproducibility, making comparisons across trials or pathogens nearly impossible.

Uneven use of next-generation tools. The assessment and analysis of mucosal immunity must keep pace with ongoing laboratory advances and breakthroughs in the understanding of human immunology.

Poorly defined mechanisms and correlates. Validated mucosal correlates of protection are lacking for most pathogens, and there are no validated mucosal correlates of protection for the pathogens included in this report. Mechanistic understanding remains limited, making it difficult to define optimal immune endpoints, design comparative studies, or align regulatory pathways.

Underexplored adjuvants. Few mucosal-specific adjuvants have been clinically validated or approved for human use, and their mechanisms of action are generally not well characterised.

Safety is paramount. Local inflammation, immune tolerance, and rare but serious adverse events have been observed in past trials of mucosally delivered vaccines, particularly with adjuvanted formulations. Careful safety profiling is essential to regain confidence and support regulatory approval.

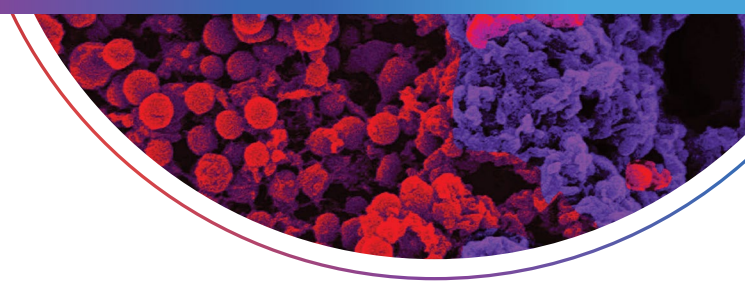
Research siloes. Research efforts are often siloed by anatomical site, pathogen, or technical speciality. Many LMICs, which bear the highest burden of mucosal pathogens, lack the infrastructure to engage in mucosal immunology research at scale.

These barriers are mutually reinforcing. The difficulty of sampling limits data generation; this lack of data discourages investment; and the absence of investment slows the development of tools and talent. The result is a vicious cycle in which promising ideas fail to translate into actionable products or policies.

Key Opportunities

Advances in immunology, delivery platforms, and analytical tools are reshaping the broader vaccine landscape, offering opportunities to address some of these persistent obstacles and enable more targeted, effective mucosal vaccine development.

- **Next-generation tools,** such as highly sensitive multiplex assays, organoid and chip-based models, and spatial imaging, are enabling the study of mucosal immunity with greater precision than ever before. AI-enabled technologies are transforming vaccine development across the product development continuum.
- **Innovative delivery platforms,** including intranasal sprays, oral tablets, and aerosolised formulations, are expanding the feasibility of mucosal vaccination.
- **Controlled human infection models** and other experimental medicine studies offer a practical and ethical way to test mucosal immune hypotheses directly in humans.
- **Respiratory pathogens present unique opportunities** for exploring mucosal immunity. Widely used systemic and mucosal vaccines for SARS-CoV-2 and influenza allow researchers to assess how mucosal immune responses contribute to protection using next-generation tools.



Summary of Recommendations

The report outlines a five-part strategy to advance the development of vaccines that induce protective mucosal immunity. These challenges are all interrelated, which is why enhanced collaboration is essential to align research priorities and ensure coordination.

1

Expand the tool kit and capacity to interrogate mucosal immunity.

- Ensure fit-for-purpose sampling and assays are conducted whenever possible.
- Leverage next-generation tools and technologies
- Develop field-adapted mucosal sampling and assay capacity suitable for LMIC settings.

2

Strengthen the evidence base for the importance of mucosal immunity for protection.

- Design experimental medicine studies to directly compare mucosal and systemic immune responses.
- Leverage planned clinical trials to link efficacy with the level of mucosal immunity.

4

Accelerate development of vaccines that are safe, induce mucosal immunity, and address major medical needs.

- Establish mucosal correlates of protection, including systemic surrogates, to guide product development.
- Incorporate mucosal endpoints in target product profiles when appropriate.
- Expand evidence base around ‘prime and pull’ strategies.
- Continue to develop and advance novel adjuvants and delivery platforms.
- Explore co-interventions to enhance mucosal immunity.

3

Improve foundational understanding of mucosal immunity.

- Determine how to induce immune responses at different mucosal sites.
- Measure the extent of mucosal responses generated by systemic vaccination and by cross-talk between mucosal sites.
- Demonstrate how population-based changes in mucosal immunity affect protection.
- Analyse vaccine-induced versus natural mucosal immunity to inform vaccine design.
- Pre-position protocols and partnerships for rapid response in outbreaks.

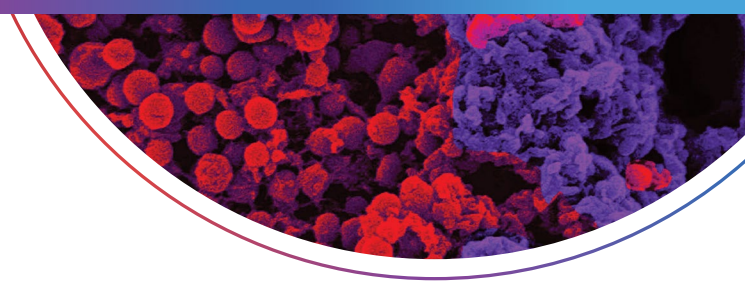
5

CORE ENABLING FACTOR

Establish and promote mechanisms and incentives for cross-disciplinary collective action.

- Create and/or strengthen cross-disciplinary consortia and working groups to align priorities, harmonise tools, and foster collaboration across the mucosal vaccine field.
- Expand training and career incentives for mucosal immunology.
- Provide additional funding within clinical trials to collect data on mucosal immunity.

While each area addresses a discrete challenge, they are mutually reinforcing: clear clinical evidence drives investment; better tools enable more rigorous and foundational science; enhanced data drives rational vaccine design and testing. Enhanced collaboration is essential to align research priorities and drive coordination, ensuring that the field generates the evidence needed to demonstrate clinical proof of concept.



Conclusion

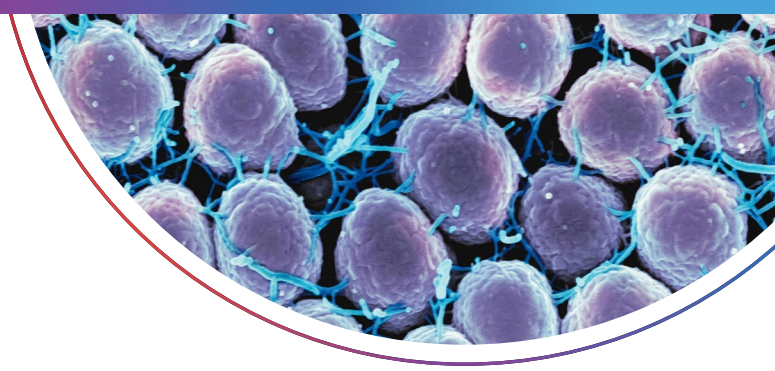
Vaccines that induce mucosal immunity offer a promising pathway to strengthen protection against many of the world's highest-burden pathogens. Yet despite this potential, progress has been constrained by several persistent scientific and structural challenges.

While these challenges are certainly daunting, advances in immunology, delivery platforms, and sampling tools provide a foundation for meaningful progress. Success is not guaranteed; unlocking the full value of mucosal immunity will require sustained investment, deeper collaboration, and a willingness to test new approaches across research and development.

This report offers a series of recommendations to address longstanding gaps in mucosal immunology and to chart a path toward the development of a new generation of safe and effective mucosal vaccines. To achieve this goal, new mechanisms that promote cross-disciplinary collective action will be required to accelerate the development of highly effective vaccines that promote mucosal immune responses.

> **"People are working on all these interesting questions, and actually doing all this interesting research, but it's the bringing of it together somehow that's missing. We need a catalyst for bringing it together."**
>
> — KOL INTERVIEW

Introduction



Introduction

About the Project

Many of the world's most significant pathogens enter the body through mucosal surfaces. Yet, there are still major gaps in understanding mucosal immunity and challenges to developing vaccines that are designed to specifically stimulate or optimise immune responses at mucosal tissues. The Wellcome Trust and the Novo Nordisk Foundation (NNF) commissioned this landscape to assess the current state of the field, identify promising areas for innovation and collaboration, and define priorities to accelerate the development of human vaccines to induce mucosal immunity.

Both Wellcome and NNF have prioritised infectious diseases as a key area of investment. This project builds on their complementary missions to support research and innovation to improve the health, well-being, and sustainability of society.

The landscape analysis for this report was conducted by Next Frontier Advisors (NFA), a scientific consultancy firm with a focus on global health R&D and deep expertise in vaccine development, immunology, and global health.

Problem Statement: Pathogens that enter the body via mucosal surfaces are responsible for significant global morbidity, mortality, economic burden, and pandemic risk. While there are highly efficacious vaccines for some of the pathogens reviewed, others offer limited protection, particularly within high-risk populations. For many other pathogens, effective vaccines remain elusive.

Vaccines capable of inducing mucosal immune responses offer theoretical benefits, including augmenting systemic immunity, blocking infection at the point of entry, reducing ongoing transmission, increasing accessibility, and lowering costs. However, critical gaps persist in our understanding of mucosal immunity and its role in vaccine protection.

Despite decades of research, it is still largely unknown which mucosal mechanisms confer protection, how to elicit and best measure protective mucosal responses in humans, and how these responses vary across populations. A combination of scientific and structural barriers has slowed progress on vaccines that could offer meaningful advantages in disease prevention, particularly in LMICs.

Scope: The report provides a review of the state of mucosal vaccine research and development for 16 pathogens spanning the respiratory, enteric, and genitourinary mucosal entry routes. Its scope includes:

- Parenteral and mucosally delivered **licensed vaccines** against mucosal pathogens
- The pipeline of **clinical-stage vaccine candidates** targeting mucosal pathogens
- The pipeline of **exploratory adjuvants** in development for mucosal vaccines targeting mucosal pathogens

Pathogens were selected based on a combination of criteria, including alignment with WHO prioritisation, foundation interest, and the potential to contribute meaningful insights into this landscape review.

- ***Respiratory:*** Group A streptococcus (GAS), influenza virus, measles virus, *Mycobacterium tuberculosis* (TB), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; COVID-19), *Streptococcus pneumoniae.*
- ***Enteric:*** *Vibrio cholerae,* rotavirus, typhoidal Salmonella, nontyphoidal Salmonella (NTS), *Shigella* spp.
- ***Genitourinary:*** *Chlamydia trachomatis,* group B streptococcus (GBS), herpes simplex virus (HSV), human immunodeficiency virus (HIV), human papillomavirus (HPV), *Neisseria gonorrhoeae* (NG).

These 16 pathogens are not intended as an exhaustive list. Both the authors and the foundations recognise that many others could add value to this report. In that spirit, the report is intentionally structured in a modular fashion to accommodate the addition of new pathogens or updates to existing ones as new data emerge, technologies evolve, and progress is made.

Research that is primarily basic in nature and preclinical data are outside the scope of this project, except as they apply to the general understanding of one of the included pathogens or mucosal biology overall.

Photo: *Neisseria gonorrhoeae* bacteria. Source: NIAID

Key Definitions

For purposes of this report, mucosal immunity and specific mucosal tissues are defined as follows:

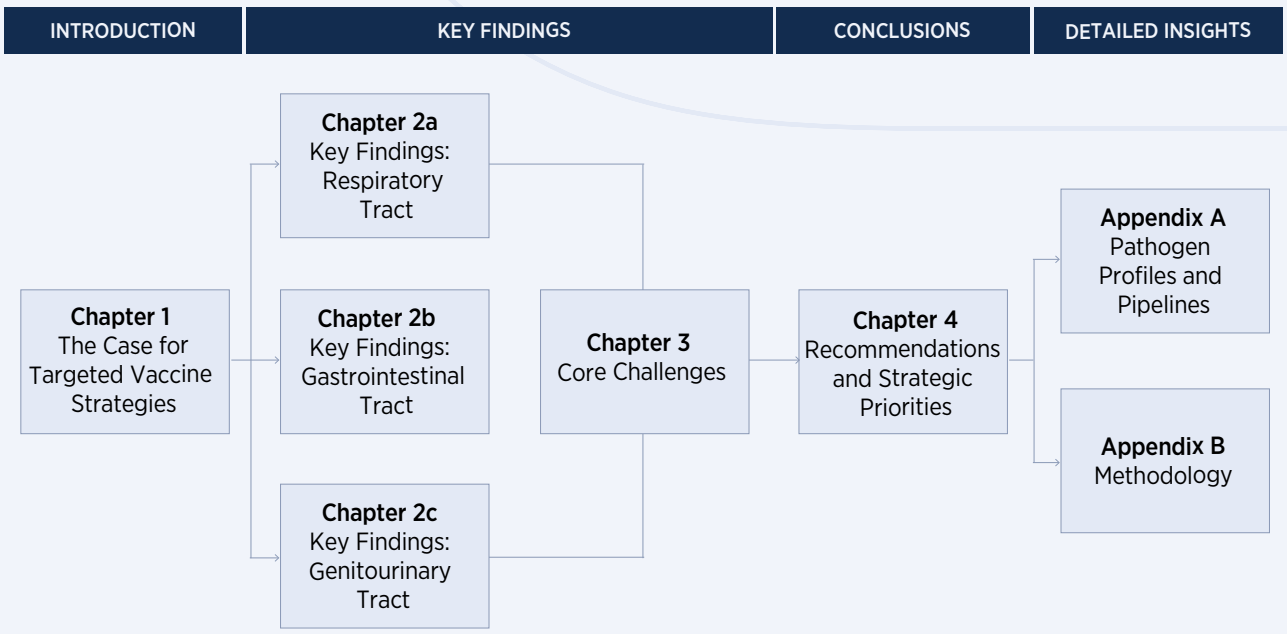
- **Mucosal immune response:** serological and cellular immune mediators present at the mucosal barrier, whether induced by vaccine (mucosally or parenterally delivered) or by infection.
- **Mucosal vaccines:** vaccines administered via mucosal routes, such as oral, intranasal, aerosol, intravaginal, and intrarectal.
- **Vaccines that induce mucosal immunity:** includes any vaccine delivered parenterally or mucosally that results in measurable immune responses at mucosal sites.
- **Mucosal barrier:** physical barriers that impede pathogen entry but are not pathogen-specific, excluding skin.
- **Mucosal surface(s):** lining of the body's organs and cavities that are exposed to the outside environment.
- **Respiratory mucosa:** tissues that line the nasal, upper airway, and lung surfaces.
- **Gastrointestinal mucosa:** tissues that line the oral, stomach, intestinal, colonic, and rectal surfaces.
- **Genitourinary mucosa:** the tissues lining the female and male reproductive tracts, bladder, and urethra.

Goals and Objectives

The report is intended as a strategic resource for a broad set of stakeholders, including funders, researchers, and vaccine developers. The pathogen-specific analysis and overarching recommendations are designed to support informed decision-making by meeting the following objectives:

- **Analyse the current understanding of vaccine-induced mucosal immunity** for human respiratory, enteric, and genitourinary pathogens.
- **Identify critical gaps** in knowledge and translational readiness, including mechanisms of protection, correlates of protection, and delivery bottlenecks.
- **Provide actionable recommendations** that can inform both near-term investment and long-term research agendas aimed at accelerating the development and deployment of vaccines to induce/optimise mucosal immunity.
- **Enable high-level comparisons across pathogens and mucosal compartments** to support priority setting and portfolio planning.

Report Structure



Approach

This landscape assessment applied a mixed-methods approach to capture the current state of mucosal vaccine development across a diverse set of pathogens.

The first step of the analysis involved a comprehensive literature review and pipeline mapping, focusing on mucosal immunology, vaccine development, and product pipelines. Systematic search strategies and targeted reviews were employed across clinical trial databases, scientific publications, and grey literature.

The second step was to gather input from experts in the field to ensure that the landscape analysis accurately reflected expert perspectives and included recent innovations and emerging trends. A formal Expert Advisory Group (EAG) convened at key milestones to review findings, validate assumptions, and advise on emerging priorities. In addition, individual Key Opinion Leader (KOL) interviews, as well as a facilitated KOL meeting, were conducted to provide detailed insights into pathogen-specific challenges and systemic barriers, and to help solidify opportunities for advancing mucosal immunity research (see acknowledgements for a complete list of experts consulted). Transcripts and notes from expert engagements were analysed thematically and informed recommendations and pathogen-specific findings.

This report provides a pathogen-specific scoring and assessment. Each of the 16 target pathogens was evaluated using a two-part process that allowed for both comparability across pathogens and the articulation of disease-specific insights. The qualitative summaries integrate recent review articles, expert input, and pipeline characteristics to understand key elements related to mucosal immunity and identify core challenges, as well as promising research opportunities. A quantitative scoring system was assigned for each pathogen, using a semi-structured rubric (Appendix A) that covered three dimensions: medical need, knowledge gaps, and vaccine development challenges.

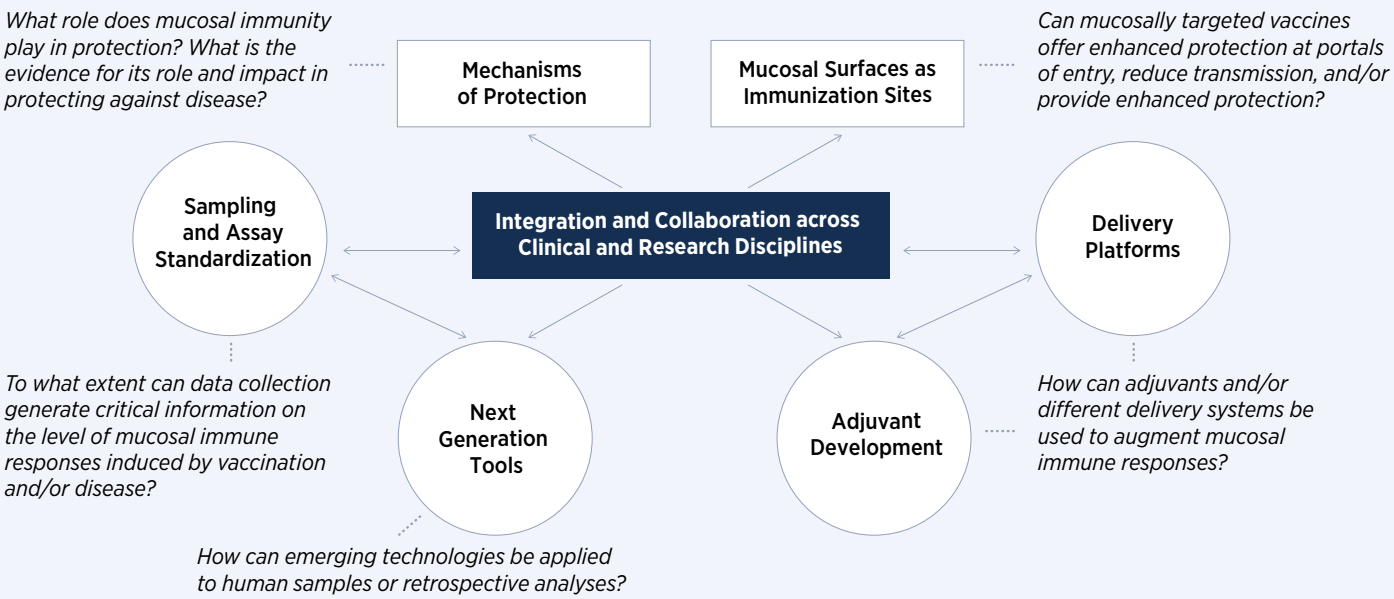
To synthesise these findings and maximise their utility, data from the literature review and pathogen research were organised by target tissues, ensuring that key distinctions and nuances are respected. Recommendations were integrated into a five-part framework designed to reflect both near-term and long-term needs for the overall mucosal field. The framework is utilised again in the pathogen snapshots (Appendix A) to categorise pathogen-specific recommendations. Outputs were validated through internal review and external feedback from the advisory group and selected stakeholders.

Framing the field: key considerations and organising themes.

This report introduces a **concept map** to help organise the assessment of the field of mucosal immunity. The concept map identifies six major topic areas that are critical to the advancement of mucosal vaccinology. These topics emerged from themes identified in multiple EAG and KOL discussions and are areas where experts agree that key scientific questions exist, potential solutions can be sought to address these questions, and deep expertise is required.

Throughout the generation of this report, the concept map helped organise the key questions, data analysis, and discussion, and was essential to the development of the conclusions and recommendations for advancing the field.

Concept Map: Key Questions



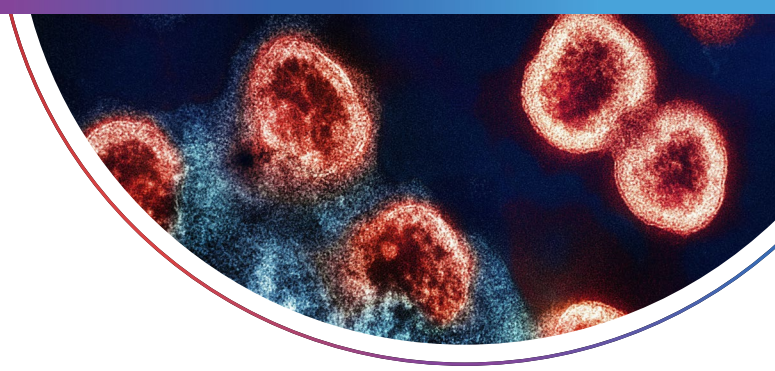
Importantly, the topic areas in the concept map are highly interdependent; therefore, addressing them adequately will depend on greater integration and collaboration across disciplines and disease areas, linking immunologists, clinical trialists, vaccinologists, and delivery experts to ensure that progress is made in overcoming both scientific and structural obstacles to mucosal vaccine development.

The authors recognise that mucosal immunity overall is shaped by a complex set of interrelated variables, many of which extend beyond the scope of this review. These include a range of product- and population-specific characteristics that may influence both the quality and durability of mucosal immune responses. While many of these determinants lie outside the primary focus of this landscape analysis, they are acknowledged throughout the report in instances when the literature or expert input underscores their relevance. In particular, population-level variables such as age, immune imprinting from prior infections, co-infections, and microbiome composition may influence mucosal immunity in ways that are currently poorly understood.

These broader immunological and implementation science questions emerged as recurring themes across the literature and expert consultations. The report's recommendations highlight the need for further investigation into these factors as part of a long-term research agenda, particularly to ensure that mucosal vaccine strategies are effective and appropriate for the diverse populations most impacted by mucosal pathogens, including those in LMICs.

Chapter 1

The case for targeted vaccine strategies



The case for targeted vaccine strategies

Mucosal immunity is a fundamental component of the immune system, serving as the body's first line of defence at the primary entry points for many pathogens, including the respiratory, gastrointestinal, and urogenital tracts. These mucosal surfaces, which constitute the largest interface between the host and the external environment, are constantly exposed to a diverse array of microbial threats.

Despite the biological importance of mucosal immunity, its relevance to vaccine-induced protection in humans remains under-defined. In theory, vaccines that can induce strong mucosal immune responses, possibly in concert with systemic responses, may offer advantages, including the potential to block initial infection where the pathogen enters the body and to prevent ongoing transmission should infection occur. Mucosally administered vaccines may also improve accessibility by simplifying distribution, enabling needle-free delivery, and facilitating uptake in resource-limited settings.

Despite the consensus that mucosal immunity is important, there is limited direct evidence in humans of its relative role in protection against natural infection.

> "I've just heard the same story many times over of why mucosal immunity is important without ever being shown proof that it's true."
>
> — KOL INTERVIEW

While mucosal compartments exhibit unique characteristics and anatomies, the available literature and KOLs confirm that mucosal immunity represents a highly coordinated immune response. Some elements of mucosal immunity are prominently mediated by secretory IgA (sIgA), which helps in immune exclusion, a process that limits the access of numerous pathogens and mucosal antigens to the thin and vulnerable mucosal barriers. While these functions are well described, their direct relevance to vaccine-induced protection in humans remains an open question.

Observations from individuals with genetic immuno-deficiencies provide concrete evidence that at least one element of the mucosal immune system, sIgA, is important for protection against certain mucosal pathogens. Specific data includes:

- **Selective IgA Deficiency:** Individuals with selective IgA deficiency, despite normal systemic immunity, experience increased rates of mucosal infections, including respiratory,[1] gastrointestinal,[2] and urinary tract infections,[3] highlighting the protective role of mucosal IgA in natural infection contexts.
- **Selective IgA Deficiency and COVID-19:** The COVID-19 pandemic has renewed focus on the role of mucosal immune responses, especially as SARS-CoV-2 predominantly enters the host via the respiratory mucosa. Data suggest that mucosal IgA responses correlate with reduced viral load, decreased transmission, and enhanced protection, possibly even in the face of viral variants. Individuals with selective IgA deficiency not only face a higher risk of severe COVID-19 outcomes,[4] they also demonstrate poor vaccine-induced mucosal responses,[5] highlighting the limitations of COVID-19 vaccines that do not engage mucosal pathways.

These findings provide some direct evidence that mucosal immunity contributes to protection against natural infection in humans.

Additionally, there is limited clear evidence that vaccine-induced mucosal responses are necessary or advantageous for protection.

Comparative studies of mucosal versus parenteral vaccination can offer valuable insights into the distinct contributions of systemic and mucosal immune responses, helping to clarify the incremental or essential value of mucosal immunity for key elements of vaccine efficacy. For example, comparative studies of the **oral poliovirus vaccine (OPV)** and the **inactivated poliovirus vaccine (IPV)** have shown that while IPV effectively prevents paralytic disease through systemic immunity, it falls short in preventing intestinal replication and shedding of the virus.[6,7] In contrast, OPV stimulates both systemic immunity, which prevents the spread of poliovirus to the central nervous system and protects against paralysis, and robust mucosal immunity, which halts poliovirus replication at the major entry points, nasopharyngeal and gastrointestinal mucosal surfaces.[8,9]

Photo: HIV-1 virus particles replicating from an HIV-infected H9 T-cell (blue). Source: NIAID

This makes OPV an important tool in efforts toward polio eradication in LMICs, and suggests that, in the case of polio, induction of mucosal immunity is necessary for some, but not all, elements of efficacy.

Additional data from a meta-analysis of comparative clinical trials indicate that the **live-attenuated influenza vaccine (LAIV)**, administered as an intranasal spray, is superior in the production of mucosal IgA responses, whereas the **injectable inactivated influenza vaccine (IIV)** is superior in producing systemic IgG responses. However, they are approximately equivalent in efficacy.[10,11] For IIV, the induced level of serum HI titers has been used as a correlate of protection; this measurement is not a correlate of protection for LAIV0.[12,18] Unfortunately, limited information is available for other relevant immune response parameters at the mucosa, such as T cell responses.

There is also evidence from preclinical studies on **SARS-CoV-2 vaccines** indicating that mucosal immunity can potentially offer protection against variants that partially evade systemic immune responses.[13] By neutralising the virus at the site of entry before systemic spread, mucosal vaccines offer potential value in future pandemic preparedness efforts. Developing more effective vaccines for the elderly is particularly important due to immunosenescence. Mucosal or microneedle-based intradermal administration is believed to improve the efficiency of vaccine delivery in this population.[14–16]

While direct clinical evidence remains limited, available data suggest that both systemic and mucosal responses contribute to vaccine-induced protection. However, the relative advantages of each, or their ability to provide superior protection, remain unclear. The above examples underscore the biological plausibility and strategic importance of vaccine-induced mucosal immunity, particularly for blocking infection and transmission.

An additional challenge for the field will be to determine the extent to which systemic and mucosal immune responses cooperate in protection. This question has been recently reviewed, particularly in the context of highly protective and incompletely protective vaccines for respiratory tract diseases.[17]

Generating clear, reproducible clinical proof of mucosal protection would mark a turning point, enabling prioritisation, investment, and regulatory clarity across the field.

> "I often feel like we're fighting an uphill battle within our organisations to rationalise and justify investment in mucosal vaccines."
>
> — KOL INTERVIEW

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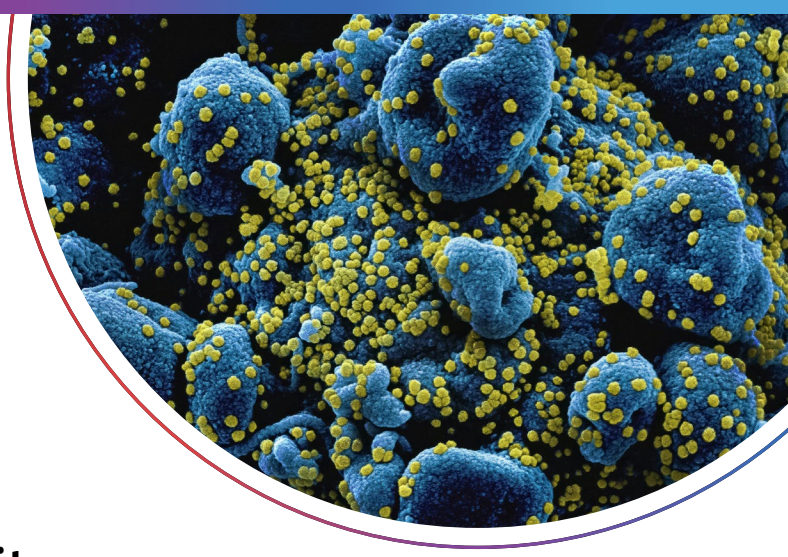
Chapter 2

Understanding mucosal immunity across anatomical sites



Understanding mucosal immunity across anatomical sites

This chapter examines mucosal immunity across three major anatomical compartments: the respiratory, GI, and GU systems. Each tract represents a distinct immunological environment with unique structural barriers, microbial exposures, and immune mechanisms. Understanding these differences is crucial for comprehending mucosal immunity in relation to various pathogens and populations.

These subchapters were developed based on findings from the literature review and pathogen-specific analyses, and aim to synthesise current knowledge, identify tract-specific barriers and enablers, and highlight opportunities for targeted innovation. Each tract is examined through the analytical framework of the concept map, including mechanisms of protection and the induction and measurement of mucosal immunity, to demonstrate areas of commonality across tracts and identify where pathogen-specific or anatomical nuances require tailored approaches.

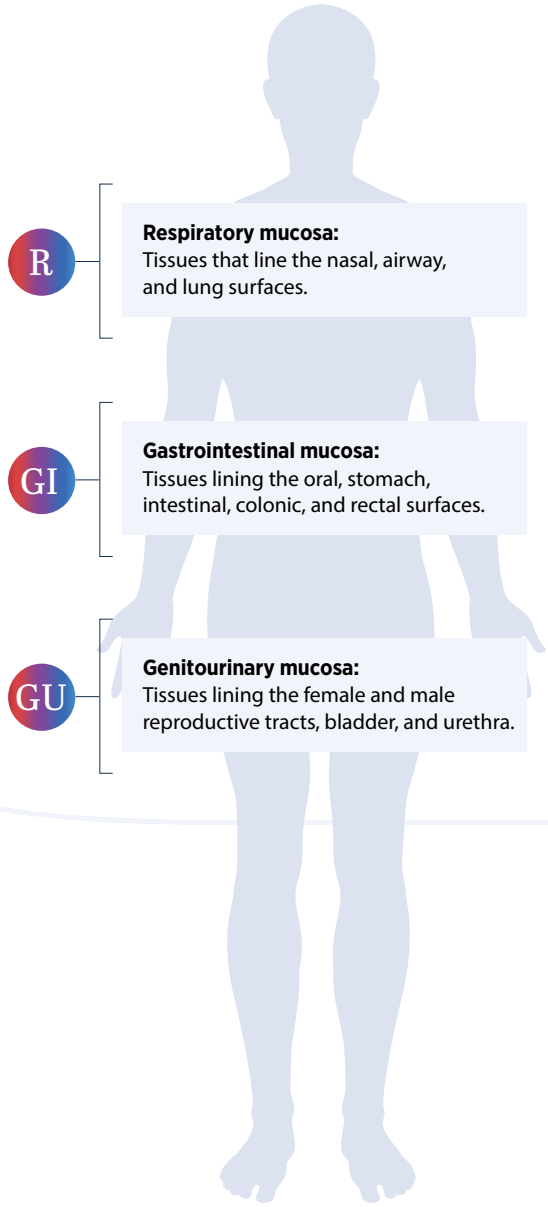
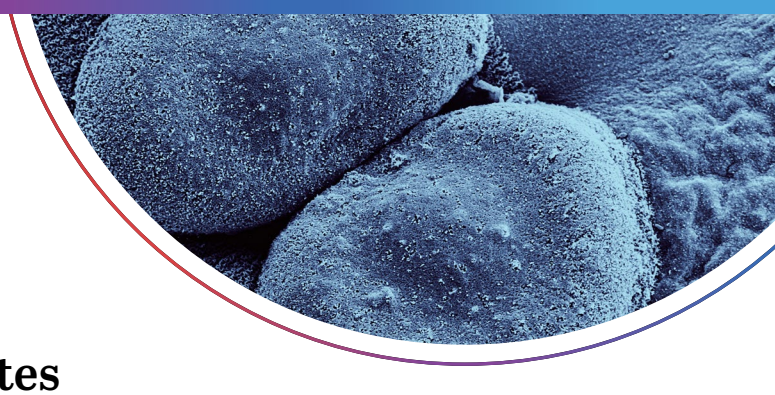


Photo: Novel Coronavirus SARS-CoV-2. Source: NIAID



Understanding mucosal immunity across anatomical sites

2a: Analysis of the Respiratory Tract

1. Global Health Context

Key Takeaway: Respiratory infections cause an enormous health burden across all age groups. Despite the success of numerous parenteral vaccines, challenges with pathogen diversity, limited durability, and ongoing transmission highlight the potential for vaccine approaches that elicit mucosal immunity.

Respiratory infections caused by pathogens such as *Mycobacterium tuberculosis*, group A streptococcus, influenza virus, SARS-CoV-2, *Streptococcus pneumoniae, Haemophilus influenzae,* and measles virus claim millions of lives each year, with the very young, older, and immunocompromised populations being particularly vulnerable. These pathogens cause repeated hospitalisations and strain health systems worldwide. In 2021, there were an estimated 344 million incident episodes of lower respiratory infections and 2.18 million deaths (502,000 in children < 5 years).[1] Over the past 30 years, the global incidence and mortality rates for LRI have declined by 20.6% and 33.45% respectively.[1] Despite this progress, infections continue to impose disability and economic hardship, particularly in LMICs, including long-term health consequences due to post-TB lung impairment, long COVID, and rheumatic heart disease.

RESPIRATORY PATHOGENS	ANNUAL GLOBAL MORTALITY	ANNUAL INCIDENT CASES	DALYS*
Group A streptococcus[2] (2020)	517,000	600,000,000	>100,000,000
Influenza virus[3] (ANNUAL ESTIMATE)	~290,000 - 650,000	~1,000,000,000	16,700,000[4]
Measles virus[5] (2023)	107,500	10,300,000	4,880,000
Mycobacterium tuberculosis[6] (2023)	1,360,500	10,800,000	47,000,000
SARS-COV-2[7] (2021)**	7,890,000	2,280,000,000	212,000,000
Streptococcus pneumoniae[7] (2021)	505,000	97,500,000	38,100,000

* Disability Adjusted Life Years

** The impact of the COVID-19 pandemic has declined substantially from its peak. Weekly case reports peaked at >40M in 2023 and now stand at <16K. Weekly deaths peaked at over 100,000 in 2021, dropping to just 210 in August 2025.

Preventive vaccines, including those for measles, COVID-19, *S. pneumoniae*, and influenza, have sharply reduced hospitalisations and deaths. However, excluding measles, all respiratory pathogens have unmet medical needs. Challenges to vaccination include waning immunity, pathogen evolution, and limited impact on transmission, highlighting the need for enhanced vaccine strategies, including those that stimulate mucosal immunity at the site of pathogen entry.[8] The availability of licensed vaccines, established challenge models, and advanced sampling and assay technologies provides several potential opportunities to explore improved vaccines for respiratory pathogens.

Photo: SEM of *Streptococcus pneumoniae* colony. Source: Debbie Marshall / Wellcome Collection.

2. Biological Context & Immune Landscape of the Respiratory Tract

Key Takeaway: The respiratory tract is a structurally, functionally, and immunologically complex mucosal site, complicating both the induction and assessment of mucosal immunity and protection.

Respiratory tract function requires a balance between protection from airborne pathogens and the physical demands of gas exchange. Each compartment must be tolerant to non-threatening antigens, including particulates and commensals, while still responding to infections. Immune responses, including inflammation, must be regulated to prevent respiratory impairment. Additionally, immune responses in the respiratory tract are influenced by factors such as age, environment, microbiome composition, concurrent infections, and the physical structure of the mucosal epithelium.

Vaccine design and development likely must match the physiology and immunology of the pathogen at the site of entry. The upper airways contain a mucus-rich surface with tightly organised epithelia in which sIgA, MAIT (Mucosal-Associated Invariant T cells), IgA-producing B cells, and antimicrobial peptides are all thought to contribute to protection. The lower airway cells include both IgA and IgG, tissue-resident memory (TRM) T cells, and alveolar macrophages.[9] Delivery strategies for vaccines must address how to access antigen-presenting cells within the airway while avoiding physical barriers. Vaccine safety is also paramount, as inflammation can impact local respiratory function and sensitive local nervous tissue.

Human Respiratory System

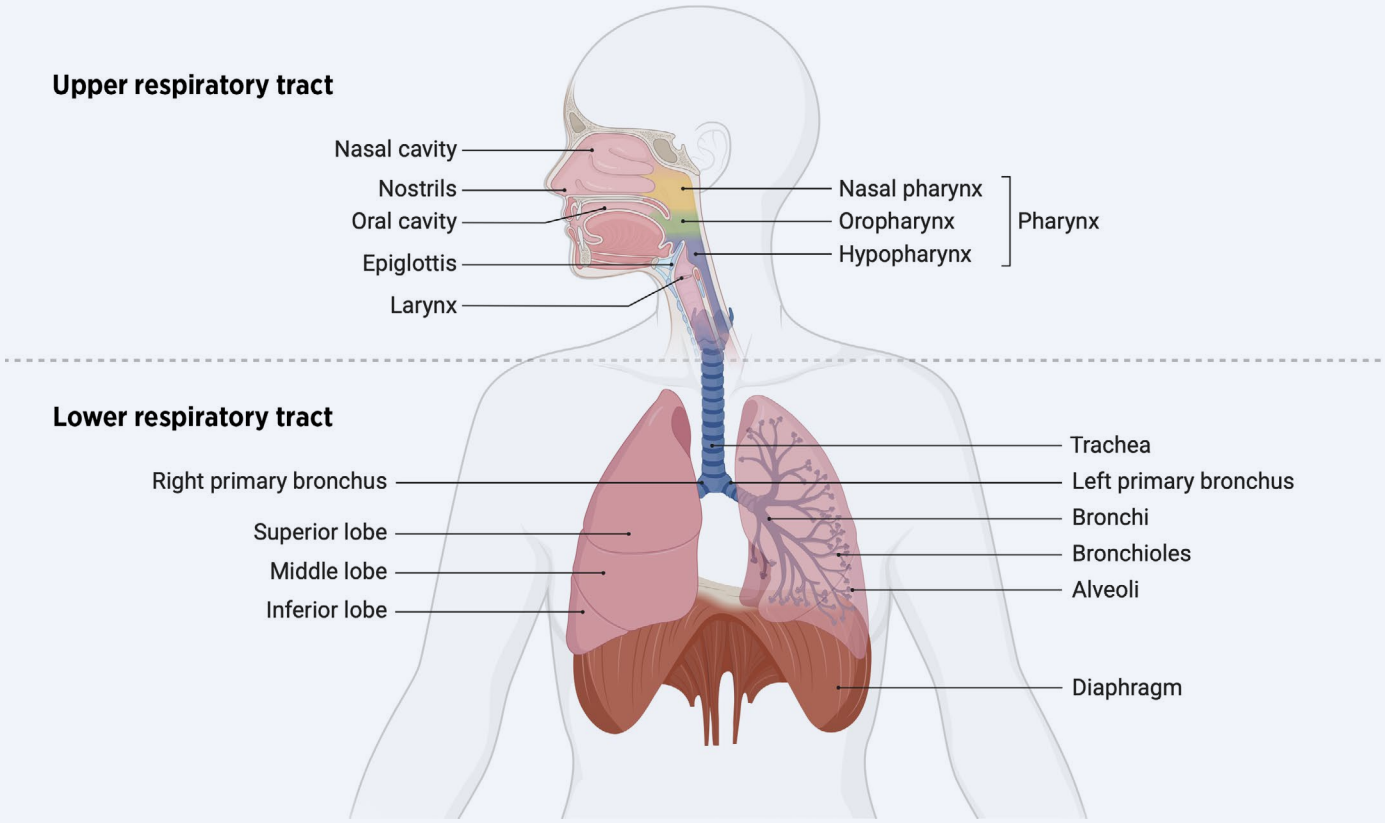


Image Courtesy of BioRender.com

3. Mechanisms of Protection

Key Takeaway: Secretory antibodies and tissue-resident T cells are believed to contribute to airway defence, yet no respiratory pathogen has a validated mucosal correlate of protection, thereby impeding vaccine design and development.

Protective immunity at the respiratory mucosa is widely anticipated to be mediated by both humoral and cellular components.[9] Mucosal IgA and IgG antibodies likely contribute to pathogen neutralisation, while TRM T and B cells likely support rapid, localised humoral responses upon re-exposure as well as clearance of infected cells. Support for R&D on mucosal vaccination is provided by natural immunity and protection by some mucosally delivered vaccines.[9] Protective immune mechanisms, including the relative contributions of systemic and mucosal immunity, will likely differ across pathogens due to various factors (e.g., mode of transmission, tissue tropism, complex pathogen biology, and host-pathogen interactions). Therefore, defining CoP should assist in vaccine development. While serum antibody levels have been used as CoP for pathogens such as the influenza virus, SARS-CoV-2, and S. pneumoniae, specific thresholds for protection remain largely undefined in both blood and mucosa.

Sampling the respiratory mucosa poses specific challenges. While nasal swabs, sponges, washes, and saliva collection are feasible and increasingly standardised, accessing the lower respiratory tract typically requires bronchoalveolar lavage or tissue biopsy, procedures that are more invasive and less widely deployable. Sampling in paediatric populations or low-resource settings is particularly constrained. The infrequent acquisition of mucosal samples and assays has limited the search for mucosal correlates of protection, complicating efforts to compare vaccine responses.

Studies exploring surrogate markers in peripheral blood, or signatures that correlate with respiratory mucosal immunity, would offer great value for both clinical development and population-level assessment. However, further understanding of the importance of local pulmonary immune responses suggests alternative approaches may be necessary. For example, non-circulating TRM T cells are thought to play a key role in host mycobacterial defences and detecting their associated biomarkers can only be achieved by interrogating respiratory samples such as bronchoalveolar lavage fluid or tissue biopsies.[4]

Pathogen-Specific Immunology Insights

- **Group A streptococcus:** Natural infection appears to confer age-related protection; however, immunologic mechanisms (local antibody or T cell responses) remain poorly defined, particularly as they relate to response at the mucosa.[10] The large number of serotypes represents an overarching challenge to vaccine design.
- **Influenza virus:** While systemic antibodies induced by IM-delivered vaccines can prevent disease, there is evidence of a role for mucosal immunity, including sIgA and TRM T cells, present in the upper airway.[11] LAIV has demonstrated the ability to induce local immune responses within the upper respiratory tract and provide equivalent protective efficacy to IIV in children despite lower systemic antibody titers, supporting the relevance of local responses.[12,13]
- **Measles virus:** Currently licensed measles-mumps-rubella (MMR) live-attenuated vaccines are highly effective and induce strong systemic immune responses. They also induce some level of mucosal immune response in the respiratory tract, as evidenced by antibodies in nasal washes and oral fluids.[14]
- ***Mycobacterium tuberculosis:*** Studies of natural and vaccine-induced immunity suggest a focus on inducing T cell responses, particularly IFN-γ-producing CD4+ T cells, possibly in conjunction with antibody responses.[15] Aerosol delivery aligns with the route of Mtb infection and holds the potential to target protective mucosal immunity to the site of infection.[15,16]
- **SARS-CoV-2:** Data suggest that sIgA is associated with reduced viral load, faster clearance, and enhanced protection.[17] Individuals with primary IgA deficiencies have shown more severe outcomes and reduced mucosal vaccine responses,[18,19] further supporting the protective role of mucosal immunity.
- ***Streptococcus pneumoniae*:** While serum IgG levels to surface carbohydrate antigens have long been used as a CoP, there is ongoing work to delineate the immune mechanisms that lead to prevention of infection, carriage, and disease, with both humoral and cellular mechanisms implicated.[20,21]

4. Induction of Mucosal Immunity

Key Takeaway: Licensed mucosal vaccines show that airway-targeted immunity is attainable; however, a better understanding of vaccine delivery platforms, adjuvants, sampling, and other confounding factors is still required.

Approved mucosal vaccines exist for influenza and COVID-19, utilising live-attenuated virus and viral vector delivery, respectively.[17] This represents an important tool for respiratory mucosal vaccine clinical research.

Alternative delivery platforms, including liposomes, nanoparticles, dry powder inhalers, and viral vectors, are being investigated to enhance mucosal targeting and uptake in the respiratory tract. Many of these technologies are still in preclinical or early clinical development, and questions remain about their ability to elicit the necessary immune profile across diverse age groups and anatomical compartments.[17] Adjuvanting vaccine responses to improve potency would be desirable but will require a clear demonstration of safety.[22]

Controlled human infection models (CHIMs) for TB,[23] GAS,[24] SARS-CoV-2,[25] influenza,[26] and *S. pneumoniae*[27] provide valuable platforms to assess mucosal immunity and test vaccine efficacy under controlled conditions. These models, in conjunction with advanced immunologic assays and intensive sampling, may inform various vaccine development efforts, including the evaluation of mucosal adjuvants and immunogen delivery strategies.

Importantly, given the immunologic sensitivity of the respiratory tract, any vaccine strategy must be carefully evaluated for safety. Local reactogenicity, risk of enhanced disease, immune-mediated pathology, and proximity to the central nervous system are concerns in respiratory vaccine development and must be addressed through rigorous preclinical and clinical testing. Both vaccine and adjuvant delivery must consider the potential for unwanted inflammation of the surrounding tissue.

As with other mucosal compartments, factors such as baseline immunity, microbiome composition, and co-infections likely influence outcomes and should be better understood to optimise next-generation respiratory vaccines and make a case for establishing and conducting CHIMs in endemic and LMIC settings, where many of these factors could impact the outcome.[28]

5. Status of Current Vaccines & Clinical Evidence

Key Takeaway: Highly effective vaccines exist for some respiratory pathogens (measles, SARS-CoV-2, *S. pneumoniae,* influenza), while other vaccines require significant improvement (TB, GAS). Even successful vaccines could benefit from enhanced durability and broader population-specific efficacy, both areas where mucosal vaccination offers great promise.

See the following page for a pipeline of respiratory vaccines in development as of April 2025.

Licensed Mucosal Vaccines for Respiratory Pathogens

Influenza

- **Flumist/Fluenz Tetra** (MedImmune / AstraZeneca): Live-attenuated / Intranasal
- **Nasovac-S** (BioDiem / Serum Institute of India): Live-attenuated / Intranasal
- **GanWu** (Changchun BCHT Biotechnology Co.): Live-attenuated / Intranasal
- **Ultravac** (Institute of Experimental Medicine): Live-attenuated / Intranasal

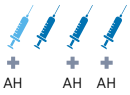
SARS-CoV-2

- **BBV154** (Bharat Biotech): Replicating viral vector / Intranasal
- **Convidecia Air** (CanSino Biologics): Non-replicating viral vector / Aerosol
- **Pneucolin** (Beijing Wantai Biological Pharmacy): Replicating viral vector / Intranasal
- **RAZI-COV PARS** (Razi Vaccine and Serum Research Institute): Replicating viral vector / Intranasal
- **Sputnik V / Gam-COVID-Vac** (Gamaleya Research Institute): Non-replicating viral vector / Intranasal

Respiratory Vaccine Pipeline

Click on pathogen title to link to the pathogen profiles and pipelines in Appendix A.

Group A streptococcus (GAS)



There is a clear medical need to target the prevention of severe and invasive disease(s) in children and associated immunological sequelae, such as rheumatic heart disease. Despite evidence that age-related immunity is protective, there is currently no mucosal vaccine in development. Serotype diversity remains a significant challenge for vaccine development.

Influenza virus[29,30]

LAIVs directly stimulate the mucosal immune system but have limited global uptake. Additional mucosal vaccine platforms, including intranasal adjuvanted subunits and aerosolised mRNA, are being developed to improve early containment and cross-strain protection.[31,32] Antigenic shift and drift present an ongoing challenge; however, whether inducing improved mucosal immune responses can lead to broader, more durable, and more effective responses remains an open question. (Due to the size of the influenza vaccine pipeline, adjuvant detail is not shown).

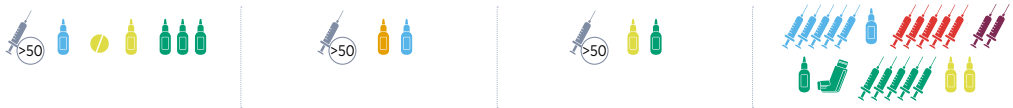
Measles virus

While the current MMR vaccine is highly effective, delivery of ID and SC (via microarray) vaccines is being explored. Measles may be a sub-optimal model for studying mucosal immunity, given that existing systemically administered measles vaccines have very high efficacy.

Mycobacterium tuberculosis[33]

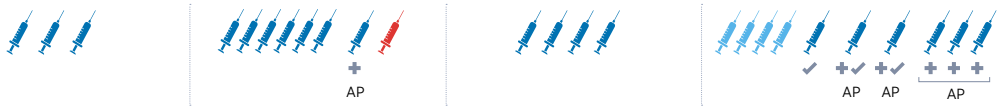
New vaccines are urgently needed to enhance protection against pulmonary TB in adults and to facilitate the clearance of carriage. TB has a complex intracellular replication pathway that is likely not susceptible to antibodies. The induction of cell-mediated immunity in the respiratory tract is considered a promising strategy. Two early-stage candidates are exploring intranasal delivery, while one Phase 2 candidate is evaluating aerosol administration.[16]

SARS-CoV-2[34,35]



Current vaccines are highly effective against severe COVID-19 disease but do not offer durable immunity from infection or to protect against new variants.[36] Vaccines have been approved for mucosal delivery in some countries, and exploration of immunity using next-generation tools is advancing to determine if the induction of mucosal immunity provides clear advantages.[32] (Due to the size of the COVID-19 vaccine pipeline, adjuvant detail is not shown).

Streptococcus pneumoniae



Despite the development of highly effective multivalent conjugate vaccines, challenges with serotype replacement and carriage remain. There is some evidence that anti-protein antibodies and TH17 CD4 cells in the mucosa may have an impact on carriage.[21,37] Approaches to broaden vaccination to new non-serotype-specific antigen targets are beginning.[21] None of the 16 vaccines in clinical development involves mucosal administration.

DELIVERY ROUTE		VACCINE TYPE	
Parenteral	+ Adjuvanted*	Subunit	DNA
Oral	✓ WHO-prequalified	Conjugate	RNA
Patch	⊘ Discontinued	Live-attenuated	Replicating viral vector
Intranasal	Ⓜ Mucosal immunity effect in humans indicated in the literature	Inactivated	Non-replicating viral vector
Aerosol		Not classified	

*Aluminium Hydroxide (AH)
Aluminium Phosphate (AP)
Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)

6. Priority Challenges for Mucosal Vaccine Development

Insufficient knowledge of protective mechanisms. Currently, developers must rely on large, costly efficacy trials to support advanced-stage decision-making and regulatory approval. For respiratory pathogens, no validated mucosal CoPs, such as neutralising IgG, hemagglutination inhibition titers, or T.cell signatures, exist to predict protection at the site of infection in the nose or lungs. As a result, immunological findings from early-stage trials often have limited utility. While promising tools such as high-sensitivity IgA assays, systems serology, and organoid airway models are emerging, they have not yet been widely applied. CHIMs and outbreak-response protocols are established for some pathogens and under development for others, offering valuable platforms to test CoPs for use in accelerating vaccine R&D.

Sampling hurdles. Direct lower-airway sampling is invasive; saliva degrades IgA, nasal washes dilute unpredictably, and induced sputum yields inconsistent cell counts, leaving protective immune signatures fragmentary. Reference standards are absent, and miniaturised multiplex assays suited to paediatric volume remain rare. Assessing cellular responses in the lungs requires biopsies or lavages, which necessitate the co-localisation of clinical trial, surgical, and expert laboratory facilities.

Biological complexity of the respiratory tract. Age, malnutrition, exposure to pollution/allergens, smoking, microbiome composition, and co-infections all shape vaccine responses and durability. Antigens and adjuvants must traverse mucus, surfactant, and rapid mucociliary clearance to reach inductive sites, while key delivery technologies remain largely untested in humans.

Pathogen diversity and immune evasion. Rapid antigenic drift (influenza, SARS-CoV-2), serotype replacement (*S. pneumoniae*), and more than 200 emm types (GAS) constantly reset immunogen design, frustrating the quest for broadly reactive vaccines.

Safety, efficacy, and acceptability of mucosal platforms. The sensitivity of airway function to inflammation and the proximity to neurological tissue require that vaccine safety be carefully considered at all stages of development. At the same time, the vaccine must be a sufficiently potent immune stimulator to achieve protection. These considerations must be combined with the development of delivery technologies and devices that will be acceptable for use in the target populations.

7. Opportunities for Advancing the Field

Robust pipelines create opportunities for insight. Respiratory pathogens provide a unique opportunity to study mucosal responses in the context of both natural infections and licensed vaccines, including through CHIMs for TB, influenza, SARS-CoV-2, *S. pneumoniae*, and GAS.

Prime-boost. Systemic primes paired with intranasal or aerosol boosts may provide improved immune responses and more durable protection than either route alone. Such strategies are becoming increasingly feasible in clinical studies, allowing for the direct investigation of mucosal responses with appropriate sampling.

Innovation in vaccine delivery. Delivery and evaluation technologies continue to evolve. Spray-dried mRNA powders, self-amplifying RNA aerosols, and polymeric nanoparticles, as well as newer adenoviral and live-attenuated vectors, may enable efficient antigen delivery to the mucosa.[17,32] Complementary advances in systems serology, single-cell profiling, and spatial transcriptomics are beginning to measure airway immune cells.[11] Organoid airway cultures may help test how formulations traverse mucus, surfactant, and epithelial barriers, informing the use of immunogens and adjuvants.[38] Further, the potential for cross-talk among mucosal tissues has been widely discussed, although there is limited confirmatory information in human vaccine trials.[39]

The complex multidisciplinary nature of respiratory mucosal vaccine development is likely to be best addressed through multi-disciplinary, collaborative approaches.

> **"What are the biggest knowledge gaps? To me, the clearest one is what is happening in the actual anatomy of immunity: location, location, location."**
>
> — KOL INTERVIEW

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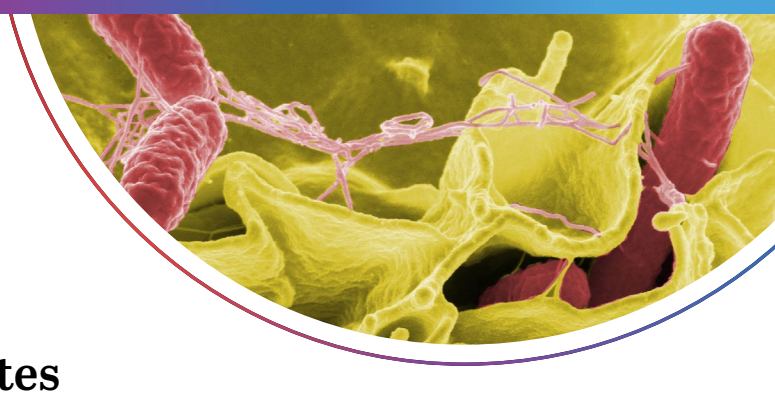

Understanding mucosal immunity across anatomical sites

2b: Analysis of Gastrointestinal Tract

1. Global Health Context

Key Takeaway: Despite the introduction of oral vaccines for numerous pathogens, enteric diseases remain a leading cause of mortality and morbidity among children, especially in LMICs. Enhancing mucosal immunity may improve the performance of vaccines in these settings.

Enteric infections are food and waterborne diseases spread through the faecal-oral route; subtypes include diarrheal diseases, typhoid and paratyphoid fever, invasive non-typhoidal Salmonella (iNTS) infections, among others.[1] In 2021, enteric infections caused approximately 4.45 billion cases and 1.3 million deaths globally.[1] Diarrhoeal diseases, the subtype of enteric illness with the highest disease burden, continue to pose a significant global health challenge, causing approximately 1 million deaths annually, and rank as the third leading cause of mortality in children under five, accounting for over 440,000 deaths in 2024.[2]

The impact of these infections extends beyond acute illness and mortality. Repeated episodes are a major contributor to chronic malnutrition, stunting, and impaired cognitive development, leading to long-term educational and economic disadvantages.[3] These infections also place an immense burden on under-resourced health systems in endemic regions.

GASTROINTESTINAL PATHOGENS	ANNUAL GLOBAL MORTALITY	ANNUAL INCIDENT CASES	DALYS*
Vibrio cholerae[4,5] (2019)	86,500	~2,500,000	4,520,000
Rotavirus[5] (2021)	176,000	>250,000,000	13,400,000
Typhoidal Salmonella[1] (2021)	107,000	9,320,000	8,090,000
Invasive non-typhoidal Salmonella[1] (2021)	62,000	510,000	4,740,000
Shigella spp.[5] (2021)	117,000	188,000,000[6]	9,410,000

* Disability Adjusted Life Years

The introduction of oral vaccines, particularly against rotavirus, the leading cause of diarrheal diseases, has resulted in significant reductions in child mortality. However, oral vaccine efficacy is consistently lower in LMICs compared to high-income countries, often by 20–40 percentage points, with protection that tends to wane within the first two years of life.[7,8] Multiple factors are thought to contribute to this reduced performance, including maternal antibodies, coinfections, micronutrient deficiencies, microbiota composition, gut dysbiosis, environmental enteric dysfunction (EED), and genetic factors in infants.[9–11] Enhancing mucosal immunity may improve the performance of vaccines in these settings.

While systemic immune responses are relatively well-characterised, there remains a limited understanding of how to induce durable, protective mucosal immunity at the gastrointestinal surface, particularly in high-burden populations. Further work is needed to address this gap and improve both individual-level protection and population-level vaccine impact.

Photo: *Salmonella Typhimurium*. Source: Rocky Mountain Laboratories, NIAID.

2. Biological Context & Immune Landscape of the GI Tract

Key Takeaway: The GI tract hosts a complex and dynamic immune environment that integrates structural barriers, diverse immune cell populations, and dynamic host-microbe interactions. These features vary across age groups, geographies, and environmental conditions, shaping immune responses and vaccine effectiveness.

The GI tract is a specialised mucosal environment constantly exposed to a broad array of dietary antigens, a dense commensal microbiota, and frequent enteric pathogens. To manage this challenging interface, a balance of immunological vigilance and tolerance has evolved. The need to defend against infection while avoiding overreaction to harmless antigens or commensals makes the intestinal immune system uniquely dynamic and tightly regulated.[12]

Anatomically, the GI tract comprises four major layers: the mucosa, submucosa, muscularis propria, and serosa. The mucosal layer contains key immune structures such as the gut-associated lymphoid tissue (GALT), including Peyer's patches and isolated lymphoid follicles. Specialised epithelial cells, including M (microfold) cells and goblet cells, facilitate the uptake of antigens from the lumen into inductive sites.

Peyer's patches, in particular, maintain chronic germinal centre activity, enabling ongoing sampling and response to microbial and dietary antigens in the gut environment.[13,14] SIgA plays a central role in mucosal defence by neutralising pathogens without provoking inflammation. TRM T cells, innate lymphoid cells (ILCs), and antimicrobial peptides further contribute to mucosal homeostasis and defence.[12]

Importantly, mucosal immunity in the GI tract is influenced by both local and systemic factors, including maternal antibody transfer (IgG transplacentally, IgA via breastfeeding), nutritional status (e.g., vitamin A, zinc), microbiome composition and diversity, age and immune development, concurrent enteric infections, EED, genetic factors and histo-blood group antigen (HBGA) expression. While the systemic and mucosal immune systems are interrelated, the dynamics of communication and coordination between them are poorly understood. For enteric vaccination, this uncertainty limits our ability to predict or measure protective mucosal responses. Understanding the unique immune architecture and regulatory mechanisms of the GI tract is foundational to designing effective oral vaccines.

Intestinal Immune System (Small Intestine)

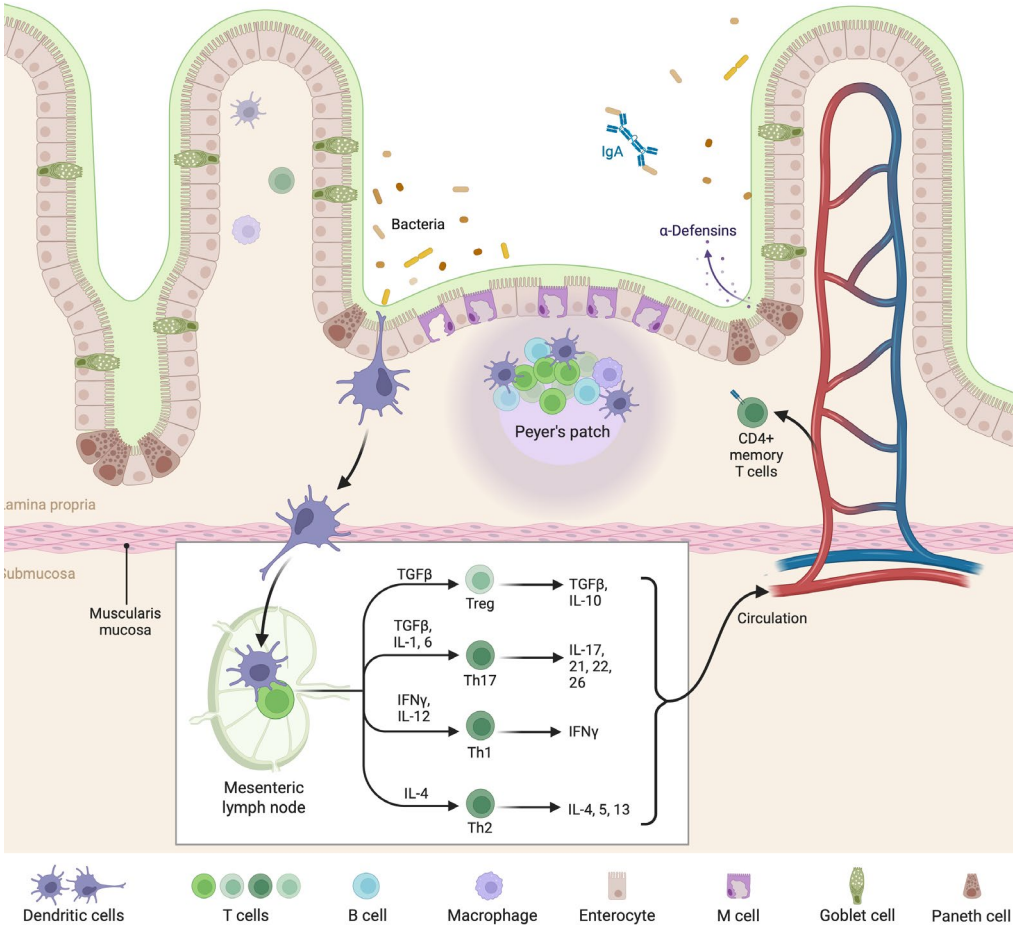

Image Courtesy of BioRender.com

3. Mechanisms of Protection

Key Takeaway: Mucosal immune responses play a crucial role in protecting against enteric infections; however, well-defined, durable correlates of protection remain elusive for most gastrointestinal pathogens, hampering rational vaccine design and evaluation.

Much of our understanding of mucosal protection in the GI tract comes from studies of natural enteric infections. These infections often lead to partial or short-lived immunity, suggesting that protective responses can be generated at mucosal surfaces. However, the reliability, durability, and universality of these responses vary widely based on host age, nutritional status, environmental exposures, and pathogen-specific factors. Across reviewed gastrointestinal pathogens, no definitive mucosal CoPs have been identified, despite the availability of partially effective vaccines for some of these pathogens.

As with the respiratory tract, mucosal sampling of the GI tract poses logical and clinical complexities and is a substantial hurdle to understanding immunity at these sites. Pinch biopsies from the colon and duodenum require trained gastroenterologists and specialised surgical equipment and facilities. Samples should ideally be processed fresh and within hours of collection to yield the maximum amount of information. This requires centres with all the requisite clinical trial and study teams, expert laboratories, and specialised surgical teams and staff. Faecal samples have been used as surrogates for assessing gut antibody levels, but insights from such samples are limited. Studies to elucidate surrogate markers in peripheral blood, such as gut-homing B and T cells, or to better understand how and which markers correlate best with gut immune responses, would be transformative. There are no established immunologic benchmarks for gut protection, complicating efforts to evaluate vaccine candidates.

These observations underscore how challenging it will be to elicit consistently protective, durable immunity in the GI tract via vaccination.

Pathogen-specific Immunology Insights

- ***Vibrio cholerae*:** Protection after natural infection is associated with intestinal sIgA, as well as systemic vibriocidal antibodies. However, vibriocidal antibodies are not a mechanistic correlate of protection, and their predictive value in different populations is variable,[15] although vibriocidal antibody responses to *V. cholerae* O1 have been used as endpoints in non-inferiority studies to support licensure of new cholera vaccines.[16,17] The efficacy and duration of protection post-vaccination are limited, particularly in young children.[18,19]
- **Rotavirus:** Natural infection induces local intestinal (sIgA) and systemic antibody (IgA and IgG) responses against viral capsid proteins.[15] While rotavirus-specific IgA, especially in the gut, is associated with protection, the thresholds needed for long-term immunity remain unclear, particularly in malnourished children or populations from low-income/endemic countries where vaccine efficacy is reduced.[20]
- **Typhoidal Salmonella:** Infections caused by *Salmonella enterica* serovars S. Typhi and S. Paratyphi present both enteric and systemic features. Oral typhoid vaccines elicit mucosal IgA responses, but systemic replication also necessitates robust peripheral immunity.[21,22] Faecal IgA may not accurately reflect mucosal immunity, underscoring the need for more reliable surrogate markers.
- **Non-typhoidal Salmonella (NTS):** Causing primarily gastroenteritis, NTS infections involve invasion of the mucosal epithelium with potential systemic spread. Animal and human studies suggest that mucosal IgA and mucosal T-cell responses contribute to protection.[21] Oral and mucosal vaccine platforms targeting GALT and Peyer's patches are under development to enhance local immunity and generate both antibody and cell-mediated defences.[21,23]
- ***Shigella*:** Protection is found to be associated with mucosal and serum IgA responses targeting the O-specific polysaccharide (OSP) component of lipopolysaccharide, necessitating the design of multivalent vaccines to cover the majority of strains. These mucosal responses are seen in high-burden settings but need further validation across different age groups and geographic regions. Cellular immunity, particularly T-cell responses, may play a role due to the pathogen's intracellular lifecycle.[24]

4. Induction of Mucosal Immunity

Key Takeaway: Although several licensed oral and parenteral vaccines target enteric pathogens, there are significant scientific and technical challenges to inducing robust and durable mucosal immunity in the GI tract.

While oral vaccines have the advantage of likely inducing mucosal immune responses at the site of pathogen entry, their effectiveness is often short-lived and less robust in low-resource settings. Factors such as malnutrition, enteric coinfections, microbiota dysbiosis, and environmental enteropathy may all contribute to impaired oral vaccine effectiveness, particularly in children from low-income countries.[25,26] A deeper understanding of microbiota modulation may help improve outcomes (e.g., for *Shigella* and rotavirus vaccines).

Parenteral vaccines have the potential to direct immune responses to specific molecular targets and leverage existing adjuvant formulations. Adaptations of these approaches for mucosal protection are beginning, including the use of gut-homing adjuvants (e.g., bacterial ADP-ribosylating enterotoxins)[27] and prime-pull strategies that incorporate oral boosts following a parenteral prime dose. Evidence for their ability to reliably induce gut-specific immunity remains to be evaluated.

A growing number of alternative delivery platforms are under investigation, including liposomes, chitosan particles, and other nanoparticle carriers and viral vectors designed to protect antigens and facilitate uptake across the intestinal epithelium. These technologies (e.g., employing mucoadhesive and M-cell–targeting features)[28] hold promise for improving vaccine performance in the GI environment, but are still largely in preclinical development.

The mucosal adjuvant pipeline is limited; few adjuvants have achieved clinical validation for use in mucosal applications. New candidates, such as Toll-like receptor (TLR) and STING pathway agonists, offer potential for targeted immune activation but require careful formulation to balance efficacy and reactogenicity. A better and more comprehensive understanding of the life cycle and pathogen clearance will lead to rationally designed adjuvants and broadly reactive vaccine immunogens and platforms.

CHIMs for *Shigella*, cholera, rotavirus, typhoidal Salmonella, provide important platforms for exploring new formulations and dosing regimens; however, population differences and field conditions limit their generalizability. Additional factors, such as breastfeeding practices, gut microbiota composition, microbiome-targeted interventions, and co-administered nutritional or probiotic/nutraceutical strategies, likely influence mucosal immune induction; however, their effects aren't well understood.

5. Status of Current Vaccines & Clinical Evidence

Key Takeaway: There is substantial experience with vaccines in humans, including licensed vaccines for cholera, rotavirus, and Salmonella Typhi, as well as a Phase 3 trial for *Shigella*.

See the following page for a pipeline of GI vaccines in development as of April 2025.

Licensed Mucosal Vaccines for GI Pathogens

Vibrio cholerae

- **Cholvax** (Incepta): Inactivated / Oral
- **Dukoral** (Valneva): Inactivated / Oral
- **Euvichol-Plus** (EuBiologics): Inactivated / Oral
- **Euvichol-S** (EuBiologics): Inactivated / Oral
- **Hillchol / BBV131** (Bharat Biotech): Inactived / Oral
- **OraVacs** (Shangai United Cell Biotech.): Inactivated / Oral
- **VaxChora** (Bavarian Nordic): Live Attenuated / Oral

Rotavirus

- **LLR** (Lanzhou Institute): Live Attenuated / Oral
- **ROTASIIL** (Serum Institute of India): Live Attenuated / Oral
- **ROTARIX** (GSK): Live Attenuated / Oral
- **RotaTeq** (Merck): Live Attenuated / Oral
- **ROTAVAC** (Bharat Biotech): Live Attenuated / Oral
- **Rotavin-M1** (POLYVAC): Live Attenuated / Oral

Typhoidal Salmonella

- **Vivotif** (Bavarian Nordic): Live Attenuated / Oral

GI Vaccine Pipeline

Click on pathogen title to link to the pathogen profiles and pipelines in Appendix A.

Existing oral, killed whole cell vaccines provide moderate protection, but their durability is limited, and vaccine efficacy is significantly lower in children under 5 years of age (approximately half that seen in older individuals).[29] The cost of the existing live-attenuated vaccine is high. These vaccines induce mucosal immunity, and the possibility of augmenting this using parenteral priming could be important.

Although oral rotavirus vaccines are licensed and widely used, their efficacy is reduced in LMICs. Whether improved mucosal responses could improve efficacy in these populations is unclear. Both oral and parenteral vaccine candidates are in development (the latter to potentially bypass enteric limitations).

The oral live-attenuated vaccine is ~50% effective in the first 3 years.[30] This vaccine stimulates mucosal, cellular, and systemic immunity.[31] It may be possible to combine parenteral vaccines with mucosal priming to increase efficacy, though the relative contributions of mucosal and systemic immunity to protection remain poorly defined.[5]

NTS vaccine development has focused largely on systemic protection. Incorporating mucosal strategies, including oral delivery and mucosal adjuvants, may enhance efficacy, particularly in populations with high exposure risk and comorbidities that compromise systemic immunity (e.g. HIV, malnutrition).[5,7]

Maternal antibody transfer appears to be highly protective in early life; consequently, there is optimism that vaccination should be effective.[12] Shigella is complicated by its intracellular replication cycle, possibly requiring local mechanisms of infected cell clearance (both Ab and T cells). High heterogeneity among strains has been a challenge for vaccine development, but there are oral and parenteral vaccine candidates in Phase I-III trials.[32]

6. Priority Challenges for Mucosal Vaccine Development

The lack of well-defined mucosal correlates of protection in the GI tract complicates vaccine evaluation, often requiring large, costly trials with clinical endpoints. In addition to validated immune correlates, uncertainty remains regarding whether peripheral markers, such as serum IgA/IgG titres or gut-homing T cells, can reliably indicate mucosal priming. However, advances in assays, integrated data analysis, and in vitro models, including organoids, offer new potential to close this gap.[26]

Sampling and assay limitations. Direct sampling of the gut is complex, and most available data on mucosal responses are fragmentary and indirect, making it hard to define the immune signatures associated with protection. Stool-based functional assays, serum bactericidal assays (SBA), opsonophagocytic killing assays (OPKA),[33] and circulating gut-homing lymphocytes (e.g. $\alpha4\beta7^+$ T or B cells) may offer alternatives. Mechanisms of cell trafficking are poorly understood; however, markers of antigen-specific cells in peripheral blood that are trafficking to GALT are being used to assess vaccine-induced mucosal responses in the blood for some pathogens.[34]

The biological complexity of the GI environment affects vaccine responses and complicates standardisation across diverse populations. Antigens and adjuvants of oral vaccines must overcome multiple barriers, including acidic pH, digestive enzymes, thick mucus, and epithelial tight junctions, to reach inductive sites in the gut. Oral vaccine delivery often results in low absorption of the antigenic particles, thereby reducing efficacy or requiring multiple or larger doses.[35] Most proposed delivery technologies remain largely untested in humans.

Immune evasion by pathogens, including antigenic drift and serotype diversity, complicates the design of effective vaccines.

Acceptability of side-effects associated with live-attenuated vaccines and replicating vectors, such as diarrhoea, temporary microbiota disruption, or shedding, limits acceptability and complicates deployment.

7. Opportunities for Advancing the Field

Evidence from both infection and vaccination suggests that mucosal responses can contribute to protection, and that oral and systemic strategies may be complementary. Attenuated strains used in current vaccines have shown efficacy, albeit with limited durability. There is interest in improving these platforms by refining formulations, adjusting dosing schedules, and exploring combined oral and parenteral approaches.

A better understanding of microbiome complexity and its potential role in modulating vaccine responses, particularly in LMICs, is opening new avenues for research. Enhanced immunological tools enable detailed mapping of host-pathogen interactions and gut-resident immune signatures. Moreover, validating markers of immune cells in peripheral blood, which home to the GALT or sites of inflammation, could address a significant bottleneck in assessing vaccine-induced mucosal responses. These advances lay the groundwork for the rational design of next-generation adjuvants, delivery platforms, optimised antigens, and assays.

Several experimental tools and delivery systems, such as thermostable particles, micromotors, mucus-penetrating nanoparticles, self-orienting capsules, and mucosa-targeting adjuvants,[36] are under investigation. Embedding these tools into natural history studies or controlled human-infection models could possibly help clarify how and when mucosal immunity contributes to protection, and/or identify mucosal correlates of immunity in peripheral blood.

> **"We need more standardised measures of mucosal immunity so we can compare across studies and aim towards having correlates for mucosal vaccines for enteric diseases."**
>
> — KOL INTERVIEW

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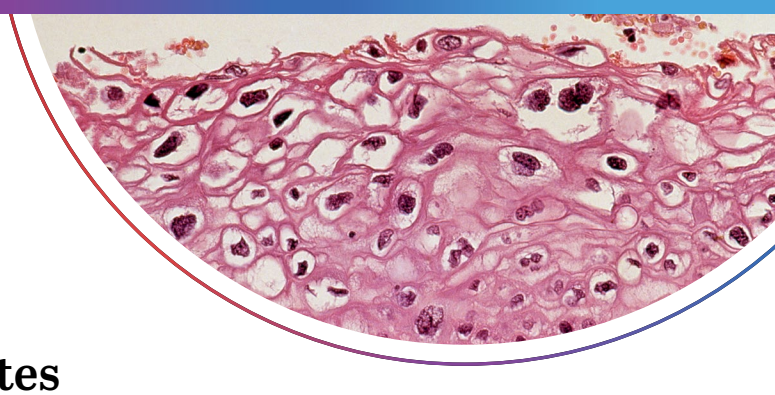


Understanding mucosal immunity across anatomical sites

2c: Analysis of Genitourinary Tract

1. Global Health Context

Key Takeaway: Despite their profound impact on the health of men and women, including reproductive and neonatal health, vaccines are not available for most GU infections, including STIs. The induction of mucosal immunity at the site of infection is thought to be crucial for the successful development of protective vaccines against numerous GU pathogens.

Genitourinary infections contribute to a broad spectrum of diseases, and the incidence of many STIs is on the rise. The pathogens evaluated as part of this review are responsible for more than 1 million deaths annually. Many more millions live with chronic pain, infertility, recurrent ulcers, or long-term consequences of neonatal complications, with the highest toll among women of reproductive age and newborns. Many diseases, including HPV, gonorrhoea, chlamydia, HSV, and HIV, are frequently asymptomatic, which further facilitates transmission. Pathogens such as group B streptococcus that colonise pregnant women threaten perinatal health. Many GU pathogens have coevolved with their hosts over thousands of years (e.g., HPV, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*). Infections can be lifelong (e.g., HSV, HIV), provide partial or short-lived protection (e.g., *Chlamydia trachomatis*), or fail to confer protection against subsequent re-infection (e.g., *Neisseria gonorrhoeae*).

GENITOURINARY PATHOGENS	ANNUAL GLOBAL MORTALITY	ANNUAL INCIDENT CASES	DALYS*
Chlamydia trachomatis[1] (2021)	1,030	128,500,000	5,600,000
Group B streptococcus[2] (2020)	147,000	392,000	11,200,000
HIV[3] (2021)	630,000	1,300,000	40,300,000
HPV[4] (2022)	420,000	831,000	9,910,000
HSV[5] (2021)	8,500	40,200,000	300,000
Neisseria gonorrhoeae[6] (2021)	400	86,000,000	100,000

* Disability Adjusted Life Years

These infections impose psychological, social, and economic burdens, particularly in low-resource settings where access to diagnosis, treatment, and follow-up care is limited. Although HPV vaccination has shown a strong population-level impact, no licensed vaccines exist for other GU pathogens. The 4cMenB vaccine has shown some cross-reactivity with and protection against *Neisseria gonorrhoeae* and is being made available to volunteers at high risk of gonorrhoeal infection in the UK.[7]

Photo: Florid human papillomavirus (HPV) infection of the ectocervix. Source: Wellcome Collection

2. Biological Context & Immune Landscape of the GU Tract

Key Takeaway: The GU tract is a biologically complex and immunologically distinct mucosal site, shaped by sex-specific anatomy, hormonal cycles, and a dynamic microbiome. These features complicate both the induction and assessment of mucosal immunity.

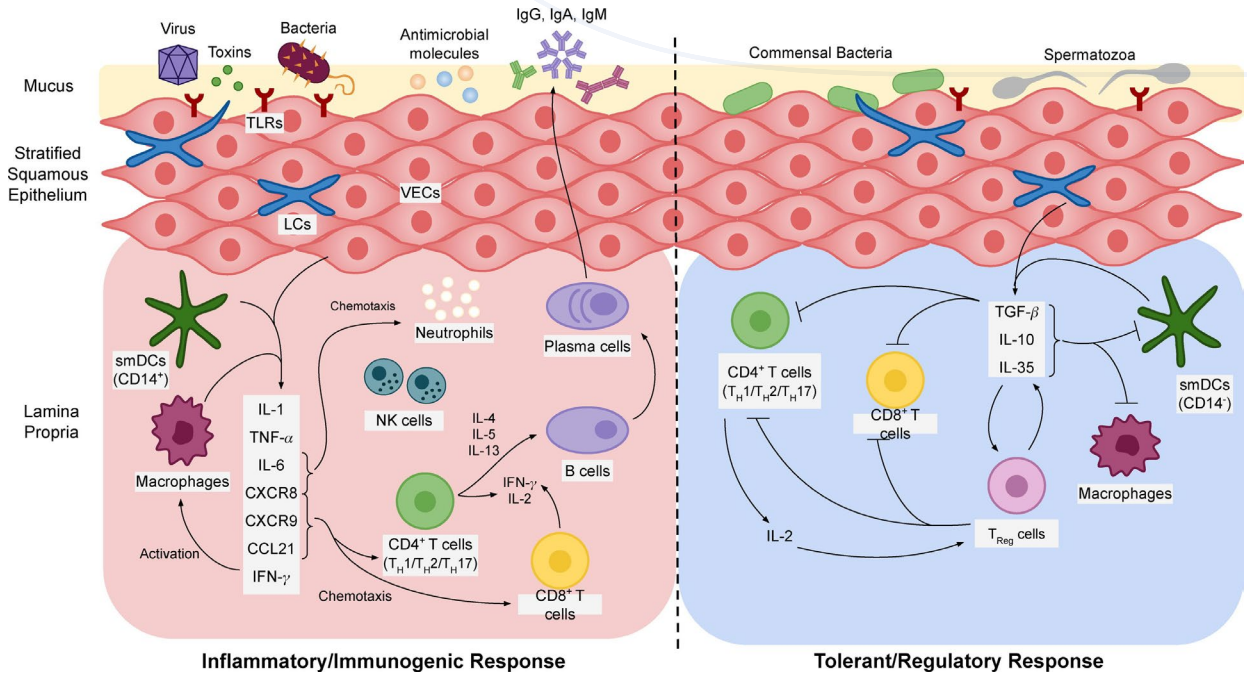
The GU tract represents a unique immunological site, given its dual role of protecting from infection as well as supporting reproduction. The antibody profiles in the female GU tract are distinctive compared with other mucosal immune sites, with a predominance of IgG (rather than IgA), for example, which is highly regulated by both hormone levels and systemic antibody levels. The GU tract is not generally an immune inductive site and lacks the organised lymphoid follicles found at other mucosal sites. The cellular immune response in the GU tract is also underexplored compared to other mucosal sites, with limited knowledge about the induction and maintenance of local cellular responses in these tissues.

The GU tract encompasses a range of tissues, each with distinct anatomical, hormonal, and microbial influences that differ markedly between sexes. These differences have important implications for both susceptibility to infection and vaccine development. Immune architecture varies across distinct compartments: the vaginal mucosa, cervical transformation zone, and penile urethra each exhibit distinct cellular compositions, microbiotas, and exposure risks, underscoring the need for site-specific analysis in studies of pathogen-specific mucosal immunity in both men and women to inform vaccine development.

The genital tracts forms a complex and dynamic protective barrier while also supporting distinct reproductive functions in men and women.[8–13] Physical barriers, including cell layering and mucus, protect against pathogens in women for example, and breaks in epithelial integrity or local inflammation in the mucosa are associated with increased susceptibility to infection with pathogens including HIV[8,10,13,14] and HPV[15] in both men and women. Sex itself consistently induces both inflammation and sub-clinical epithelial damage in both penile and vaginal tissues.[16,17] Immune responses at mucosal surfaces in the GU tract must therefore maintain a delicate balance between defence and tolerance,[8,10,11] as the tract is routinely exposed to foreign antigens through sexual contact while simultaneously supporting the reproductive microbiome, which is important in both health and fertility.[8,10,11]

The need for tolerogenic bias may blunt immune responses to vaccines or infections at mucosal sites. Immune features specific to the GU tract likely contribute to this balance by coordinating localised efficacious immune responses without triggering unnecessary inflammation.[8,11,14] The GU mucosa is also influenced by systemic factors, including sex hormones, co-infections, life stage, sexual activity, and contraceptive use, all of which can influence susceptibility and vaccine responsiveness.[8,10–14,18–23]

Immunogenic and Tolerogenic Responses in the Vaginal Mucosa



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3. Mechanisms of Protection

Key Takeaway: For GU pathogens, effective protection likely involves a combination of systemic and mucosal immune responses, and possibly a combination of cellular and humoral responses; however, precise mechanisms remain poorly defined for many pathogens. The absence of validated CoPs may pose a significant barrier to vaccine development.

Insights from natural infection studies, animal models, and clinical trials have largely focused on innate factors, including AMP levels and inflammation. Where adaptive responses have been characterised, the data suggest that both humoral and cellular immune responses contribute to protection against GU pathogens. However, precise protective mechanisms and how they operate at mucosal sites remain incompletely defined for most GU pathogens. Further, the durability, consistency, and predictive value of these responses vary across pathogens and populations. The knowledge gap has constrained rational vaccine design and limited the predictive value of preclinical and early clinical findings.

Pathogen-specific Immunology Insights

- ***Chlamydia trachomatis:*** While mucosal IgA and T-cell responses are detectable following infection, reinfection is common and protection is incomplete. Epidemiological evidence shows infection is more common in younger populations, suggesting a degree of protection with exposure as populations age. Animal models suggest $CD4^+$ T cells are important, but translation to humans has not been established.[24,25]
- **GBS:** Protection against neonatal disease is primarily mediated by maternal serum IgG transferred across the placenta; however, the role of local mucosal immunity in maternal colonisation and transmission remains unclear.[26]
- **HPV:** HPV offers the clearest vaccine success story among GU pathogens. Systemic IgG antibodies, induced by parenteral vaccination, are thought to reach the genital mucosa via both exudation and transudation to prevent infection at the point of entry. However, the specific threshold of immune response, mucosal, systemic, or both, that correlates with protection has not been formally established in humans.[31]
- **HIV:** HIV is located at the mucosa for around 72 hours post-infection, during which time post-exposure prophylaxis is highly effective. The virus rapidly disseminates, replicates, and evolves in the days and weeks that follow, suggesting this short time frame at the mucosa represents a unique opportunity for local protection. Infection is established by one or two viruses, which rapidly evolve, indicating that HIV is under early immune pressure and has an incredible ability to mutate and escape. A relatively small proportion of individuals spontaneously control the virus over many years, and this has been attributed to highly effective CD8+ T-cell responses. Local $CD8^+$ T-cell responses in the cervical and rectal mucosa (and GI tract) have been associated with reduced viral replication, and CMV-based vaccines inducing broadly reactive T cells have been associated with virus control and clearance in NHP.[10,13,23,27–29] The induction of TRM could play a crucial role in protection at the site of viral entry.[30] Broadly neutralising antibodies may block mucosal entry, but given the diversity and carbohydrate density of the HIV outer envelope, immunogens to elicit such antibodies have also been elusive.[14,20,27,28]
- **HSV:** Natural infection leads to the development of tissue-resident T cells in the genital mucosa, which exerts immune pressure and likely shortens the duration of shedding episodes and can limit recurrence.[32–38] Repeated exposure fails to generate protection, highlighting the challenge of achieving durable responses.[33,36,38–43] Following natural infection, HSV establishes latency and can reactivate, providing opportunities for therapeutic vaccination. Correlates of durable protection remain undefined, even in vaccine recipients.
- ***Neisseria gonorrhoeae*:** Natural infection does not confer immunity, and repeated infections can occur following exposure. Despite some evidence of local immune activation, no definitive protective mucosal response has been identified. Local immune activation is also the basis of immune pathology. [21,44]

Taken together, these findings suggest that mucosal immune responses may be important for protection, but mechanisms of induction and protection, as well as the magnitude, specificity, and quality of these responses, are likely to vary considerably.

Consistent with the measurement of both respiratory and GI responses, measurement of mucosal immune responses in the GU mucosa using standardised methods for sampling and assessing is limited. The GU tract is a mucosal environment that is relatively easy to access and sample. However, cervicovaginal and penile rectal sampling techniques require specialised training and can face social and logistical barriers in clinical trials.

The female genital tract is relatively easy to access and acceptable for sampling via swabs, menstrual cups, and cytobrushes. These sampling methods can be somewhat standardised and potentially self-administered, but can yield variable specimens.[45,46] Elution of swabs further dilutes samples, which can make it challenging to detect and quantify some analytes with accuracy. However, this can be accomplished if the initial volume of secretions is precisely known, e.g., by collection using a menstrual cup. Compared with cytobrushes, pinch biopsies yield cell populations from deeper within the mucosal tissue, including submucosal as well as intraepithelial cells, but are somewhat invasive. These may require processing or careful cryopreservation in laboratories close to the clinics, coupled with counselling to ensure the breach in the mucosal barrier does not increase the risk of infection, for example, in women at risk of HIV. Cell numbers are limited and, as with other mucosa surfaces, may require fresh processing and analysis, along with in vitro stimulation to detect antigen-specific cells.

Standardised protocols, assay standards, and sampling tools are needed to better characterise immune responses at these sites. Miniaturisation of assays is required, and multiplex technologies, -omics, and data analysis tools offer powerful next-generation platforms to maximise and integrate information from small samples.

4. Induction of Mucosal Immunity

> ***Key Takeaway:*** While systemic vaccines can elicit some mucosal responses, their consistency and durability are uncertain; no validated strategies currently exist to reliably generate localised immunity in the GU tract, highlighting the need for targeted delivery methods, better measurement tools, and focused research to inform vaccine design.

Efforts to induce protective mucosal immunity in the GU tract face several biological and technical constraints. Unlike oral or intranasal routes, which can target mucosal inductive sites directly, there is currently no widely accepted method for delivering mucosal vaccines to the genital tract. Moreover, the female genital tract appears to be poorly immune-inductive, lacking structures such as the Peyer's patches of the GI tract, and significant concern exists that inflammation caused by local vaccination may increase the risk of acquiring GU pathogens or jeopardise reproduction.

The lack of routine GU sampling in vaccine trials, combined with the need for validated assays on limited mucosal samples, has further constrained progress. The male GU tract is even more challenging to access, and less information is available.

HPV provides a compelling example of how systemic vaccination can induce mucosal antibody responses, with both IgA and IgG detected in cervicovaginal secretions following immunisation.[47,48] However, HPV is a relatively slow replicator, is easily neutralised by antibodies, and does not disseminate, unlike other more rapidly replicating GU pathogens. For many pathogens, responses may not be induced (or re-induced) rapidly enough or be of sufficient potency and breadth to provide protection through transudated antibodies alone. They may also have limited durability and/or be influenced by factors such as age, sex, and hormonal status.

The GU tract may be "linked" to other more immune-inductive sites, and it has been shown that IN and GI-delivered vaccines may also induce responses at GU mucosal surfaces.[34,49,50] A clear test of this concept could be readily confirmed through GU sampling in ongoing or planned vaccine trials. Moreover, there is a need to induce and assess intrarectal immunity, given that many GU pathogens are transmitted rectally.

Innovative delivery strategies are being explored, including mucosal boosting, the use of adjuvants that enhance mucosal homing, and vaginal or rectal delivery platforms.[13,49,50] Prime-pull strategies show promise in recruiting TRMs and IgA-secreting B cells in NHPs. Whether such trafficking translates into protection remains to be seen and would require pairing with rational immunogen design.

Mucosal vaccines encounter physical and chemical barriers, including proteolytic enzymes, acidic conditions, mucociliary clearance, and poor diffusion across epithelial monolayers, which hinder effective antigen delivery and can result in low absorption rates. Nanoparticle carriers offer antigen protection and epithelial uptake but are largely in preclinical development.

5. Status of Current Vaccines & Clinical Evidence

> ***Key Takeaway:*** The mucosal adjuvant pipeline is sparse, likely reflecting the fact that balancing potency with reactogenicity is paramount. Among the ~60 GU vaccine candidates tracked, only three in early development are formulated for direct mucosal delivery; the remainder rely on systemic administration.

See the following page for a pipeline of GU vaccines in development as of April 2025.

GU Vaccine Pipeline

Click on pathogen title to link to the pathogen profiles and pipelines in Appendix A.

Chlamydia trachomatis

CAF10b (M)

The chlamydia vaccine pipeline is limited and early stage, with current candidates targeting major outer membrane protein (MOMP) and containing B- and T-cell epitopes covering four serovars.[6] While no CHIM exists, experts suggest that high chlamydia prevalence may offer opportunities for natural exposure cohorts.

Group B streptococcus (GBS)

AH

The primary goal is to induce high levels of maternal systemic IgG antibodies for transfer to the newborn. As such, the primary focus of vaccine trials is predominantly on systemic antibody responses in the mother. These antibodies have been shown to influence maternal GBS colonisation at mucosal sites.[26]

Human Immunodeficiency Virus (HIV)[51]

15 12

Progress has been slow in identifying approaches to generate protective neutralising antibodies and T-cell responses. There has been some effort to understand the induction and measurement of immunity at the genital and rectal surfaces. Preclinical NHP studies may involve mucosal challenge, though concerns that activating CD4+ T cells in the mucosa may enhance HIV acquisition have slowed progress. (See pathogen snapshot for adjuvant detail).

Human Papillomavirus (HPV)

Alum | AH, Novel | AH, AP, Alum | Alum, A13, Alum ✓, ASO4 ✓ (M), AAHS ✓ (M), AAHS ✓ (M)

In contrast with other GU pathogens, the vaccine development pipeline for HPV is robust. There are six highly efficacious multivalent HPV vaccines available globally that are highly effective at inducing type-specific nAbs in serum that reach the mucosa by direct exudation and transudation. There are more than a dozen prophylactic candidates in the pipeline (and more than 30 therapeutic candidates), with some investigation into mucosal HPV-specific antibodies in cervicovaginal secretions in vaccine trials.

Herpes simplex virus (HSV)

There is a recognised importance of stimulating mucosal immune responses at the site of infection (prophylactic and therapeutic). There are numerous therapeutic products in the pipeline (outside the scope of this review), but only one prophylactic product, a systemically delivered mRNA vaccine. Preclinical animal models may use mucosal immunisation and challenge.

Neisseria gonorrhoeae (NG)

There is a limited product pipeline, with development of a fast-tracked Phase 2 candidate recently halted.[52] Strategies to elicit local IgA and tissue-resident Th17/Th1 cells, especially via mucosal delivery or adjuvants, could be critical for effective protection.[13]

† Fast-track designation
†† Breakthrough designation

DELIVERY ROUTE

- Parenteral
- Oral
- Patch
- Intranasal
- Aerosol

- \+ Adjuvanted*
- ✓ WHO-prequalified
- ⊘ Discontinued
- (M) Mucosal immunity effect in humans indicated in the literature

*Aluminium Hydroxide (AH)
Aluminium Phosphate (AP)
Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)

VACCINE TYPE

- Subunit
- Conjugate
- DNA
- RNA
- Live-attenuated
- Inactivated
- Replicating viral vector
- Non-replicating viral vector
- Not classified

6. Priority Challenges for Mucosal Vaccine Development

Progress in GU vaccine development is hindered by poorly defined immune correlates, challenges in mucosal delivery and sampling, and a lack of validated platforms tailored to the GU environment.

Limited immunogenicity of local vaccination approaches. To date, intravaginal and rectal vaccine trials have been sparse, yielding weak and inconsistent immune responses. This suggests that both immunogens and delivery platforms require optimising, but may also indicate that local delivery alone may not be optimal or indeed sufficient to elicit durable mucosal immunity.[14,34]

Mucosal immune responses. Mucosal sampling in vaccine trials is not widely or consistently incorporated into vaccine studies. GU antibody responses can vary substantially based on age, sex, microbiome, co-infections, hormonal status, and menstrual cycle phase, complicating both vaccine design and the interpretation of immune correlates.

Challenges in sampling and measurement. Elution from swabs dilutes samples, making absolute measurements challenging. Sampling mucosal tissues in the GU tract is invasive and requires supporting clinical and laboratory capacity. Cellular responses can be assessed in the female GU tract, and the impact of ongoing inflammation or hormonal cycle on TRM can be established,[11] but there has been limited standardisation across studies and no widely accepted surrogate endpoints, hindering the ability to compare immunogenicity across candidates or populations.

Lack of clinical proof-of-concept models. There are few CHIMs relevant to GU pathogens, with gonorrhoea in men being the primary example. This restricts opportunities to generate clinical data on mucosal vaccine efficacy and limits the development of immune benchmarks.

Cross-talk between mucosal sites. There is some evidence that IN vaccination can induce significant responses in the GU tract, and more recently, also in the GI tract; this requires further validation.[34,49,50]

7. Opportunities for Advancing the Field

Scientific and technological advances provide new approaches to addressing long-standing challenges in eliciting and measuring mucosal immunity in the GU tract.

Share and standardise tools across disciplines. Accelerate progress by sharing delivery technologies, adjuvants, assay methods, and data integration and analysis tools across mucosal sites and disease areas. Cross-disciplinary platforms can reduce duplication and accelerate the adoption of successful approaches.

Collect more mucosal samples and data. Systematically collect mucosal samples in epidemiology studies, studies of natural infection and vaccine trials, particularly those utilising mucosal delivery routes and apply next-generation assays and platforms to analyse these samples. This could yield important clues regarding baseline gut immunology, commonalities across mucosal sites, correlations between blood and mucosal antibodies and cellular responses, and build a knowledge base for immune correlates and rational vaccine design and delivery.

Optimise and standardise sample collection and assays through collaboration, core training, and standardised protocols. The GU tract is relatively accessible and offers an opportunity to optimise and qualify assays and standards utilising mucosal secretions and cells.

Expand use of models and imaging. Broaden the use of organoids, explants, and advanced imaging tools to study transmission and immune responses, as well as to help screen immunogens and generate mechanistic insights ahead of clinical testing.

Test for "linkage." Evaluate potential linkages between other mucosal tissues and the GU tract by assessing individuals enrolled in GI and respiratory vaccine trials. Include evaluation of potential cross-talk between female genital tract and rectal surfaces.

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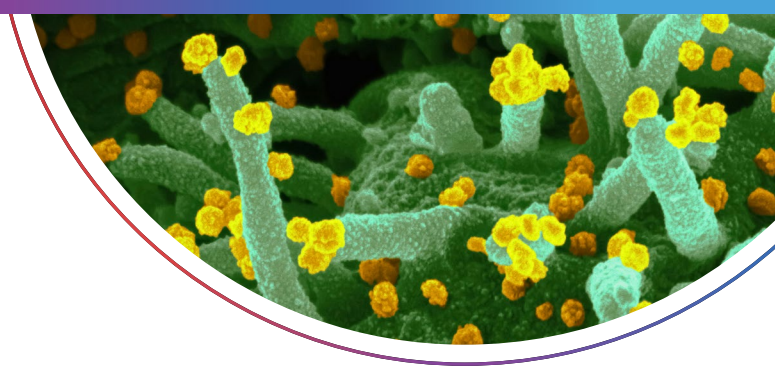
Chapter 3

Core challenges to advancing mucosal vaccine development



Core challenges to advancing mucosal vaccine development

The detailed analyses presented in Chapter 2 for the respiratory, GI and GU tracts revealed a series of core scientific and structural challenges impeding progress in both understanding mucosal immunity and optimising or developing mucosal vaccines. These core challenges, characterised in the concept map below, have made it difficult to close knowledge gaps, leading to dampened commercial interest and slowed progress across the vaccine development pipeline. Each of these challenges is introduced below and corresponds to an actionable list of recommendations detailed in Chapter 4, designed to advance rational mucosal vaccine research and development efforts.

Mucosal immunity resides at the interface of high biological and pathogen-specific complexity.

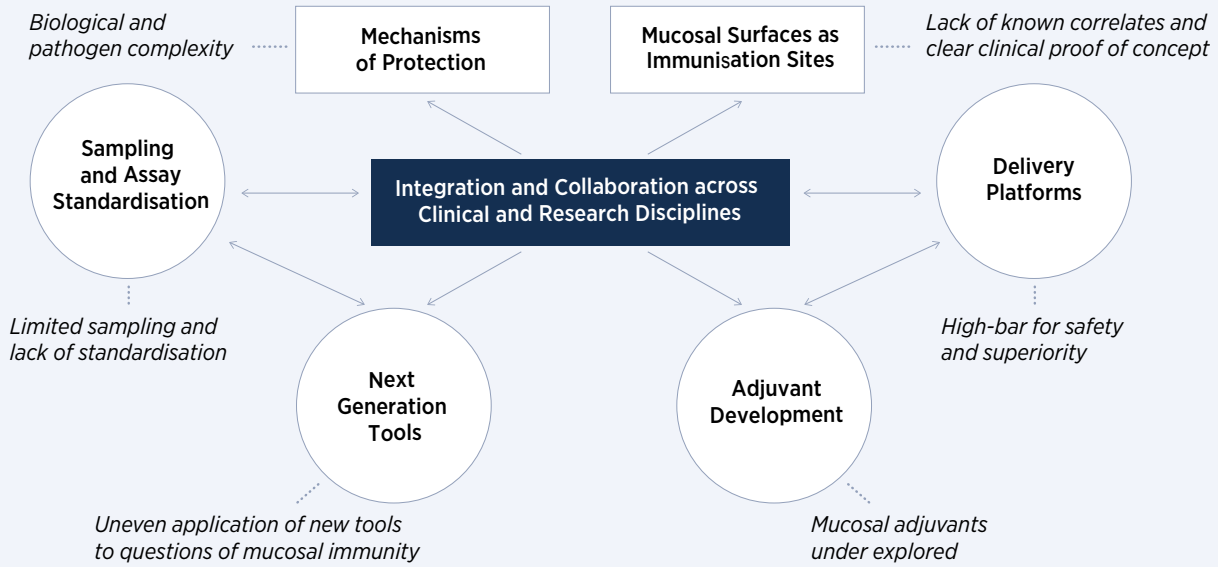
Mucosal surfaces are not a single immunological compartment. The immune architecture of the gut, genital tract, and respiratory system varies significantly and is shaped by distinct microbial environments, tissue structures, and immune cell distributions. These complexities make it difficult to extrapolate from one mucosal site to another, and make it even harder to generalise the immune requirements for protection across vaccine platforms or pathogens. Additionally, the relative contributions of mucosal versus systemic immunity remain poorly defined.

Mucosal-targeted vaccines will serve distinct indications depending on the pathogen: for some respiratory pathogens, the goal may be to prevent infection and transmission at the upper airway; for other diseases, reducing disease progression or recurrence may be more relevant. For pathogens like HPV, parenteral vaccines have demonstrated strong protection, suggesting that direct mucosal targeting is not always necessary. In other cases, robust mucosal responses may be essential for effective vaccines or may offer incremental benefits to overcome suboptimal efficacy, waning immunity, serotype variability, or accessibility issues. These variations influence vaccine design, correlate discovery, and endpoint selection.

What is needed?

- Improved mechanistic understanding of how to elicit, sustain, and measure protective mucosal responses in humans.

Concept Map: Core Challenges



Limited sampling hampers progress.

High-quality mucosal sampling is often not conducted in clinical trials, representing a significant bottleneck in assessing vaccine-induced mucosal immunity. Many studies omit mucosal sampling altogether due to logistical and resource constraints, sampling complexity, lack of harmonisation, and operational design issues. In low-resource settings, mucosal endpoints are often excluded due to cost, technical challenges, or a lack of harmonised protocols.[1] When sampling is conducted, inconsistent techniques and protocols reduce comparability. Strengthening the quantity and quality of mucosal sampling is therefore a critical enabler for any effort to assess vaccine-induced mucosal immunity.

What is needed?

- Standardised protocols, best-practice guidelines for diverse sample types, and integration into clinical trial infrastructure, including in LMICs. This includes specialised training, equipping local labs, deploying mobile sampling units, and distributing standardised kits to reduce cost and complexity.
- Development and adoption of less-invasive tools, such as mucosal sampling strips and breath condensate collectors, that enable more frequent and participant-friendly sampling.

Lack of assay standardisation limits interpretation.

The development and qualification of assays that measure mucosal immune parameters are at a relatively early stage. Few fully qualified assays for mucosal immune markers exist, and a lack of reference standards hinders the comparability of responses. Additionally, there is inherent sample variability and complexity compared to blood-based assays, which limits their usefulness. These gaps hinder efforts to identify biomarkers or define mucosal correlates of protection. Most available immune assays (ELISA, ELISpot, and flow cytometry) are optimised for blood, not mucosal samples, which are more limited and have lower analyte concentrations.[2]

What is needed?

- Well-characterised, sensitive, precise, and scalable assays, especially those able to detect low-abundance mucosal responses in complex samples of small volumes.
- Agreement among stakeholders to optimise and standardise assay packages, along with a strategy that facilitates cross-trial comparison.

> "Systems biology and in vitro modeling may be expensive, but is it really cheaper to just fumble around in the dark and do clinical trial after clinical trial?"
>
> — KOL INTERVIEW

Uneven use of next-generation tools with the potential to unlock understanding of localised immune mechanisms.

The assessment and analysis of mucosal immunity must keep pace with ongoing breakthroughs in the understanding of human immunology. Next-generation tools, such as spatial transcriptomics, single-cell RNA sequencing, advanced imaging, high-sensitivity multiplex assays and systems immunology platforms, and human-relevant in vitro models are currently being applied to enhance the basic understanding of human immunology and must now be applied to human mucosal immune responses induced by vaccines and natural infection.

What is needed?

- Accelerated application of promising technology platforms to human testing and to broaden access to these tools, particularly in the assessment of target populations.
- Training and protocol harmonisation to standardise data handling, integration, and AI-driven pattern recognition.

Lack of known correlates and clinical proof of concept has slowed progress in vaccine development.

The extent to which mucosal immunity, as opposed to systemic immunity, contributes to protective outcomes varies widely by pathogen and route of infection and is not yet fully understood, which significantly complicates the rational design of vaccines intended to elicit mucosal responses. Despite decades of research, there are still no validated mucosal correlates of protection for the pathogens included in this review. The underlying immunological mechanisms that govern mucosal protection are incompletely characterised. This knowledge gap presents major obstacles in defining optimal immune endpoints for vaccine development. It also limits the ability to conduct meaningful comparative studies across vaccine candidates or platforms and align regulatory pathways.

Targeted clinical research is an essential but underutilised approach to improving our understanding of mucosal immunity, including its role in protection, durability, and safety. Smaller, mechanistic studies (e.g., CHIM and other experimental medicine trials) should be used for hypothesis validation and exploration of immune mechanisms. Larger, well-designed clinical trials should incorporate robust, relevant mucosal end-point sampling (e.g., nasal swabs, bronchoalveolar lavage, faecal samples) and be powered to assess variables such as microbiome composition, baseline inflammation, and host genetics or sociocultural factors.

What is needed?

- Both small-scale mechanistic and large-scale pragmatic trials with qualified mucosal assays, harmonised sampling protocols, and agreed-upon immune correlate frameworks to ensure that clinical data are reliable, generalizable, and actionable for development and policy decisions.
- Make clinical data from such trials widely available to enable the evidence-based decision-making that is necessary to advance mucosal vaccines.

Adjuvants are essential but underexplored.

The development and application of adjuvants suitable for mucosal delivery are essential components of advancing mucosal vaccine strategies. Yet, most licensed adjuvants are optimised for systemic use and may not translate effectively to mucosal tissues, where immune activation must balance efficacy with local tolerance and safety. Few mucosal-specific adjuvants have been clinically validated, and their mechanisms of action, especially regarding tissue-resident and compartment-specific immunity, are not well characterised. The mucosal-specific adjuvants most studied in preclinical and early phase clinical studies include detoxified enterotoxin derivatives.

What is needed?

- Continued investment in mucosal adjuvant translational research and development, including the exploration of novel molecules, delivery systems, and compartment-targeted formulations, to enhance the immunogenicity and protective efficacy of mucosal vaccine candidates.

> "When you compare the work that has been done on adjuvants with parenteral vaccines vs. mucosal vaccines, the mucosal vaccine space is much thinner – and the parenteral space is limited enough by itself!"
>
> — KOL INTERVIEW

Safety is paramount and has contributed to development hesitancy.

Local inflammation, immune tolerance, and rare but serious adverse events have been observed in past trials of mucosally delivered vaccines, particularly with adjuvanted formulations. These issues have slowed progress and contributed to hesitancy around innovation in mucosal adjuvants. Going forward, careful safety profiling will be crucial to regaining confidence and securing regulatory approval.

What is needed?

- Rigorous preclinical and clinical evaluation of mucosal vaccine candidates, with a strong focus on local and systemic safety. This includes developing standardised protocols for assessing mucosal inflammation, monitoring for immune tolerance, and identifying adverse events of special interest.

Limited mechanisms for collaboration and incentives for investment.

Limited collaboration among those pursuing different aspects of mucosal vaccine R&D is impeding progress in the field. Building globally accessible resources, such as standardised assays, mucosal sampling protocols, and common data platforms, can improve harmonisation and reduce duplication of effort. Currently, heterogeneity in mucosal trial designs and endpoints (e.g., variations in measuring sIgA and tissue-resident T cells in BAL or nasal mucosa) hampers everything from study design to meta-analysis and regulatory alignment.

Without clinical proof of concept, the field remains reluctant to invest, despite the theoretical promise mucosal immunity holds for some high-priority pathogens. Investment is also constrained by regulatory uncertainty. The lack of validated correlates and standardised assays complicates both clinical trial design and regulatory evaluation of mucosal vaccines. Without established endpoints, sponsors face additional risks in development timelines and approval pathways.

What is needed?

- Increased collaboration across diseases and geographies to facilitate the exchange of knowledge, encourage cross-training, and support innovation at the interface of immunology, microbiology, and vaccinology.
- Collaborative research studies to generate proof-of-concept evidence on the value of mucosal immunity and inform the next generation of mucosal vaccines.

The core scientific and structural challenges identified in this report are substantial, and overcoming them will require significant innovation and collaboration. However, they are not insurmountable. The technological advances in vaccine development seen in the previous decade, including the momentum created by the COVID-19 pandemic, can prove transformative. The next chapter outlines five strategic pathways to help close these knowledge gaps, accelerate vaccine R&D, and enable the development of more effective mucosal vaccines to address pressing global health needs.

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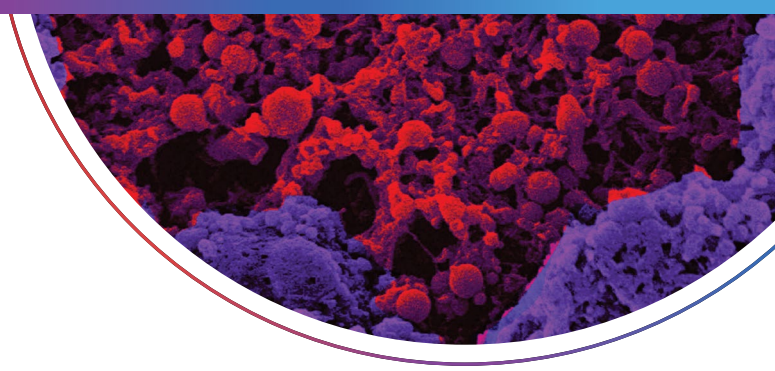
Chapter 4

Recommendations and strategic priorities



Recommendations and strategic priorities

Five areas to advance progress towards mucosal vaccines

1

Expand the tool kit and capacity to interrogate mucosal immunity.

- Ensure fit-for-purpose sampling and assays are conducted whenever possible.
- Leverage next-generation tools and technologies
- Develop field-adapted mucosal sampling and assay capacity suitable for LMIC settings.

2

Strengthen the evidence base for the importance of mucosal immunity for protection.

- Design experimental medicine studies to directly compare mucosal and systemic immune responses.
- Leverage planned clinical trials to link efficacy with the level of mucosal immunity.

4

Accelerate development of vaccines that are safe, induce mucosal immunity, and address major medical needs.

- Establish mucosal correlates of protection, including systemic surrogates, to guide product development.
- Incorporate mucosal endpoints in target product profiles when appropriate.
- Expand evidence base around 'prime and pull' strategies.
- Continue to develop and advance novel adjuvants and delivery platforms.
- Explore co-interventions to enhance mucosal immunity.

3

Improve foundational understanding of mucosal immunity.

- Determine how to induce immune responses at different mucosal sites.
- Measure the extent of mucosal responses generated by systemic vaccination and by cross-talk between mucosal sites.
- Demonstrate how population-based changes in mucosal immunity affect protection.
- Analyse vaccine-induced versus natural mucosal immunity to inform vaccine design.
- Pre-position protocols and partnerships for rapid response in outbreaks.

5

CORE ENABLING FACTOR

Establish and promote mechanisms and incentives for cross-disciplinary collective action.

- Create and/or strengthen cross-disciplinary consortia and working groups to align priorities, harmonise tools, and foster collaboration across the mucosal vaccine field.
- Expand training and career incentives for mucosal immunology.
- Provide additional funding within clinical trials to collect data on mucosal immunity.

Building on findings from the literature review, expert consultations, and pathogen research, this report outlines a five-part strategy to overcome the core scientific and structural challenges hampering the field of mucosal immunology and the development of vaccines that induce protective mucosal immunity. The five Recommendation Areas (RAs) are not prioritized, neither are they standalone: while each area addresses a discrete challenge, they represent a cohesive approach and are designed to work in concert to close gaps and facilitate progress.

Strengthening cross-disciplinary collective action is the linchpin that binds the other recommendations together, thereby increasing the probability of success for each. Such coordination is considered essential for progress toward highly effective vaccines that elicit mucosal responses.

Recommendation Area 1

Expand the toolkit and capacity to interrogate mucosal immunity.

In the absence of appropriate sampling methods and assessment strategies that are technically fit for purpose, mucosal immune responses remain poorly characterised and are frequently overlooked in clinical studies. Recent advances in next-generation tools offer potential insights into the components and mechanisms of immunity.

Research is exploring systemic responses, such as the detailed molecular structure and function of antibodies and cellular interactions needed to promote immune maturation and memory, but is only just beginning to be applied to the mucosal immune system. To fully realise their potential, they will need to be adapted to the complexity and small sample volumes of mucosal samples.

The field should prioritise the development and implementation of safe, practical, scalable, and standardised methodologies, specific to each mucosal site and sample matrix, to collect mucosal samples and measure mucosal responses. New information on the components of mucosal immunity can, in principle, enhance study design, enable more sensitive analysis of mucosal responses, and potentially allow retrospective analysis of stored clinical specimens to generate new insights. Collectively, these tools will ensure that proposed clinical studies and mechanistic investigations (RA2, 3, 4) are supported by reliable methods for understanding how to induce, detect, and interpret protective mucosal immune responses.

1.1 Ensure fit-for-purpose sampling and assays are conducted whenever possible.

A significant obstacle to understanding mucosal immunity is the lack of routine mucosal sampling in vaccine trials and clinical research studies. Core to this issue is both the time and capabilities required to reproducibly access high-quality mucosal samples in sufficient quantities, given both the invasive nature of sampling within complex anatomies and the time, clinical expertise and laboratory optimisation and capabilities required for sample collection and analysis.

Develop and adopt standardised, implementable clinical protocols for the collection, processing, and analysis of mucosal samples across anatomical sites.

This recommendation is closely linked to RA2 and RA4, as it will require clinical researchers to collect mucosal samples in a subset of the participants in trials with efficacy endpoints. Working groups may be required to develop a set of standards to ensure data can be reliably compared across assays. Further, a shared, well-integrated, de-identified database of mucosal trial data, detailing methods, samples, and immune parameters, would accelerate field-wide progress and foster prioritisation of methods.

> "A prerequisite investment to get to clinical proof-of-concept would be to standardise assays and the methods of sample collection. Without that, you are blind and fishing around variable assays. I think that's a very worthy investment."
>
> — KOL INTERVIEW

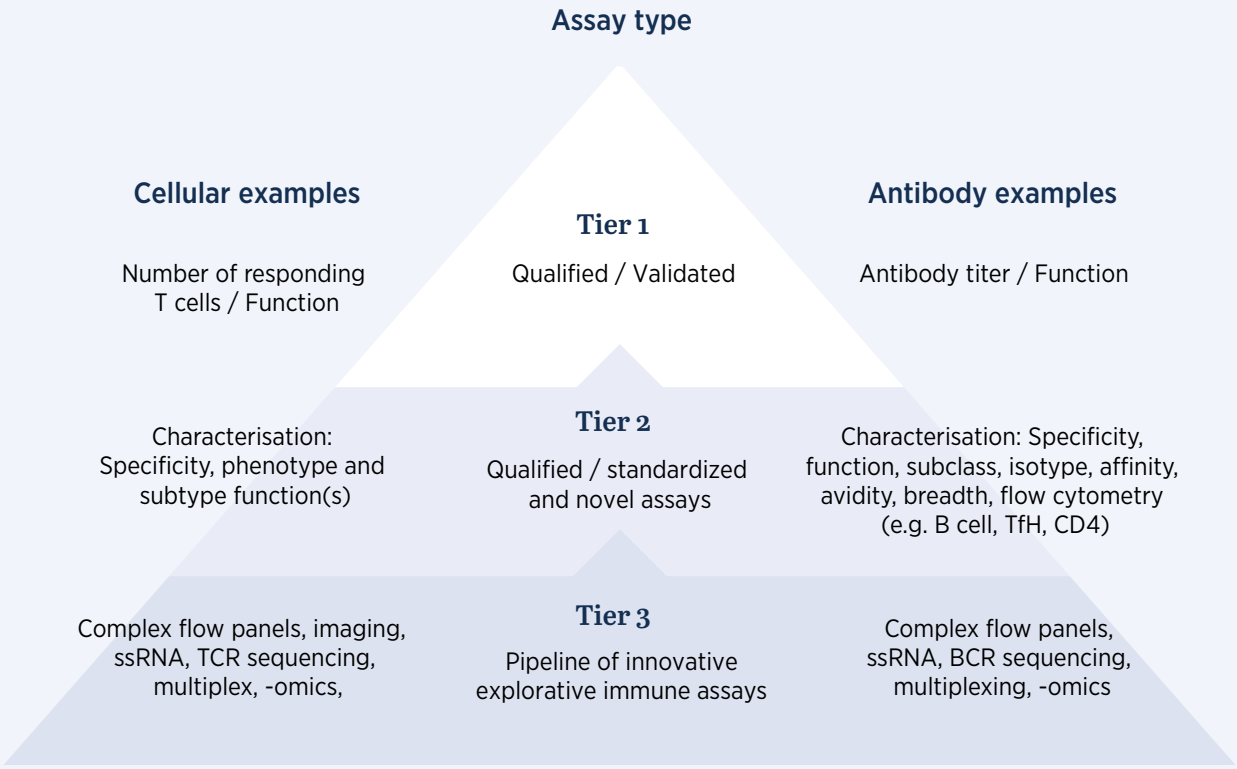
1.2 Leverage next-generation tools and technologies.

In addition to improved and broader mucosal sampling, advancing the field will require efforts to standardise and qualify assays as a prerequisite to validation and to support mucosal vaccine trial endpoints.[1] Increased application of next-generation technologies will deepen the evidence for, and understanding of, the complex interplay between host, pathogen, and vaccine at mucosal sites.

Different assay strategies are needed across the vaccine development continuum. Assays should be adapted to operate effectively on the small sample volumes and limited cellular content typically obtained from mucosal tissues. Moreover, mucosal assays must be designed to account for biological and procedural variability, including differences in sample quality due to inflammation, menstrual cycle, microbiome, enzymatic activity, mucus content, and other factors that can impact assay performance and data interpretation. This reinforces the need for consistency in standards and quality control in both assay application and mucosal sample handling, as detailed above.

Adopt a tiered assay framework to align immunologic tools with vaccine development stages, supporting the clinical evaluation and rational design of mucosal vaccines.

Tiered Assay Framework



- **Tier 1: Primary Immunogenicity Assays** must be qualified or validated for accurate assessment of immunogenicity endpoints in clinical trials (Ph I - Ph3), and should meet regulatory requirements. Highly sensitive multiplex platforms are approved for serum/plasma use by the FDA[2] and should be validated or adapted for diverse mucosal samples, which may require extensive adaptation of protocols. These platforms can be scaled to high throughput and simultaneously quantify multiple analytes from small sample volumes with large dynamic ranges and precision, making them ideal for mucosal studies. Cellular assays will require significant optimisation and qualification for mucosal immunity. For example, ELISpot or flow cytometry assays have been validated for assessing T cell responses in peripheral blood but may require re-stimulation in vitro to detect mucosal responses. There may be a requirement to demonstrate antibody or cellular function as potential surrogates of efficacy.
- **Tier 2: Secondary Immunogenicity Assays** to further characterise vaccine-induced mucosal responses and support key clinical development decisions must be standardised and/or qualified. These assays support deeper immunologic characterisation and comparison across vaccine platforms and regimens, including characterisation of affinity, avidity, antibody class, epitope mapping, functional assays, and characterisation of associated cellular responses by Elispot and high-dimensional flow cytometry for antibodies, for example.
- **Tier 3: Research Assays** provide a pipeline of advanced tools to generate deeper mechanistic insights, enabling comprehensive analysis of host–pathogen–vaccine interactions at mucosal surfaces and helping uncover a new understanding of immune mechanisms of protection at the mucosa. Discoveries should feed back into Tier 1 and 2 development for broader applicability and qualification.

This tiered approach enables discoveries from advanced tools to inform the development and qualification of clinical assays, supporting both rational vaccine design and evaluation (RA 1 and 3). As tools are validated, they can also be applied to retrospective analysis of stored clinical trial samples, generating new insights from existing data.

Researchers should also consider investing in organoid models and utilising in vitro systems, including organ-on-a-chip[3] and 3D cell culture systems[4] to evaluate mucosal immune responses in a physiologically relevant context. While many of these models are currently still in the development stage and require validation, organoid systems derived from human tissues can closely mimic native architecture and cellular diversity, enabling detailed studies of host-pathogen interactions, antigen presentation, and functional immune responses to vaccines.[5]

When integrated into organ-on-a-chip systems, these models can incorporate physiological flow, multi-cellular complexity, and mechanical cues, and mirror the dynamic environment of mucosal tissues. In vitro models support precise manipulation (e.g., antigen exposure and cytokine challenge), longitudinal sampling, and integration with -omics and high-dimensional imaging technologies, allowing for mechanistic insight into mucosal immune induction, cellular pathways, and identification of CoPs, while reducing reliance on animal experiments.[5] These models will require ongoing validation.

1.3 Develop field-adapted mucosal sampling and assay capacity suitable for LMIC settings.

In addition to improved and broader mucosal sampling, advancing the field will require efforts to standardise and qualify assays as a prerequisite to validation and to support mucosal vaccine trial endpoints.[1] Increased application of next-generation technologies will deepen the evidence for, and understanding of, the complex interplay between host, pathogen, and vaccine at mucosal sites.

Some of the greatest needs for mucosal vaccines exist in target populations residing in underserved settings, where clinical and scientific infrastructure may be limited. Consequently, the acquisition of mucosal immune response data may face logistical and technical hurdles, but should not be ignored.

Establish/strengthen regional centres of excellence to support mucosal immunology research and vaccine trials in settings where disease burden is high and/or vaccine responses are attenuated.

These centres should have integrated capabilities for clinical research, including surgical capacity where needed for mucosal sampling, and expert laboratories equipped to conduct state-of-the-art mucosal immunology assays.

These centres would be instrumental in addressing pivotal questions, for example, why mucosal immune responses in the GI tract are often attenuated in LMIC populations, and could serve as critical platforms for vaccine trials and experimental medicine studies.

Such centres will require targeted investment and international collaboration, including training programs, career development pathways, and mechanisms for technology transfer. Such capacity-building efforts will help expand the global research footprint and enable sustainable, locally led research on mucosal immunity and vaccinology (R5).

Mucosal sampling methods

- **Female GU:** swab, menstrual cup, cytobrush, pinch biopsy
- **Male GU:** semen collection, swab, circumcision to collect foreskin
- **Upper Respiratory:** nasal swabs, nasal lavage, nasal turbinate, nasosorption, exhaled breath condensate
- **Lower Respiratory:** bronchoalveolar lavage, induced sputum, punch biopsy, bronchial brushing samples
- **GI:** saliva, buccal scraping, colonoscopy, rectal biopsy, cyto-brush, swab, faece

Recommendation Area 2

Strengthen the evidence base for the importance of vaccine-induced mucosal immunity for protection.

It is generally accepted that vaccine-induced mucosal immunity for respiratory, GI, and GU pathogens should enhance the effectiveness of vaccines by preventing the infection or transmission of such pathogens. But there is still limited direct evidence to confirm this. This lack of definitive human data on the benefits of vaccine-induced mucosal immunity has been a primary constraint on investment. There are several viable paths to strengthening this evidence base, including well-designed studies demonstrating protective mucosal responses in humans, which could catalyse substantial progress.

2.1 Design experimental medicine studies to directly compare mucosal and systemic immune responses across delivery routes and correlate with protection.

Experimental medicine studies, including CHIMs, are early-phase clinical studies designed to investigate biological mechanisms of protection, test scientific hypotheses, and/or evaluate immune responses, rather than to establish safety or efficacy endpoints. They offer unique opportunities to directly compare mucosal and systemic immune responses across delivery routes to determine whether optimising mucosal immunity can improve efficacy. Multiple immunologic parameters can be investigated to identify potential CoPs that could be validated in test-of-concept efficacy trials. Systemic prime and mucosal boost strategies could be compared to parenteral and mucosal vaccination alone. In addition, experimental delivery approaches, including intranasal, aerosol, oral, or rectal administration of vaccines, could be compared with parenterally administered vaccines to gain a better understanding of their relative immunogenicity and vaccine efficacy.

Prioritise clinical research testing the level of mucosal immunity induced by vaccination and its contribution to protection.

These studies can also help test mechanistic hypotheses derived from foundational research (RA3), particularly around how different platforms and delivery routes influence mucosal immune induction. Protocols, pathogen selection, and readouts would need to be refined by a multidisciplinary expert group, ideally associated with facilitated cross-collaboration (RA5). Success is contingent upon access to validated sampling protocols and qualified assays (RA1), underscoring the need for increased coordination.

2.2 Leverage planned clinical trials to link efficacy with the level of mucosal immunity.

Clinical trials of candidate vaccines provide a critical platform for evaluating the extent and efficacy of mucosal immune responses. The COVID-19 pandemic could have provided an unprecedented opportunity to assess mucosal responses at scale; however, the urgency of the vaccine rollout meant that meaningful mucosal investigation was largely deprioritised. With next-generation intranasally delivered COVID-19 and influenza vaccines now in development, there is renewed opportunity to apply mucosal sampling tools more systematically within efficacy trials and real-world studies.

Include/increase mucosal sampling and immunological assessment in vaccine development studies.

Incorporating mucosal endpoints into these studies would enable evaluation of mucosal immunity at a larger scale, including durability and transmission dynamics. It would also support optimisation and standardisation of mucosal sampling and assays, discovery of mucosal CoPs, and help validate systemic surrogates—advancing both foundational science and regulatory pathways. There may also be benefits to including mucosal sampling in Phase 4 effectiveness studies.

To fully capitalise on these studies, improvements are needed in mucosal sampling and mucosal assay qualification (RA1).

Recommendation Area 3

Improve foundational understanding of mucosal immunity.

Efforts to develop mucosal vaccines are constrained by an incomplete understanding of the unique immunological mechanisms that govern protective responses at mucosal surfaces. The mucosal immune system is distinct in its organisation and function, and is shaped by complex interactions between local tissues, commensal microbiota, and the systemic immune system. This complexity makes it difficult to predict how vaccines will perform, particularly in diverse populations with varying environmental exposures and health profiles.

A coordinated effort is needed to advance foundational immunology and clarify how to elicit, sustain, and measure protective mucosal responses in humans. Achieving this will depend on the implementation of clinical platforms and tools, including robust sampling, standardised assays, and diverse study populations (RA1, RA2) to generate high-quality, comparative mucosal immunology data.

> "We need targeted studies that answer specific questions under common protocols and rolled up to greater analysis."
>
> — KOL INTERVIEW

3.1 Determine how to induce immune responses at different mucosa.

While RA 2 focuses on definitively demonstrating whether mucosal immunity contributes to protection, a parallel priority is to optimise how mucosal immune responses are elicited and targeted. Recent advances in the development of vector platforms, experimental adjuvants, and delivery modalities provide enhanced tools for determining how to induce and target mucosal immune responses. Advances in antibody and cellular immune assays, coupled with single-cell technologies and multi-parametric systems biological (-omics) assays and analyses (RA1), provide additional opportunities to interrogate the induction of systemic and mucosal immunity.

Accelerate the rational design of new vaccines and appropriately structure clinical trials to optimise the induction of mucosal immune responses in target tissues.

Comparative trials could be designed to vary the vaccine platforms to evaluate how this affects the immune response at various mucosal surfaces. Such trials should be possible with licensed COVID-19 vaccines, for example, by testing the same vaccine antigen delivered via mRNA, viral vector, or as an adjuvanted virus-like particle. A trial could also be designed to test the same vaccine using intranasal or aerosolised delivery to see how this affects the induction of upper and lower respiratory tract mucosal immunity. Interactions with different mucosal tracts could also be tested. These trials should also incorporate the sampling and analysis methods outlined in RA1, to ensure that mucosal immune responses are accurately characterised and comparable across platforms.

Together, these studies will support rational design and platform selection for mucosal vaccines, even in the absence of established immune correlates, by improving our understanding of how specific technologies and delivery routes shape the quality, magnitude, and localisation of mucosal immune responses.

3.2 Measure the extent of mucosal responses generated by systemic vaccination and by cross-talk between mucosal sites.

While it is generally accepted that some parenteral vaccines may induce mucosal responses, the conditions under which they do so, and how this varies by antigen, platform, and delivery route, are not well characterised. For instance, HPV vaccines can induce robust systemic immune responses, which reach the mucosa via direct exudation and transudation, providing excellent protection against HPV. For other pathogens, targeted induction of immune responses at the mucosa may be necessary for protection; however, our understanding of how to induce mucosal responses is limited.

Incorporate mucosal sampling for both parenterally and mucosally delivered vaccines to enable the generation of critical data to improve understanding of the extent of cross-talk between sites.

The phenomenon of immunological cross-talk between anatomically distinct mucosal sites (e.g. gut-lung axis) has been investigated in preclinical models and observed in human studies, but remains mechanistically under-characterised.[6] Emerging evidence suggests that prime-pull strategies may boost mucosal immunity, but more work is needed to validate these approaches across pathogens (4.3).

3.3 Demonstrate how population-based changes in mucosal immunity affect protection.

It is well established that some vaccines, such as those for rotavirus, cholera, and typhoidal Salmonella, demonstrate reduced efficacy in LMICs compared to high-income settings. While this variability is well documented, the immunological mechanisms driving these differences remain poorly understood. Differences in host genetics, microbiome, diet and nutritional status, concomitant infections, age, pre-existing immunity, and environmental exposures may all contribute to variable mucosal immunity.[7,8]

Monitor changes in vaccine-induced mucosal immunity and association with efficacy in target populations.

Recent advances in human immunology, systems biology, and computational analysis provide powerful tools for dissecting mucosal and systemic immune responses with high precision. These capabilities should be leveraged to determine whether, and how, variation in mucosal immunity contributes to differential vaccine performance across populations and geographies. Variability could be explored in the context of different delivery platforms and adjuvants to determine gaps in the understanding of immunocompromised populations.

3.4 Analyse vaccine-induced versus natural mucosal immunity to inform vaccine design.

The immune responses that occur in response to infection are often different from those induced by vaccination, including at mucosal surfaces. Understanding these differences provides opportunities for informing next-generation vaccine design. CHIMs provide excellent systems to analyse natural versus vaccine-induced mucosal immunity.

Conduct comparative analyses of natural and vaccine-induced mucosal immunity using CHIMs and complemented by high-dimensional immune profiling and advanced computational tools.

These models, coupled with next-generation tools (RA1) and mucosal sampling, can be used to provide additional information to help identify immunological mechanisms and CoPs and support the design of vaccines that more effectively target key mucosal immune pathways (RA2, RA4).

3.5 Pre-position protocols and partnerships for rapid response in outbreaks.

Outbreaks present rare but powerful opportunities to investigate mucosal immunity under real-world conditions. In this context, research could help elucidate correlates of protection, response durability, and transmission-modifying effects without the need for new large-scale trials. However, seizing these opportunities requires preparation, including harmonised translational databases, pre-approved protocols, standardised reagents, and coordinated investigator networks.

Develop and pre-position the infrastructure, protocols, and partnerships needed to study mucosal immunity during outbreaks.

A global mucosal vaccine consortium with this focus could help establish the necessary systems to act quickly in response to emerging epidemics. This includes building the clinical and ethical frameworks needed for rapid deployment of mucosal sampling, immunoassays, and systems biology analyses in affected regions. By activating these tools in outbreak settings, researchers can collect high-value data across diverse populations, pathogens, and exposure scenarios.

Recommendation Area 4

Accelerate the development of vaccines that are safe, induce mucosal immunity, and address major medical needs.

The pipeline of vaccines that promote mucosal responses varies significantly across pathogens. Accelerating the development of vaccines that induce mucosal immunity on their own or contribute to improving the efficacy of vaccines designed to induce systemic immune response may help address significant unmet medical needs.

> "If you want to have mucosal vaccines, you need to find whatever is out there and bring them to clinical trials. Invest! You will have failures, but you are going to learn."
>
> — KOL INTERVIEW

4.1 Establish mucosal correlates of protection to guide product development.

Currently, there are limited serologic CoPs defined for licensed vaccines and no validated mucosal immune CoPs identified for many respiratory, enteric, or genitourinary diseases.[9] While levels of sIgA antibodies are increased following mucosal infections and with experimental vaccines delivered mucosally, there is limited human clinical trial data which conclusively demonstrates that sIgA levels correlate with protective immunity. Similarly, in cases in which serum IgG has been identified as a correlate of protection, such as with hemagglutinin-inhibiting (HAI) antibody titers for parenterally administered hemagglutinin-containing influenza vaccines,[10] it is unclear what level of these antibodies transudates across the respiratory mucosa to confer protective immunity.

Develop and pre-position the infrastructure, protocols, and partnerships needed to study mucosal immunity during outbreaks.

This work is essential to improve the design and evaluation of next-generation vaccines, including those targeting pathogens for which no vaccine is currently licensed. Achieving this goal will require building on the efforts described in RA 1–3: using clinical platforms (RA1), standardised measurement tools and assays (RA1), and a deeper mechanistic understanding of mucosal immune responses (RA3).

This objective would be greatly facilitated by including CoP studies within efficacy trials during which both mucosal and systemic samples are collected, and a broad array of assays are applied (RA1 and RA3). Where feasible, CHIMs could identify correlates by enabling direct comparison of immune responses in protected versus unprotected individuals.

4.2 Incorporate mucosal endpoints in target product profiles when appropriate.

Once the benefits of mucosal immunity in enhancing or enabling protection are demonstrated, whether through improved efficacy, durability, or reduced transmission, such findings should be incorporated into updated target product profiles (TPPs) for mucosal vaccines. Interviews and research for this report suggest that industrial vaccine developers are hesitant to invest in the development of mucosal vaccines, particularly when a licensed parenteral vaccine is already on the market. This is largely due to a perceived lack of a clear regulatory path in the absence of clearly defined benefits for inducing mucosal immunity (RA2).

Update TPPs to reflect mucosal endpoints where evidence from experimental medicine studies or clinical trials supports such claims.

Experimental medicine trials of mucosal vaccines, CHIM studies, and Phase 2/2b trials aimed at identifying the benefits of mucosal vaccines over parenterally delivered vaccines (RA2) would facilitate the incorporation of mucosal endpoints in TPPs, when appropriate, providing greater clarity to product developers, aligning regulatory expectations, and incentivising investment.

4.3 Expand evidence base around 'prime and pull' strategies.

Prime and boost strategies, particularly a nucleic acid or viral vector prime followed by a recombinant protein or virus-like particle boost, have been shown to improve humoral and cellular responses across a wide array of experimental vaccines.[11,12] A specific adaptation of this approach, known as prime and pull, aims to optimise mucosal immune responses by combining a parenterally delivered priming dose with a mucosally delivered booster.

Ideally, this strategy enables induction of both systemic and mucosal immune responses, optimising protection at the sites where pathogens enter or cause disease. For example, priming with an mRNA-based influenza vaccine followed by boosting with an intranasally delivered or aerosolised formulation would aim to elicit humoral and cellular responses systemically as well as in the upper and lower respiratory tracts.[13–15]

Conduct dedicated experimental medicine studies with integrated mucosal sampling, functional immune assays, and, when feasible, CHIMs to identify the most effective combinations of prime-and-pull approaches and inform correlates of protection.

This work is closely linked to RA1, 2, and 3, as studies in small numbers of volunteers will require well-qualified assays with excellent precision to test hypotheses and translate mechanistic insights into actionable vaccine design strategies.

4.4 Continue to develop and advance novel adjuvants and delivery platforms.

The COVID-19 pandemic accelerated vaccine development efforts and led to the rapid introduction of several vaccine technologies, including the mRNA vaccine platform (Moderna, Pfizer and BioNTech), the use of viral vectors (AstraZeneca), virus-like particle vaccines (Novavax), and novel delivery platforms. It also facilitated the discovery and development of novel adjuvants. These innovations were instrumental in preventing severe disease and death, but offered limited protection against infection and transmission.

These shortcomings have catalysed efforts to develop mucosal delivery platforms and novel adjuvants to enhance mucosal immunity for COVID-19 vaccines, as well as for other pathogens. Mucosally-targeted technologies hold promise for improving protection at the site of pathogen entry, blocking transmission, enhancing immune durability, and supporting broader access through needle-free administration.

Prioritise R&D for pathogen-specific, mucosally-targeted technologies and novel adjuvants for enhancing mucosal responses across respiratory, GI, and GU tissues.

Local inflammation, immune tolerance, and rare but serious adverse events have been observed in past trials of mucosally delivered vaccines, particularly with adjuvanted formulations. Rigorous preclinical and clinical evaluation of mucosal vaccine candidates with a strong focus on local and systemic safety is essential for progress and to instill confidence.

Develop standardised protocols for assessing mucosal inflammation, monitoring immune tolerance, and identifying adverse events of special interest.

Innovation will require coordinated investment, iterative testing in experimental medicine and clinical trials, and linkage to the sampling and measurement strategies described in RA1 and 2. Together, they offer a pathway to vaccines designed explicitly to optimise mucosal protection.

4.5 Explore co-interventions to enhance mucosal immunity.

As mentioned, mucosally delivered vaccines are often less effective in LMICs. The underlying mechanisms behind these disparities are not fully understood but may include differences in microbiome and diet, host genetics, co-infections, and baseline immune health. Addressing these factors may impact mucosal immune responses and contribute to vaccine performance.

Conduct studies of interventions to address modulating factors, such as the microbiome, diet, and treatment of concomitant infections.

Recent systems immunology studies have shown that pre-vaccination immune profiles can predict the magnitude and quality of vaccine-induced responses.[16] This highlights the potential of systems-based approaches to identify modifiable baseline factors that impact vaccine performance.

As new technologies and methodologies are tested, it will be important to confirm altered or augmented responses using the sampling and testing approaches described in RA1 and the link between such responses and protection RA3.

Recommendation Area 5

Establish and promote mechanisms and incentives for cross-disciplinary collective action.

To date, scientific advancement in mucosal vaccinology has been hindered by siloed expertise and research efforts, limited platforms for collaboration, and the absence of shared priorities and technical standards. Consequently, a coordinated and cooperative effort across disciplines, disease areas, geographies, and sectors should be pursued. This will require not only scientific advances, but also talent development, improved operational capacity, and sustained coordination mechanisms aligned to long-term impact. Establishing a plan for cross-disciplinary collective action is strongly recommended.

> "We need a culture change to promote solidarity and collaboration between researchers working across mucosal compartment communities and disease areas."
>
> — KOL INTERVIEW

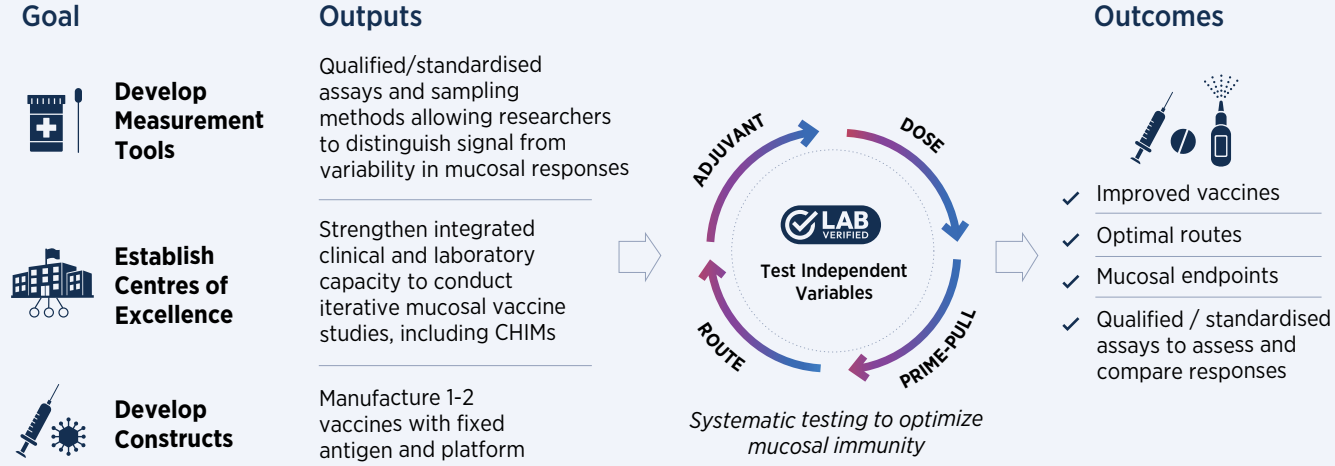
5.1 Create and/or strengthen cross-disciplinary consortia and working groups to align priorities, harmonise tools, and foster collaboration across the mucosal vaccine field.

A range of mechanisms involving different degrees of coordination and funding are available for collective action. They range from structured consortia designed to achieve specific goals and objectives to more modest initiatives that seek to guide ongoing activities. The identification of the exact formula remains to be determined in concert with various stakeholders, but progress on this front is likely essential to achieving overall goals.

A well-structured, collaborative consortium focused on mucosal vaccines was broadly viewed by field experts as having the potential to significantly advance the field by de-risking development and catalysing investment across multiple pathogens. In the near term, such a consortium could focus on strengthening sampling and assays (RA1), which are essential for the generation of definitive clinical evidence on the contribution of mucosal immunity to protection (RA2). Over time, the scope of the consortium could expand to address longer-term goals, including foundational research in mucosal immunology and vaccine product development (RAs 3 and 4). Private sector participation, as well as public sector scientists and stakeholders, should be included from the outset to ensure that discoveries are translated into deployable products.

Another potential objective for a consortium could be the conduct of iterative trials to evaluate the impact of specific variables (e.g., adjuvants, dosing, route of administration) on a variety of outcomes. In both scenarios, enhanced collaboration and multidisciplinary contributions will be essential to develop the tools, research facilities, data integration and analysis, and products needed to achieve pre-determined objectives and milestones.

An integrated model for mucosal vaccine evidence generation



A less ambitious approach would be to establish one or more working groups that connect key stakeholders by facilitating scientific exchange or by actively identifying potential collaborative efforts. Continuous communication will be necessary to achieve alignment, and it is expected that the level and speed of progress under this approach may be less certain and less rapid.

An intermediate approach might be for a funder to support a task force dedicated to one or more of the key objectives from the recommendations identified in this report. Specific goals and objectives could be articulated with attention to longer-term and more integrated objectives. Multiple funders might be encouraged to work cooperatively across objectives, supported by an external coordination mechanism.

Any collaborative effort should be guided by previous experience, as the approach has been employed across many scientific disciplines, and several important consortia are already contributing to mucosal vaccine research and development. Among these are the Mucosal Immunity in Human Coronavirus Challenge (MusiCC), which focuses on mucosal immunity for coronaviruses; the Collaborative Clinical research program for Airway Immune Monitoring (CLAIM), which is working on mucosal sampling and immune analyses for influenza; and the US National Institute of Allergy and Infectious Diseases (NIAID), supported Mucosal Immunology Studies Team (MIST), which is advancing foundational understanding of immune defences and regulation at mucosal surfaces. These efforts are valuable models and potential collaborators, but are not on their own sufficient to address the scientific and systemic obstacles hindering progress in mucosal vaccinology.

5.2 Expand training and career incentives for mucosal immunology.

Only a small proportion of translational researchers and clinical investigators have experience in mucosal-specific research, particularly in LMICs. This is in part due to the lack of dedicated funding, limited recognition of mucosal expertise, and insufficient incentives to encourage early-career investigators to engage in this work. Factors inherent to this type of work, such as complicated mucosal sampling processes, require cross-disciplinary (clinical, laboratory, and sometimes social science) expertise and substantial time commitments that often conflict with clinical trial timelines. Furthermore, the current career development framework does not support high-cost, high-risk science.

Expand investment in training early-career scientists and provide structured incentives, such as fellowships, targeted research calls, young investigator prizes, and mentorship programs, to encourage new investigators into the field and to retain expertise over the long term.

Consortia and working groups have the potential to integrate training components into collaborative research activities, coordinate cross-disciplinary mentorship networks, and create targeted opportunities for early-career investigators. By embedding talent development into their core priorities, consortia could help reduce barriers to entry, promote skill-building in real-world contexts, and ensure the involvement of a new generation of scientists in mucosal vaccine development.

5.3 Provide additional funding within clinical trials to collect data on mucosal immunity.

Even when investigators acknowledge the importance of mucosal endpoints in clinical trials, these components are often deprioritised due to budget constraints or perceived misalignment with primary trial objectives. In large-scale studies, mucosal sampling is frequently excluded unless dedicated funding is provided. By offering additional funding for mucosal immunity sampling and research, donors can help address priority knowledge gaps and build specialised capacity and experience. Strategic funding can begin to normalise the inclusion of mucosal sampling and immunological assessment as standard elements of trial design, rather than optional add-ons.

> "Philanthropy can catalyse some of this, but if we really want to answer these questions, public sector investment is crucial."
>
> — KOL INTERVIEW

Conclusion

Advancing mucosal vaccinology offers an important avenue for expanding the impact of vaccines on global health. Despite compelling biological rationale, investment in mucosal vaccine development has been constrained by scientific uncertainty, siloed research efforts, and structural disincentives. Yet, foundational research combined with recent scientific advances, from immunology and systems biology to next-generation platforms and clinical trial design, has created new opportunities to better understand and harness mucosal immunity. This growing momentum is reflected in the enthusiasm and interest expressed by KOLs throughout this project.

The recommendations presented in this report are intended to complement and accelerate those efforts through a cohesive, cross-disciplinary framework. Central to this area is the need for a mechanism for collective action to align priorities, coordinate research and translate insights into tangible outcomes. The challenges to fully understanding mucosal immunity and to developing a new generation of mucosal vaccines are great, but these challenges can be overcome. With sustained investment, collaboration, and a shared commitment to innovation, the field is now well-positioned to realise the full potential of mucosal immunity and broaden protection, improve equity, and strengthen preparedness against both endemic and emerging infectious threats.

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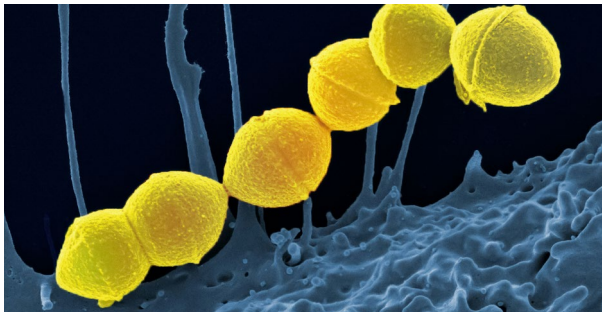
Appendix A

Pathogen profiles and pipelines

PATHOGEN

Group A streptococcus



Overview

Streptococcus pyogenes, or group A streptococcus (GAS), is a gram-positive bacterium that colonises the throat and skin and is responsible for a broad spectrum of disease. GAS causes over 600 million cases of pharyngitis annually; severe invasive manifestations include necrotising fasciitis, streptococcal toxic shock, and puerperal sepsis.[1] GAS can trigger serious post-infectious sequelae, including acute rheumatic fever (ARF) and rheumatic heart disease (RHD), resulting from autoimmune responses caused by infection.[2] Globally, GAS is estimated to cause over 500,000 deaths per year, primarily in LMICs.[1,3] There is no licensed vaccine, and the WHO has prioritised GAS as a target for accelerated R&D.[4] Vaccine development has been hindered by strain diversity, immune evasion, and the lack of defined immune correlates, particularly at mucosal surfaces.[5,6] It is worth noting that safety concerns in the 1960s led to a 30-year FDA ban on GAS vaccine testing in humans, which has had enormous implications for the field.[7]

Potential Role for Mucosal Immunity

GAS initially colonises the oropharynx, making it a prime target for mucosal vaccination. GAS colonisation can be transient or persistent, and while natural infection appears to confer age-related protection, the immunologic mechanisms, especially local antibody or T-cell responses, remain poorly defined.[6] Current vaccine candidates are administered intramuscularly and rely on systemic antibody responses. Induction of mucosal immune responses could improve colonisation control, reduce transmission, and target immune mechanisms that prevent progression to invasive disease or RHD,[3,8] which could translate into a significant reduction in global mortality and morbidity.[9]

Selection of the appropriate antigen(s) for a GAS vaccine is complicated due to the high strain variation in carbohydrate structure and protein sequence variation, as well as the induction of potential targeting of normal tissue. Current clinical candidates focus on the M protein with attempts to cover different levels of strain variability.[9,10]

A CHIM was recently established using a dose-escalation trial to determine the dose requirements for a pharyngitis attack rate of ≥ 60% in healthy adult volunteers.[11] The successful establishment of the model creates enormous opportunities for both vaccine development and the expansion of understanding of immune responses to GAS, including the identification of CoPs.[12,13]

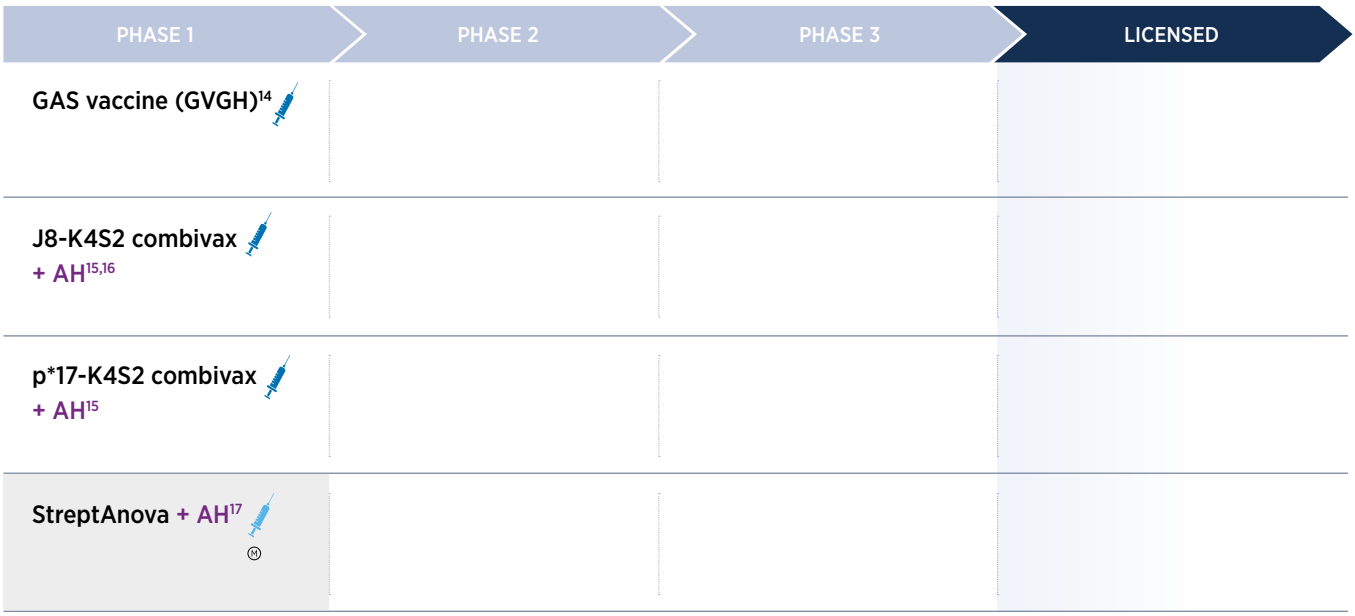
Pathogen Dashboard

Group A streptococcus

STRATEGIC INDICATORS	BARRIERS TO DEVELOPMENT				
NEED	KNOWLEDGE GAPS		VACCINE DEVELOPMENT LANDSCAPE		
	PATHOGEN TARGETS	MUCOSAL MECHANISMS & COPS	VACCINE PIPELINE	MUCOSAL VACCINE PIPELINE	CHIM AVAILABILITY
ANNUAL MORTALITY **517,000**	HIGH	HIGH	HIGH	HIGH	LOW
ANNUAL INCIDENT CASES **600,000,000**	Significant knowledge gaps of pathogen targets	Significant knowledge gaps of mucosal mechanisms and correlates of protection	Sparse vaccine pipeline	No mucosally delivered products in the pipeline	Established CHIM
DALYS **>100,000,000**					

Gaps in understanding / progress: High Fairly High Moderate Fairly Low Low

Vaccine Pipeline



Recommendations

Expand the toolkit

- **Develop and validate mucosal assays.** Invest in adapting high-throughput assays to analyse nasopharyngeal secretions. Tools such as multiplexed antibody detection and functional assays (e.g. IL-8 cleavage, hemolysis inhibition) are needed to characterise the immune mechanisms active at the point of GAS entry.[5,6]

Strengthen the evidence base

- **Leverage human challenge models to compare routes of administration.** Actively expand the use of CHIMs to explore dose-response dynamics, mucosal endpoints (e.g. sIgA, shedding, T-cell activation), and directly compare parenteral vs. mucosal delivery to optimise protection.

Continued on following page

Improve foundational understanding

- **Accelerate immune surveillance studies.** Utilise longitudinal studies that collect oropharyngeal samples, alongside infection and clinical outcome data, to clarify how local mucosal immunity develops with age and which immune markers predict resistance to GAS acquisition or progression.[6,8]
- **Design pediatric trials to explore naive immune responses.** Since peak disease burden is in children, who are immunologically naive to GAS, efficacy trials should focus on the reduction in pharyngitis or impetigo. This approach also offers unique opportunities to study the development of mucosal immunity. Careful planning will be required due to limited sample volumes and ethical constraints.[17,18]

Accelerate vaccine development

- **Advance mucosal formulations using conserved antigens.** Promote intranasal candidates based on conserved non-M protein antigens such as SpyCEP, Streptolysin O, and Group A Carbohydrate, as these immunogens avoid autoimmunity risks and may better engage mucosal immune responses.[8,18]
- **Expand antigen discovery using systems serology.** A systematic search for new mucosal targets, via reverse vaccinology, monoclonal antibody screening, and analysis of natural immune responses in children, may reveal key antigens missed by current candidates. This effort would benefit from well-characterised mucosal biobanks and multi-site collaboration.[3,6]
- **Define target product profiles.** Develop TPPs tailored for mucosal GAS vaccines, clearly articulating intended use (e.g. prevention of pharyngitis, RHD, and transmission), target populations, immunological endpoints, safety/tolerability expectations, and preferred delivery characteristics.

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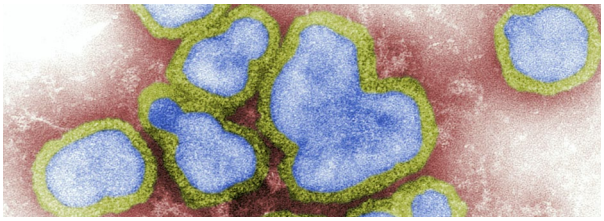
PATHOGEN

Influenza virus



Overview

Influenza viruses are segmented, negative-sense RNA viruses of the *Orthomyxoviridae* family that cause seasonal epidemics and pose an ongoing pandemic threat.[1] Influenza A and B are the primary types responsible for human disease, with each further classified into subtypes based on surface proteins; influenza A is the primary cause for large-scale epidemics. Annual influenza epidemics result in an estimated 1 billion cases, leading to ~3–5 million cases of severe illness and from 290,000–650,000 deaths.[2] Those at greatest risk of severe disease or complications when infected include children under 5 years of age, older people, individuals with chronic medical conditions and immunosuppression and pregnant women.

Transmission occurs predominantly via respiratory droplets and aerosols, initiating infection at the mucosal surfaces of the upper respiratory tract. Current intramuscular vaccines offer moderate protection that varies by age, prior exposure, and antigenic match. Frequent antigenic drift and occasional major shifts necessitate annual reformulation, making vaccine development challenging due to strain selection and resulting in sub-optimal vaccine effectiveness, particularly in older adults and young children.[3] Intranasal live attenuated influenza vaccines (LAIVs) directly stimulate the mucosal immune system but have limited global uptake. Additional mucosal vaccine platforms, including intranasal adjuvanted subunits and aerosolised mRNA, are being developed to improve early containment and cross-strain protection.[4,5] CHIM evaluation is possible, and thus improvements to enhance mucosal immunity are under consideration.[6]

Potential Role for Mucosal Immunity

Influenza virus entry and replication occur at the respiratory mucosa, and the local immune responses are important for early defence.[7] While systemic antibodies, particularly serum IgG, can prevent severe outcomes, there is evidence that mucosal immunity, including sIgA and TRM T cells, is present in the upper airway with natural infection, suggesting a potential role in reducing viral replication, disease severity, and transmission.[8] LAIV administered intranasally has demonstrated the ability to induce local immune responses within the upper respiratory tract and provide approximately equivalent protective efficacy to the inactivated influenza vaccine (IIV) despite lower systemic antibody titers, which supports the relevance of local responses.[9,10,11] However, mucosal correlates of protection for influenza vaccines, including LAIV, remain poorly defined.[12] With recent advances in systems immunology and airway sampling, influenza offers a prime opportunity to establish correlates of mucosal protection, examine imprinting by previous infection, compare delivery routes, and evaluate pandemic response strategies—including transmission blocking.[7,8]

Pathogen Dashboard

Influenza virus

STRATEGIC INDICATORS	BARRIERS TO DEVELOPMENT				
NEED	KNOWLEDGE GAPS		VACCINE DEVELOPMENT LANDSCAPE		
	PATHOGEN TARGETS	MUCOSAL MECHANISMS & COPS	VACCINE PIPELINE	MUCOSAL VACCINE PIPELINE	CHIM AVAILABILITY
ANNUAL MORTALITY **290,000 - 650,000**	MODERATE	MODERATE	LOW	LOW	LOW
ANNUAL INCIDENT CASES **1,000,000,000**	Some knowledge gaps of pathogen targets	Some knowledge gaps of mucosal mechanisms and correlates of protection	Very robust vaccine pipeline	Very robust pipeline of mucosally delivered products	Established CHIM
DALYS **16,700,000**					

Gaps in understanding / progress: High Fairly High Moderate Fairly Low Low

Vaccine Pipeline[13,14]

Parenteral Delivery

PHASE 1	PHASE 2	PHASE 3	LICENSED
Ad4-H5-VTN[15,16] Ⓜ	Chimeric HA constructs[14]	Gamfluvac[14]	GanWu[17] Ⓜ
BPL-1357[18,19]	deltaFLU[20-22]	OVX836[29-32] Ⓜ	Flumist/Fluenz Tetra[23,24] Ⓜ
Codavax[25-27]	M2SR[28] Ⓜ	Trivalent + LTh(αK)[26]	Nasovac-S[33,34] ✓ Ⓜ
delNS1-trivalent[36]	NasoVAX[25] Ⓜ		Ultravac[35]
rH5-NE[38]	VXA-A1.1 + TLR3[37] Ⓜ		

*Select mucosal candidates as of April 2025

Mucosal product or mucosal effect

DELIVERY ROUTE		VACCINE TYPE	
Parenteral	Purple text: Adjuvanted*	Subunit	DNA
Oral	✓ WHO-prequalified	Conjugate	RNA
Patch	⊘ Discontinued	Live-attenuated	Replicating viral vector
Intranasal	Ⓜ Mucosal immunity effect in humans indicated in the literature	Inactivated	Non-replicating viral vector
Aerosol	*Aluminium Hydroxide (AH) Aluminium Phosphate (AP) Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)	Not classified	

Recommendations

Expand the toolkit

- **Integrate systems immunology and airway analysis.** Apply -omics approaches to mucosal samples during vaccine trials. Benchmark vaccine-induced local immunity against natural infection signatures to improve understanding of protective mechanisms.[8]

Strengthen the evidence base

- **Conduct head-to-head trials comparing systemic vs mucosal delivery** and prime-boost strategies to measure differences in mucosal imprinting, local immunity, and protection against viral challenge to inform rational vaccine sequencing.
- **Evaluate LAIVs using modern immunologic tools** and consistent mucosal sampling. Consider co-administration with systemic vaccines to achieve dual-site immunity.

Improve foundational understanding

- **Leverage influenza as a model to test fundamental mucosal questions,** including imprinting, delivery route, efficacy, and correlates of transmission blocking, which may potentially apply to COVID-19 and future pandemic threats.

Accelerate vaccine development

- **Define mucosal correlates of protection.** Advance human challenge models and early-phase trials with standardised mucosal sampling to identify immune responses that predict, and distinguish, protection from infection and transmission reduction.
- **Test universal antigens in mucosal platforms.** Combine antigen and delivery innovation in CHIM experiments.[6]

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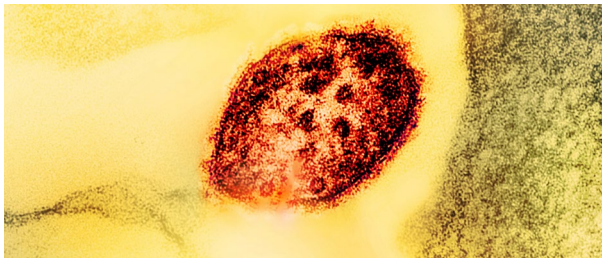
PATHOGEN

Measles virus



Overview

Measles, caused by the measles virus of the *Paramyxoviridae* family, is one of the most contagious diseases affecting humans. The measles virus is considered antigenically stable, with a single serotype and limited serotype variability.[1] Transmission occurs primarily via respiratory droplets and aerosols, and it infects nearly all unvaccinated individuals it contacts. Licensed live-attenuated MMR vaccines are extremely effective (>90%), yet in 2023, there were over 10 million cases and 107,500 deaths reported globally, mostly in children under the age of five years.[2]

Rising measles cases globally are largely due to declining vaccination rates; in 2023, an estimated 83% of children received the first dose of measles vaccine, well below the 95% needed to prevent outbreaks.[3] The burden is highest in low-resource settings, particularly where health systems face challenges in sustaining high routine immunisation coverage. However, vaccine hesitancy is also leading to rising rates in high-income countries. Measles can lead to pneumonia, encephalitis, blindness, ear infections, severe diarrhoea, and long-term immune suppression that increases vulnerability to other infections.[1]

Potential Role for Mucosal Immunity

The measles virus enters via the respiratory mucosa, initially replicating in myeloid cells before spreading systemically through lymphoid tissues.[4] Currently licensed live attenuated vaccines are highly effective and induce strong systemic immune responses and some detectable mucosal antibodies in oral/nasal fluids.[5] Despite its proven efficacy, the precise mechanisms by which the live-attenuated measles vaccine induces lifelong protection remain incompletely understood,[4] complicating the rational design of next-generation mucosal formulations. Challenges associated with existing vaccines include the requirement of a cold chain, contraindications for use in immunocompromised and pregnant individuals, and suppression of infant antibody response due to pre-existing maternal antibodies.[1] It has been proposed that respiratory delivery might improve coverage,[5] but there is little information on whether it would also offer improvements in vaccine durability or effectiveness against transmission. Aerosol delivery of measles vaccine has been reported,[5] and shown to be safe and immunogenic, although at a seroconversion rate slightly less than the systemically delivered vaccine.[6]

There are currently no novel molecular entities in the measles vaccine pipeline, reflecting the high, sustained efficacy of the licensed live-attenuated vaccine. Alternative routes of delivery, including intradermal, are under investigation to explore the potential benefits of vaccine-induced mucosal immunity. However, given the high level of safety and efficacy for existing vaccines, advances for measles vaccination would likely need to show very compelling data in a non-human system first.

Pathogen Dashboard

Measles virus

STRATEGIC INDICATORS	BARRIERS TO DEVELOPMENT				
NEED	KNOWLEDGE GAPS		VACCINE DEVELOPMENT LANDSCAPE		
	PATHOGEN TARGETS	MUCOSAL MECHANISMS & COPS	VACCINE PIPELINE	MUCOSAL VACCINE PIPELINE	CHIM AVAILABILITY
ANNUAL MORTALITY **107,500**	LOW	MODERATE	FAIRLY LOW	HIGH	HIGH
ANNUAL INCIDENT CASES **10,300,000**	Good understanding of pathogen targets	Some knowledge gaps of mucosal mechanisms and correlates of protection	Robust vaccine pipeline	No mucosally delivered products in the pipeline	No available CHIM
DALYS **4,880,000**					

Gaps in understanding / progress: High Fairly High Moderate Fairly Low Low

Vaccine Pipeline

PHASE 1	PHASE 2	PHASE 3	LICENSED
Vaxxas HD-MAP[7]	Micron MRV-MNP[8]		Mearubik[9]
	GSK4406371[10]		Measles + Rubella vaccine[11] (Minhai)
			Measles + Rubella vaccine (Takeda)
			M-M-R® II (M-M-RVAXPRO)[12,13]
			ProQuad®[14]
			MR-VAC[15,16] (M-VAC) ✓ Ⓜ
			PRIORIX-Tetra[17] ✓ Ⓜ
			PRIORIX® MMR[17] ✓ Ⓜ
			MRBEV[18] ✓ Ⓜ

Mucosal product or mucosal effect

DELIVERY ROUTE		VACCINE TYPE	
Parenteral	Purple text: Adjuvanted*	Subunit	DNA
Oral	✓ WHO-prequalified	Conjugate	RNA
Patch	⊘ Discontinued	Live-attenuated	Replicating viral vector
Intranasal	Ⓜ Mucosal immunity effect in humans indicated in the literature	Inactivated	Non-replicating viral vector
Aerosol		Not classified	

*Aluminium Hydroxide (AH)
Aluminium Phosphate (AP)
Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)

Recommendations

Expand the toolkit

- **Expand non-human primate (NHP) models for mucosal vaccine testing:** NHPs remain the most relevant species for evaluating mucosal immunity, including respiratory delivery targeting the lower respiratory tract (e.g. aerosol droplets).[19] Expanding access to and standardisation of NHP protocols, including nasal sampling, tissue-resident memory T cell (TRM) analysis, dose-ranging, and histopathology, may accelerate preclinical validation of mucosal candidates.[4]

Strengthen the evidence base

- **Utilise NHPs to evaluate potential mucosal advantages.** The existing measles vaccine is very effective and safe, and therefore next-generation vaccines need to show a very compelling advantage. To determine if mucosal responses provide such an advantage, it may be possible to assess this question in non-human primates.

Improve foundational understanding

- **Utilise NHPs to define mucosal responses.** The development of a measles vaccine that induces mucosal immunity likely requires an improved understanding of how mucosal responses can enhance effectiveness. This will probably emerge from NHP studies to define how measles-specific mucosal sIgA, TRM cells, and mucosal-draining lymph node responses influence protection and transmission.[4]

Accelerate vaccine development

- **Consider novel platforms and formulations.** Measles vaccine R&D is clearly complicated by the outstanding efficacy of existing vaccines, in that improvements may be difficult to demonstrate. As such, some KOLs have suggested measles is a sub-optimal model for studying mucosal immunity. Others suggest that novel vaccine platforms and formulations should be explored, including adjuvanted intranasal formulations[20] and needle-free delivery modalities (e.g. aerosol, microneedle patch), which may reduce cold-chain logistics and increase accessibility. However, their potential for mucosal immunity induction remains to be demonstrated.[21]

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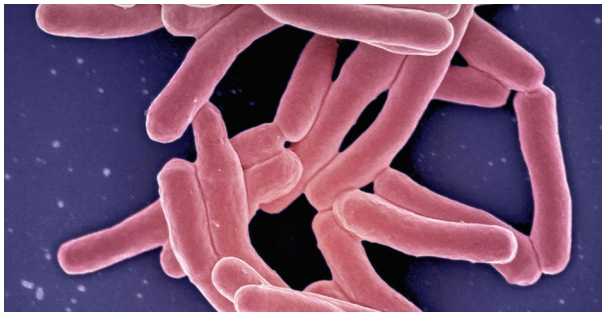
PATHOGEN

Mycobacterium tuberculosis



Overview

Tuberculosis, caused by *Mycobacterium tuberculosis (Mtb)*, is the world's leading cause of death from a single infectious agent, with an estimated 10.8 million new cases and 1.36 million deaths annually;[1] it is the leading cause of death for people with HIV.[1] Mtb is transmitted through inhalation of airborne particles, typically infecting the lung mucosa. An estimated 25% of the global population harbours latent infection, and 5-10% of people infected with Mtb eventually become symptomatic and develop disease.[2] While multi-drug regimens are curative in most cases, many people in LMICs go undiagnosed and untreated and drug-resistant strains are a growing problem. The only licensed vaccine, BCG, offers protection against severe childhood TB but fails to prevent adult and adolescent pulmonary disease consistently. Effective vaccines for adults and adolescents are urgently needed; however, designing and conducting clinical trials is challenging.[3]

Potential Role for Mucosal Immunity

As a respiratory pathogen, Mtb initiates infection at the mucosal surfaces of the lungs, where it is adept at evading and suppressing human immune responses. Mtb's slow growth and varied disease states (infection, latency, active disease) make defining protective immunity and well-defined CoPs challenging.[4] Mucosal immune responses are likely to play a role in early containment, and current research focuses on IFN-γ-producing CD4⁺ T cells, mucosal-resident memory T cells, and antibody responses. However, relative contributions to protection and disease progression are not well understood, as well as the roles of dendritic cells, Mucosal-Associated Invariant T (MAIT) cells, cytokine responses and trained innate immunity.[5–7] Animal models offer insights but often fail to predict vaccine efficacy in humans, underscoring the need for more reliable translational tools.

There are currently 16 prophylactic vaccine candidates in development, with eight in active clinical trials and a limited number of products in in early-stage and pre-clinical development.[8] Mucosal delivery strategies, such as intranasal or aerosol administration, may offer promise for enhancing localised immunity in the lung towards preferred indications (e.g., prevention of infection, disease and recurrence).[6,9] Two candidates are exploring aerosol delivery, while one Phase 2 candidate is evaluating intranasal administration. Additionally, CHIMs using aerosolised BCG or double knock-out MTB[10] as challenge agents are under development and may provide valuable tools for accelerating vaccine evaluation.[4]

Pathogen Dashboard

Mycobacterium tuberculosis

STRATEGIC INDICATORS	BARRIERS TO DEVELOPMENT				
NEED	KNOWLEDGE GAPS		VACCINE DEVELOPMENT LANDSCAPE		
	PATHOGEN TARGETS	MUCOSAL MECHANISMS & COPS	VACCINE PIPELINE	MUCOSAL VACCINE PIPELINE	CHIM AVAILABILITY
ANNUAL MORTALITY **1,360,500**	MODERATE	HIGH	FAIRLY LOW	MODERATE	MODERATE
ANNUAL INCIDENT CASES **10,800,000**	Some knowledge gaps of pathogen targets	Significant knowledge gaps of mucosal mechanisms and correlates of protection	Robust vaccine pipeline	Moderate pipeline of mucosally delivered products	BCG CHIM / KO MTB in development
DALYS **47,000,000**					

Gaps in understanding / progress: High Fairly High Moderate Fairly Low Low

Vaccine Pipeline[8]

PHASE 1	PHASE 2	PHASE 3	LICENSED
H107e + CAF10b[11]	DAR 901[8]	BCG vaccine (travel)[12]	BCG[13–15] ✓ Ⓜ
AdHu5Ag85A[16]	ID93 + GLA-SE[17,18]	MIP (ImmunoVac)[19]	
	ChAdOx1 85A / MVA85A[20,21] Ⓜ	MTBVAC[22–25]	
	AEC + BC02[26]	VPM1002[27,28]	
	TB/FLU-05E[29–31]	M72 + AS01E[32-35]	
	BNT 164a1[36-37]	GamTBvac + CPG 0DN[33]	
	BNT 164b1[36,37]	GC3107A[22,23]	

Mucosal product or mucosal effect

DELIVERY ROUTE

- Parenteral
- Oral
- Patch
- Intranasal
- Aerosol

- Purple text: Adjuvanted*
- ✓ WHO-prequalified
- Discontinued
- Ⓜ Mucosal immunity effect in humans indicated in the literature

*Aluminium Hydroxide (AH)
Aluminium Phosphate (AP)
Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)

VACCINE TYPE

- Subunit
- Conjugate
- Live-attenuated
- Inactivated
- Not classified
- DNA
- RNA
- Replicating viral vector
- Non-replicating viral vector

Recommendations

Expand the toolkit

- **Apply systems immunology and AI.** Use -omics technologies and machine learning to decode the molecular architecture of protective responses and identify novel mucosal biomarkers.
- **Harmonise trial endpoints and assays.** Establish standards for mucosal sampling, immune readouts, and trial endpoints to enable comparability across TB vaccine studies.
- **Expand available samples.** Leverage upcoming Phase 2 trials and ongoing efficacy studies to capture mucosal samples. Consider expanding studies to include human bronchoalveolar lavage, mucosal biopsies, and lung organoid models.

Strengthen the evidence base

- **Expand experimental medicine studies.** Use early-phase studies to map systemic and mucosal immune responses, including less accessible compartments (e.g., lower respiratory tract) and accelerate the timeline to answers.
- **Leverage and evolve challenge models.** Maximise insights from existing human TB challenge models while developing next-generation platforms to evaluate mucosal vaccine efficacy more directly.[6]

Improve foundational understanding

- **Define correlates of protection.** Pair imaging with localised sampling to identify potential systemic and mucosal (lung) immune markers predictive of protection, considering the differences in protection across disease states (e.g., primary infection, persistent latent infection, reactivation, etc.).

Accelerate vaccine development

Prioritise research of promising vaccine strategies, including:

- ***Prime-Pull strategies:*** Combining systemic priming with mucosal boosting to maximise immune breadth and lung-localised responses (e.g. BCG or DNA priming with an intranasal viral vector or protein/adjuvant boost);
- ***Mucosal delivery:*** Mucosal delivery (intranasal/oral/pulmonary) to elicit mucosal antibody responses and/or lung-localised T cells and tissue-resident memory and novel adjuvants;
- ***Antigens:*** Multi-stage TB vaccines combining antigens (from various stages of Mtb infection) to potentially induce broad protection and memory formation; pathogen surface antigenic components may be of particular interest for the first encounter at mucosal surfaces;
- ***Vaccine platforms:*** Viral vectors and live attenuated vaccines with mucosal tropism and lung antigen expression.

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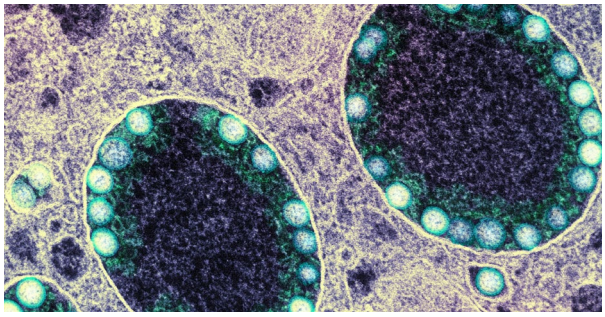
PATHOGEN

SARS-CoV-2 (COVID-19)



Overview

SARS-CoV-2, a novel coronavirus first described in 2019, is the causative agent of COVID-19. It is an enveloped, positive-sense RNA virus that primarily targets the respiratory tract. Transmission occurs through respiratory droplets, aerosols, and contact with contaminated surfaces.[1] While the official death toll stands at 7 million deaths globally,[2] excess mortality figures suggest that the true impact of the epidemic is much higher.[3] The COVID-19 pandemic catalysed the fastest vaccine development in history. Multiple systemic vaccine platforms, including mRNA, adenoviral vectors, and protein subunits, have been deployed globally, providing robust protection against severe disease, hospitalisation, and death. However, protection against infection and transmission has been incomplete and short-lived, particularly with the emergence of immune-evasive variants, which have reduced the efficacy of existing systemic vaccines.

Potential Role for Mucosal Immunity

SARS-CoV-2 primarily enters through the upper respiratory tract, where mucosal defences can potentially contain viral replication and prevent aerosolised spread.[4,5] Data suggest that sIgA is associated with reduced viral load, faster clearance, and enhanced protection.[6,7] While current vaccines elicit strong systemic immunity, including neutralising antibodies and T-cell responses, they generate limited mucosal responses, particularly sIgA at the site of viral entry.[5] Individuals with primary IgA deficiencies have shown more severe outcomes to natural infection and reduced mucosal vaccine responses,[8,9] further supporting the protective role of mucosal immunity. Five active mucosal vaccines have been approved for human use. iNCOVACC/BBV154 has been shown to induce higher serum IgA titres and equivalent T cell memory responses compared to IM (Covaxin).[10]

Additional intranasal and oral vaccine candidates are in development, but standardised sampling, validated mucosal assays, and well-defined correlates of protection remain significant barriers to evaluating and advancing these approaches. Because COVID-19 is a well-characterised, high-incidence disease with rapid diagnostic tools and immunological assays, it serves as a valuable model to address broader mucosal vaccine questions around delivery route, immune imprinting, durability, and transmission-blocking potential.[11,12]

Pathogen Dashboard

SARS-CoV-2 (COVID-19)

STRATEGIC INDICATORS	BARRIERS TO DEVELOPMENT				
NEED	KNOWLEDGE GAPS		VACCINE DEVELOPMENT LANDSCAPE		
	PATHOGEN TARGETS	MUCOSAL MECHANISMS & COPS	VACCINE PIPELINE	MUCOSAL VACCINE PIPELINE	CHIM AVAILABILITY
ANNUAL MORTALITY* **7,890,000**	LOW	MODERATE	LOW	LOW	LOW
ANNUAL INCIDENT CASES **2,280,000,000**	Good understanding of pathogen targets	Some knowledge gaps of mucosal mechanisms and correlates of protection	Very robust vaccine pipeline	Robust pipeline of mucosally delivered products	Established CHIM
DALYS **212,000,000**					

Gaps in understanding / progress: High Fairly High Moderate Fairly Low Low

*The impact of the COVID-19 pandemic has declined substantially from its peak. Weekly case reports peaked at >40M in 2023 and now stand at <16K. Weekly deaths peaked at over 100,000 in 2021, dropping to just 210 in August 2025.[13]

Vaccine Pipeline[4,14]

Parenteral Delivery

PHASE 1	PHASE 2	PHASE 3	LICENSED
ACM-001[15]	CIGB-669[16]	CoviLiv[21] Ⓜ	Ad5-nCoV-IH[17] (Convidecia Air)
ChAdOx1/AZD1222[18]	CVAX-01[19,20]	DelNS1-2019-nCoV-RBD-OPT[26]	BBV154 (INCOVACC)[10,22–24] Ⓜ
CVXGA1/PIV5 -SARS-CoV-2[25] Ⓜ			RAZI-COV PARS[28]
hAd5-S-Fusion + N-ETSD[27]			Sputnik V/Gam-COVIDVac[30]
MV-014-212[29]			dNS1-RBD (Pneucolin®)[35]
SC-Ad6-1[31]			

*Select mucosal candidates as of April 2025

Mucosal product or mucosal effect

DELIVERY ROUTE

- Parenteral
- Oral
- Patch
- Intranasal
- Aerosol

Purple text Adjuvanted*
✔ WHO-prequalified
Discontinued
Ⓜ Mucosal immunity effect in humans indicated in the literature

*Aluminium Hydroxide (AH)
Aluminium Phosphate (AP)
Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)

VACCINE TYPE

- Subunit
- Conjugate
- Live-attenuated
- Inactivated
- Not classified
- DNA
- RNA
- Replicating viral vector
- Non-replicating viral vector

Recommendations

Expand the toolkit

- **Leverage ongoing product development and clinical testing** to develop mucosal immunity sampling, endpoints and methods. COVID-19 offers an opportunity to move towards consensus on sampling and assay methodologies and to test under-utilised and emerging technologies to interrogate mucosal immune parameters in greater depth.

Strengthen the evidence base

- **Define clear mucosal immunity objectives.** Invest in identifying specific mucosal immune correlates, such as nasal IgA, mucosal homing markers, and TRMs, to complement systemic readouts. Reliance on serum-based endpoints underrepresents local protection and may mischaracterise vaccine performance.[32]
- **Leverage CHIMs to de-risk next-gen vaccines.** Use CHIMs to obtain early mucosal and efficacy readouts for new platforms, enabling head-to-head comparisons and supporting rapid progression into broader field testing.

Improve foundational understanding

- **Use COVID-19 vaccines to answer broader mucosal questions.** Capitalise on the COVID-19 platform to explore foundational mucosal vaccine science: imprinting, delivery route, immunity type, durability, and transmission-blocking. Side-by-side comparisons with influenza can offer cross-pathogen insight.[11]
- **Characterise antibody transudation kinetics to the mucosa.** Launch PK studies tracking how and when systemic antibodies appear in the nasal mucosa.
- **Optimise delivery routes and prime-boost combinations.** Systematic evaluation of delivery modalities, including aerosol, intranasal, and heterologous prime-boost regimens, can reveal how route shapes immune quality, localisation, and imprinting.[33]

Accelerate vaccine development

- **Use sieving data to inform rational vaccine design.** Integrate emerging insights on virus sequence variation and antibody specificity from clinical trials to design vaccines that have broader protective efficacy by inducing both humoral and cellular immunity at the site of viral entry.[34]

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PATHOGEN

Streptococcus pneumoniae

Overview

Streptococcus pneumoniae is a gram-positive encapsulated bacterium with over 90 serotypes; a subset of which (1, 4, 5, 7F, 8, 12F, 14, 18C, and 19)[1] accounts for most invasive disease. Clinical manifestations of *S. pneumoniae* range from asymptomatic colonisation to milder diseases (e.g., otitis media, sinusitis) to invasive disease (e.g., meningitis, endocarditis, pneumonia, sepsis).[2] *S. pneumoniae* contributes to over 500,000 deaths annually (2021) with a particularly heavy burden in children under five in LMICs.[3] Antibiotic resistance is a growing problem, and WHO includes *S. pneumonia* as a priority pathogen for prevention and control of AMR.[4]

Current vaccines, primarily pneumococcal conjugate vaccines (PCVs), have significantly reduced disease burden but are limited by serotype coverage and reduced efficacy against mucosal carriage and non-invasive disease in LMICs.[5,6] Further, serotype replacement has led to an increase in disease associated with non-vaccine serotypes;[7] expanded valency vaccines face cost and delivery barriers.[8]

Potential Role for Mucosal Immunity

Transmission of *S. pneumoniae* occurs via respiratory droplets, with nasopharyngeal colonisation being a prerequisite for both transmission and invasive disease.[1] While serum IgG to surface carbohydrate antigens has long been used as a correlate of protection, there is limited information that it correlates directly to preventing disease or infection. There is some evidence that anti-protein and TH17 CD4 cells in the mucosa may have an impact on carriage.[5] The development of next-generation vaccines that target conserved pneumococcal proteins and elicit stronger mucosal responses could address current limitations, particularly in the context of high serotype diversity and the need for broader, more durable protection. An established CHIM is available and has been transferred for use in Malawi, providing a potentially valuable platform to understand host-pathogen interactions and evaluate vaccine-induced immune responses in low-resource settings.[9]

Pathogen Dashboard

Streptococcus pneumoniae

STRATEGIC INDICATORS	BARRIERS TO DEVELOPMENT				
NEED	KNOWLEDGE GAPS		VACCINE DEVELOPMENT LANDSCAPE		
	PATHOGEN TARGETS	MUCOSAL MECHANISMS & COPS	VACCINE PIPELINE	MUCOSAL VACCINE PIPELINE	CHIM AVAILABILITY
ANNUAL MORTALITY **505,000**	LOW	MODERATE	FAIRLY LOW	HIGH	LOW
ANNUAL INCIDENT CASES **97,500,000**	Good understanding of pathogen targets	Some knowledge gaps of mucosal mechanisms and correlates of protection	Robust vaccine pipeline	No mucosally delivered products in the pipeline	Established CHIM
DALYS **38,100,000**					

Gaps in understanding / progress: High Fairly High Moderate Fairly Low Low

Vaccine Pipeline

PHASE 1	PHASE 2	PHASE 3	LICENSED[14-24]
MVX 01[25]	AFX 3772/ Pn-MAPS24v*[26-30]	PPSV-23[31] (BLB)	Synflorix (PCV-10) ✓
PBPV[13,32]	AV0328[33]	PCV-13[34,35]	Pneumosil (PCV-10) + AP ✓
V 117[36]	Gamma-PN[37,38]	PPSV 23[39] (Aimei)	Prevnar 13 + AP ✓
	GSK2830929A[40,41]	GBP410 / SP0202[42]	WEUPHORIA (PCV-13) + AP
	IVT 25 + AP[43]		VAXNEUVANCE PCV 15 + AP
	PF-07872412[36]		Prevnar 20 + AP
	VAX 24[42,44]		PPSV23 (Walvax)
	VAX 31[45,46]		PPSV23 (Sinovac)
			Chengdu PPSV23
			Pneumovax 23

Mucosal product or mucosal effect

DELIVERY ROUTE

- Parenteral
- Oral
- Patch
- Intranasal
- Aerosol

Purple text: Adjuvanted*
✓ WHO-prequalified
⊘ Discontinued
Ⓜ Mucosal immunity effect in humans indicated in the literature

*Aluminium Hydroxide (AH)
Aluminium Phosphate (AP)
Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)

VACCINE TYPE

- Subunit
- Conjugate
- Live-attenuated
- Inactivated
- Not classified
- DNA
- RNA
- Replicating viral vector
- Non-replicating viral vector

Recommendations

Expand the toolkit

- **Apply genomics to antigen discovery.** Use machine learning and global genomic surveillance to identify novel adhesins and conserved surface antigens expressed during colonisation. Such targets can inform next-generation mucosal formulations that address serotype replacement and regional variation.[8]
- **Enhance functional assays.** Functional opsonophagocytic assays (OPA) and mucosal IgA may both be needed to assess mucosal vaccine efficacy. Regulators should provide clarity on acceptable endpoints for licensure of non-conjugate and mucosally delivered vaccines.[5,12]

Strengthen the evidence base

- **Pair ultra-valent PCVs with mucosal boosters.** 24- and 30-valent PCVs in late-stage development could be paired with mucosal vaccines to enhance local immunity while covering most invasive serotypes. This layered approach may overcome the limits of either strategy alone.[5,10] Experimental medicine studies comparing intramuscular and mucosal vaccination routes could inform platform optimisation.[8,11]

Improve foundational understanding

- **Define correlates of protection.** Develop a unified toolkit for mucosal immune evaluation, including multiplex assays for secretory IgA, qPCR for carriage load, and single-cell RNA-seq of nasal swabs. Correlates should be validated across age groups and linked to reduction in colonisation and transmission.

Accelerate vaccine development

- **Advance intranasal platforms using conserved antigens.** Prioritise development of nasal vaccines based on conserved proteins (e.g. PspA, PhtD, pneumolysin) or whole-cell/killed-cell formulations. These have shown broad, serotype-agnostic protection in preclinical and early human data.[13]
- **Define Target Product Profiles (TPPs):** Articulate use cases for mucosal pneumococcal vaccines—e.g. prevention of colonisation, transmission, or invasive disease—alongside target populations (e.g. young children, older adults). In particular, it will be important to articulate how and why next-generation vaccines will be tested and deployed in the context of existing approved vaccines.

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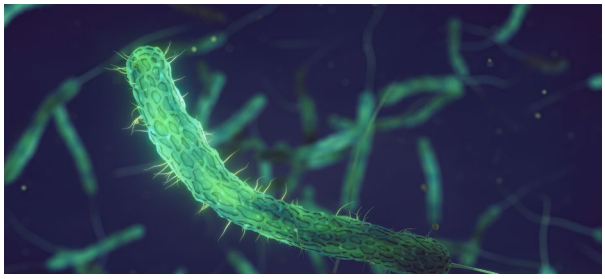
PATHOGEN

Vibrio cholerae (Cholera)



Overview

Cholera is an acute diarrheal infection caused by *Vibrio cholerae*, a gram-negative bacterium spread by consuming contaminated food or water, frequently linked to poor sanitation and limited access to safe drinking water. *V. cholerae* is classified by the structure of the lipopolysaccharide O-antigen. There are more than 200 serogroups, of which only O1 and O139 have been known to cause epidemics due to their ability to produce cholera toxin (CT).[1,2] There have been seven cholera pandemics since 1817, all caused by subtype O1. The current pandemic began in 1961 and has expanded to all inhabited continents.[1] O139 emerged in the 1990s in South Asia, and by 2015, it had largely disappeared; it is the only non-O1 strain known to cause large-scale epidemics.[3]

Cholera continues to pose a significant public health challenge, particularly in Asia and sub-Saharan Africa, with an estimated 1.3–4 million cases and ~86,500 deaths annually; it is one of the few bacterial diseases capable of pandemic spread.[4,5] Outbreaks are exacerbated by climate change and extreme climate events, along with a lack of investment in water, sanitation and hygiene infrastructure. Emerging multidrug resistance complicates treatments and prolongs outbreaks, enhancing the need for vaccines and environmental control.[6,7] Orally dosed killed whole-cell vaccines in adults can be up to 80% effective at preventing moderate to severe disease at 3 months post-vaccination, though protection wanes rapidly. Current vaccines are less effective in children under 5 years of age and in endemic settings, require multiple doses, and have limited durability.[1,8]

Potential Role for Mucosal Immunity

Cholera's pathogenesis involves intestinal colonisation and production of CT, the primary virulence factor in disease, with secretory IgA and TRM B and T cells responses believed to play key roles in protection.[8,9] Protection appears to be mediated by functional antibodies that target the O-polysaccharide-coated V. cholerae outer membrane.[10] Vibriocidal antibody titers are often used as a correlate of protection, but they are poor predictors of long-term immunity, particularly at the mucosal level.[1,10] Oral vaccines induce mucosal immunity and protection partly via sIgA (intestinal); however, there are limitations and knowledge gaps regarding the quality, breadth, consistency, and durability of these responses. Challenges include degradation in the stomach, lack of adjuvants, and release at mucosal immune inductive sites.[1,9] CHIMs are available to evaluate candidate vaccines; notably, Vaxchora was the first US-licensed vaccine which used CHIM data as the primary evidence supporting effectiveness.[11]

Pathogen Dashboard

Vibrio cholerae

STRATEGIC INDICATORS	BARRIERS TO DEVELOPMENT				
GLOBAL HEALTH BURDEN	KNOWLEDGE GAPS		VACCINE DEVELOPMENT LANDSCAPE		
	PATHOGEN TARGETS	MUCOSAL MECHANISMS & COPS	VACCINE PIPELINE	MUCOSAL VACCINE PIPELINE	CHIM AVAILABILITY
ANNUAL MORTALITY **86,500**	LOW	MODERATE	MODERATE	LOW	LOW
ANNUAL INCIDENT CASES **~2,500,000**	Good understanding of pathogen targets	Some knowledge gaps of mucosal mechanisms and correlates of protection	Moderate vaccine pipeline	Very robust pipeline of mucosally delivered products	Established CHIM
DALYS **4,500,000**					

Gaps in understanding / progress: High Fairly High Moderate Fairly Low Low

Vaccine Pipeline

PHASE 1	PHASE 2	PHASE 3	LICENSED[8,10–26]
OSP:rTTHc + Alum[11–13]			Hillchol / BBV131[9,14–19]
DuoChol + rCTB[20]			CVD 103-HgR (VaxChora)[9,21–23]
PanChol[24]			Dukoral[18,19,25–30]
MucoRice-CTB 19A[31]			Euvichol-S[9]
CV 638[32]			Euvichol-Plus[9,22,33]
			OraVacs[9]
			Cholvax[35]

Mucosal product or mucosal effect noted in the literature

DELIVERY ROUTE		VACCINE TYPE	
Parenteral	Purple text: Adjuvanted*	Subunit	DNA
Oral	✓ WHO-prequalified	Conjugate	RNA
Patch	⊘ Discontinued	Live-attenuated	Replicating viral vector
Intranasal	Ⓜ Mucosal immunity effect in humans indicated in the literature	Inactivated	Non-replicating viral vector
Aerosol		Not classified	

*Aluminium Hydroxide (AH)
Aluminium Phosphate (AP)
Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)

Recommendations

Expand the toolkit

- **Comprehensively evaluate mucosal immunity in vaccine development.** Develop harmonised assays and panels for key cellular and molecular markers, including sIgA in faeces and saliva, antigen-specific memory B cells and antibody-secreting cells, homing markers (α4β7, CCR9/CCR10) on memory B cells, mucosal-associated invariant T cells, mucosal innate immune cells and neutralising assays using mucosal secretions to complement serum vibriocidal antibody titers (VAT).

Strengthen the evidence base

- **Expand CHIM and outbreak studies to map mucosal immunity and test innovation.** Use CHIMs and outbreak-response studies to compare vaccine platforms, evaluate mucosal protection, and test correlates beyond serum VAT to accelerate Phase 2/3 readiness and real-world deployment strategies.

Improve foundational understanding

- **Apply systems immunology to compare vaccine and natural immunity across settings.** Use transcriptomics, proteomics, and multi-omics tools to compare vaccine-induced and natural mucosal immunity, especially across endemic and non-endemic populations. This approach can reveal key pathways linked to durable protection and help benchmark next-gen platforms.

Accelerate vaccine development

- **Extend duration of protection through novel mucosal strategies.** Advance oral vaccine platforms that improve gut retention and sIgA durability via microencapsulation, adjuvants, or modified delivery. Investigate formulation features that enhance mucosal memory B and T cell recruitment, especially in young children. Explore thermostable and targeted delivery systems to improve antigen survival and uptake in Peyer's patches/M cells and enhance sIgA induction.
- **Evaluate priming and boosting to enhance gut imprinting.** Assess hybrid regimens (e.g., systemic priming followed by oral or intranasal boosting) to enhance gut imprinting and tissue-resident mucosal memory. Determine optimal timing and combinations to shape both mucosal and systemic compartments.
- **Accelerate development of next-generation platforms.** Support next-gen candidates that induce both toxin-neutralising and colonisation-inhibiting immunity; prioritise platforms with the potential for single-dose protection and broader serovar coverage.
- **Improve performance in young children via microbiome and gut health interventions.** Investigate how microbiota composition, gut inflammation, and environmental enteropathy affect vaccine efficacy. Pair oral vaccines with nutritional or microbiome-based interventions to improve mucosal architecture and immune response in children under five.

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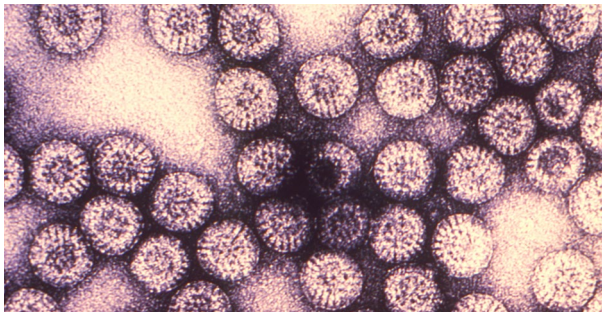
PATHOGEN

Rotavirus



Overview

Rotaviruses are non-enveloped double-stranded RNA viruses belonging to the *Sedoreoviridae* family. Rotavirus is the leading cause of diarrheal disease and deaths across all ages, especially in children under five, where it is responsible for ~176,000 deaths annually, predominantly in LMICs.[1] The virus infects the small intestine via the faecal-oral route, causing diarrhea and dehydration. Nine distinct rotavirus groups have been identified serologically based on common group antigens, with Group A representing more than 95% of isolated strains in humans. Two rotavirus surface proteins, VP4 and VP7 are targets for neutralizing antibodies and are important for protection.[2]

The WHO recommends that rotavirus vaccines be included in all national immunization programs and four orally dosed live-attenuated vaccines have received WHO prequalification. While oral vaccines have dramatically reduced disease burden, efficacy of licensed vaccines varies between countries, with a 23–47% relative difference in effectiveness between countries with low and high child mortality.[3] This disparity is attributed to numerous factors, including genetic heterogeneity, intestinal microbiome/virome composition, environmental enteric dysfunction, maternal antibody interference, interference from other oral vaccines, nutritional deficiencies, and co-infections.[4]

Potential Role for Mucosal Immunity

Protection from rotavirus is believed to be mediated by local gut IgA, serum IgG, and cellular immunity. Natural infection provides partial protection that improves with repeated exposures.[5] Secretory and faecal IgA are necessary for the clearance of rotavirus infection from the intestine and protection from re-infection, and serum IgG helps in systemic viral clearance.[6] Post-vaccination anti-rotavirus IgA is considered thus far the best correlate of protection.[7,8] Further, seroconversion, defined as a ≥4-fold rise in serum IgA, provides an informative threshold for assessing rotavirus vaccine performance.[9] However, environmental and host factors, particularly in LMICs, significantly reduce vaccine virus replication and the resultant IgA response and can influence immune responses and vaccine performance.[10]

Next generation rotavirus vaccines have focused on either enhancing mucosal immunity or utilizing systemic responses to elude known barriers.[11] Direct measurements of mucosal immune responses, such as faecal IgA, stool virus shedding, and gut-homing lymphocytes, are infrequently incorporated into clinical trials, limiting understanding of how oral vaccines work at the site of infection.

Pathogen Dashboard

Rotavirus

STRATEGIC INDICATORS	BARRIERS TO DEVELOPMENT				
NEED	KNOWLEDGE GAPS		VACCINE DEVELOPMENT LANDSCAPE		
	PATHOGEN TARGETS	MUCOSAL MECHANISMS & COPS	VACCINE PIPELINE	MUCOSAL VACCINE PIPELINE	CHIM AVAILABILITY
ANNUAL MORTALITY **176,000**	LOW	MODERATE	FAIRLY LOW	LOW	MODERATE
ANNUAL INCIDENT CASES **>250,000,000**	Good understanding of pathogen targets	Some knowledge gaps of mucosal mechanisms and correlates of protection	Robust vaccine pipeline	Very robust pipeline of mucosally delivered products	CHIM proxy*
DALYS **13,400,000**					

*Pseudo-challenge studies available using live oral vaccines

Gaps in understanding / progress: High Fairly High Moderate Fairly Low Low

Vaccine Pipeline

PHASE 1	PHASE 2	PHASE 3	LICENSED
Live Reassortant Hexavalent[12]	MAXVAX[13]	RV3 BB[14,15]	ROTARIX[16] ✓ Ⓜ
Inactivated (BZL)[17]	HSRV[7,18] Ⓜ	UK-BRV Hexavalent[19]	Rota Teq[20] ✓ Ⓜ
CDC-9[21]	IMBCAMS + AH[22]	LLR-3[23]	ROTAVAC[24] ✓ Ⓜ
			ROTASIL[6,25-27] ✓ Ⓜ
			LLR (China)[28] Ⓜ
			Rotavin-M1 (Vietnam)[29] Ⓜ

Mucosal product or mucosal effect

DELIVERY ROUTE		VACCINE TYPE	
Parenteral	Purple text: Adjuvanted*	Subunit	DNA
Oral	✓ WHO-prequalified	Conjugate	RNA
Patch	⊘ Discontinued	Live-attenuated	Replicating viral vector
Intranasal	Ⓜ Mucosal immunity effect in humans indicated in the literature	Inactivated	Non-replicating viral vector
Aerosol		Not classified	

*Aluminium Hydroxide (AH)
Aluminium Phosphate (AP)
Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)

Recommendations

Expand the toolkit

- **Expand measurement methods.** Develop validated methods to measure faecal IgA, neutralizing activity in stool, and gut-homing lymphocytes. Incorporate these assays into Phase II/III trials, across diverse geographic settings, to enable cross-site comparisons of mucosal vaccine performance.
- **Apply systems immunology.** Apply systems-level, including transcriptomic and proteomic, profiling to next-generation live-attenuated and/or parenteral rotavirus vaccine candidates in both preclinical and CHIM studies to understand immune mechanisms in protected vs under-protected individuals.

Strengthen the evidence base

- **Leverage CHIMs.** Use CHIMs with homologous re-challenge and faecal shedding endpoints to evaluate immune correlates, vaccine impact, and protective thresholds at mucosal sites.

Improve foundational understanding

- **Define immune trajectories.** Conduct longitudinal cohort studies and CHIM studies to define the immune trajectories following natural infection and identify mucosal and systemic markers predictive of durable protection or progression to severe disease.
- **Clarify breast milk antibody effects.** Clarify the mechanisms by which breast milk-derived antibodies affect vaccine virus replication and mucosal priming. Explore mitigation strategies that preserve nutritional benefits while enhancing vaccine take.

Accelerate vaccine development

- **Evaluate prime-boost strategies.** Explore oral vaccine priming with a systemic vaccine boost strategy to enhance both mucosal and systemic immunity.
- **Test complementary interventions.** Test microbiota-directed strategies (e.g. synbiotics, postbiotics), immune modulators (e.g. vitamin A, zinc, anti-inflammatory agents), and new mucosal adjuvants to improve replication, immunogenicity, and efficacy of live oral vaccines in EED-prone populations.

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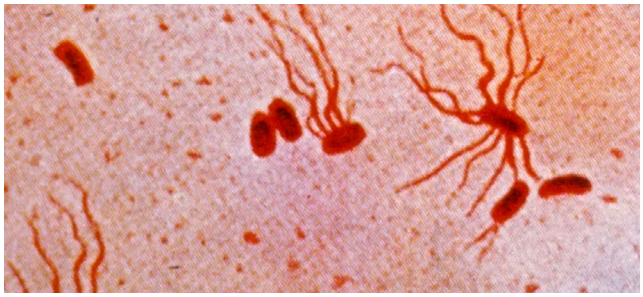
PATHOGEN

Typhoidal Salmonella



Overview

Salmonella enterica is a gram-negative bacterium consisting of over 2,500 serovars, classified into typhoid and nontyphoid (NTS) groups based on the distinct diseases they cause in humans. Typhoidal serovars, *Salmonella* Typhi and *Salmonella* Paratyphi, cause typhoid (or enteric) fever with clinical presentation ranging from mild to severe life-threatening systemic illness. Typhoidal *Salmonella* causes more than 9.3 million cases of typhoid fever and ~107,000 deaths annually.[1] It is widespread in South Asia and sub-Saharan Africa, and children under 5 years are particularly vulnerable.[2] Transmission occurs primarily through contaminated food and water in low-resource settings. Chronic carriage of typhoidal *Salmonella* may contribute up to 10 times more to transmission compared to acute cases.[3] The rise of extensively drug-resistant strains, especially in South Asia, has intensified the urgency for better prevention tools.[4]

Until recently, live attenuated oral and subunit vaccines have provided important but suboptimal protection, with limitations in efficacy, duration, and use in children under the age of two.[5] In 2020, the licensure of parenteral typhoid conjugate vaccines (TCVs) addressed many of the shortcomings of earlier vaccines. A Phase 3 trial in Malawi with Typbar TCV provided 78% efficacy in children 9 months to 12 years for at least four years.[6] However, *S.* Paratyphi causes an estimated 20% of all enteric fever cases, and there are still no licensed vaccines for *S.* Paratyphi serovars, leaving a substantial portion of the disease burden unaddressed (though there may be some cross-protection with *S.* Typhi vaccines).[7]

Potential Role for Mucosal Immunity

Infection begins in the small intestine with the bacteria crossing the epithelium, invading the Peyer's patches and disseminating systemically to the liver, spleen, and bone marrow.[8] Systemic immunity, including circulating IgG and T cell responses, is critical for bacterial clearance and long-term protection.[9] Licensed TCVs predominantly induce systemic responses, while the oral live-attenuated vaccine elicits both mucosal and systemic immunity. Mucosal immunity, particularly secretory IgA at the intestinal surface, may play a role in limiting initial colonisation and translocation across the epithelium.[10] CHIMs for Typhi and Paratyphi are available and were used to support the WHO endorsement of the conjugated Vi vaccine.[11] Areas for mucosal immunity research may include optimising mucosal immunity for prevention of intestinal invasion to reduce carriage and limit transmission, as well as increasing protection in at-risk subgroups; and establishing a fuller understanding of the dynamics of systemic vs. mucosal protection.

Pathogen Dashboard

Typhoidal Salmonella

STRATEGIC INDICATORS	BARRIERS TO DEVELOPMENT				
NEED	KNOWLEDGE GAPS		VACCINE DEVELOPMENT LANDSCAPE		
	PATHOGEN TARGETS	MUCOSAL MECHANISMS & COPS	VACCINE PIPELINE	MUCOSAL VACCINE PIPELINE	CHIM AVAILABILITY
ANNUAL MORTALITY **107,000**	LOW	MODERATE	FAIRLY LOW	MODERATE	LOW
ANNUAL INCIDENT CASES **9,320,000**	Good understanding of pathogen targets	Some knowledge gaps of mucosal mechanisms and correlates of protection	Robust vaccine pipeline	Moderate pipeline of mucosally delivered products	Established CHIM
DALYS **8,100,000**					

Gaps in understanding / progress: High Fairly High Moderate Fairly Low Low

Vaccine Pipeline

PHASE 1	PHASE 2	PHASE 3	LICENSED[12-17]
Entervax[18]	GSK 4077164A / iNTS-GMMA + Vi-CRM$_{197}$ TCV[19,20]	EuTCV[21–24]	Peda Typh - TCV
GSK 3536867A + Alum[25,26]	Trivalent Salmonella Conjugate Vaccine[27] (OSP-DT + Vi-DT)		SkyTyphoid - TCV
Typhax + AP[28-30]	UMD–Bharat Biotech Trivalent Vaccine (TSCV)[31,32]		Typbar
			Typbar TCV
			TYPHIBEV - TCV
			TYPHIM Vi
			vax-TyV
			Vivotif
			Zyvac TCV

Mucosal product or mucosal effect

DELIVERY ROUTE		VACCINE TYPE	
Parenteral	Purple text: Adjuvanted*	Subunit	DNA
Oral	✓ WHO-prequalified	Conjugate	RNA
Patch	⊘ Discontinued	Live-attenuated	Replicating viral vector
Intranasal	Ⓜ Mucosal immunity effect in humans indicated in the literature	Inactivated	Non-replicating viral vector
Aerosol		Not classified	

*Aluminium Hydroxide (AH)
Aluminium Phosphate (AP)
Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)

Recommendations

Expand the toolkit

- **Advance and standardise mucosal assays for comparative evaluation.** Develop functional assays that measure high-avidity Vi-specific sIgA, T cell responses, and innate effector engagement. Harmonise sampling protocols and immune readouts to enable head-to-head comparison of vaccine platforms.

Strengthen the evidence base

- **Refine CHIM studies to establish mucosal correlates of protection.** Use CHIMs to compare mucosal versus systemic immune responses across vaccine platforms. Prioritise detection of gut-homing CD4+ T cells, TRM T cells in liver and gut, and antigen-specific IgA in stool, saliva and mucosal secretions.

Improve foundational understanding

- **Apply systems omics to benchmark immunity.** Utilise systems omics to better understand how responses differ in infection and vaccination, including endemic and non-endemic settings, to inform the dynamics of protection and risk in various populations.

Accelerate vaccine development

- **Explore prime-boost strategies and tailor schedules to population needs.** Assess the dynamics of mucosal immunity via live oral vaccine priming with systemic conjugate boosters to coordinate intestinal sIgA circulating IgG responses. Assess the duration of protection and identify optimal boosting intervals, especially in children under 5 years of age and populations with altered gut integrity or prior exposure.
- **Develop mucosal-targeted adjuvants and delivery platforms.** Investigate safe mucosal adjuvants (e.g. TLR ligands) and delivery formats such as liposomes or enteric-coated microcapsules that enhance local immune activation without GI side effects.
- **Address age-related immune barriers and enteropathy.** Tailor immunisation approaches for children less than five years of age by integrating microbiome or synbiotics interventions to improve vaccine efficacy, given enteropathy's impact on mucosal barrier function and immune priming.
- **Progress bivalent vaccine candidates covering *S.* Paratyphi A.** Accelerate development of bivalent typhoid-paratyphoid vaccines, as high rates of *S.* Paratyphi A in some regions threaten to undermine gains from S. Typhi-only vaccines due to serotype replacement.

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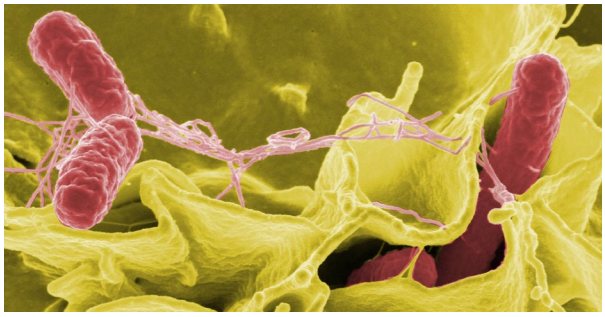
PATHOGEN

Non-Typhoidal Salmonella (NTS)



Overview

Salmonella enterica is a gram-negative bacterium consisting of over 2,500 serovars classified into typhoid and nontyphoid (NTS) subsets based on the distinct diseases caused in humans. NTS is primarily caused by serotypes Typhimurium and Enteritidis, although other serovars have also been associated with epidemic outbreaks.[1] Transmission occurs primarily through contaminated food and presents as self-limiting gastroenteritis (ranging from asymptomatic to severe) with an estimated 93.8 million cases annually.[2] In a subset of patients, NTS causes invasive disease (iNTS), resulting in bacteraemia, meningitis, and other focal infections, often with extremely high case fatality rates.[3]

Invasive NTS causes a large burden of disease in LMICs, particularly in Africa. In 2019, there were more than 500,000 cases of iNTS and ~62,000 deaths.[4] Those with compromised immunity, including malnourished children, the elderly, people living with HIV, and those with recent malaria or sickle-cell anaemia, are considered at high risk. Multidrug-resistant strains capable of causing iNTS are widespread in Africa; they complicate treatment and outcomes and reinforce the need for effective vaccines, of which there are none licensed. The WHO has listed *Salmonella enterica* as a priority pathogen, and one that poses a significant risk to human health due to microbial resistance.[5]

There are four known vaccines in clinical testing, including three combination approaches with typhoid conjugate vaccines designed to maximise commercial viability. All current vaccine candidates are O-antigen-based.[6] Vaccine development is complicated by the genetic variation of the disease-causing serovars as well as the potential for serovar replacement in response to vaccination. Lack of clear correlates of protection, including the understanding of the role of mucosal immunity and the need to generate immunity in immunologically distinct or vulnerable populations, further complicates the picture.[6]

Potential Role for Mucosal Immunity

NTS invades through the gastrointestinal mucosa and can travel via the lymphatic system to rapidly enter major replication sites such as the spleen, liver, and bone marrow.[7] Systemic immune responses are essential for controlling established iNTS infections,[8] and iNTS vaccine development has focused mainly on such protection. Studies of immunodeficient individuals in Africa have suggested the key role of IFNγ-mediated immunity as well as the need for both antibody and cell-mediated immunity to protect against iNTS.[1] Given the susceptibility of immunovulnerable populations, vaccine-induced mucosal immunity may provide additional levels of protection necessary to reduce mortality and morbidity. Research to date has suggested that sIgA and other mucosal effectors, such as CD4 Th1 cells, may have the potential to reduce intestinal invasion and bacterial load. Incorporating mucosal strategies, including oral delivery and mucosal adjuvants, may enhance efficacy and improve delivery and uptake in low-resource settings.[8,9] CHIM models are currently under development, particularly for *S.* Typhimurium infection, and could provide insights into pathogenesis, mucosal mechanisms and correlates of protection, as well as a platform to test vaccines.[10,11]

Pathogen Dashboard

Non-Typhoidal Salmonella (NTS)

STRATEGIC INDICATORS	BARRIERS TO DEVELOPMENT				
NEED	KNOWLEDGE GAPS		VACCINE DEVELOPMENT LANDSCAPE		
	PATHOGEN TARGETS	MUCOSAL MECHANISMS & COPS	VACCINE PIPELINE	MUCOSAL VACCINE PIPELINE	CHIM AVAILABILITY
	MODERATE	HIGH	FAIRLY HIGH	HIGH	MODERATE
ANNUAL MORTALITY **62,000**	Some knowledge gaps of pathogen targets	Significant knowledge gaps in mucosal mechanisms and correlates of protection	Limited vaccine pipeline	No mucosally delivered products in the pipeline	In development
ANNUAL INCIDENT CASES **510,000**					
DALYS **4,700,000**					

Gaps in understanding / progress: High · Fairly High · Moderate · Fairly Low · Low

Vaccine Pipeline

PHASE 1	PHASE 2	PHASE 3	LICENSED
iNTS-GMMA[12]	**GSK 4077164A / iNTS-GMMA + Vi-CRM$_{197}$ TCV**[13,14]		
	Trivalent Salmonella Conjugate Vaccine[15] **(OSP-DT + Vi-DT)**		
	UMD–Bharat Biotech Trivalent Vaccine (TSCV)[16,17]		

Mucosal product or mucosal effect

DELIVERY ROUTE		VACCINE TYPE	
Parenteral	Purple text: Adjuvanted*	Subunit	DNA
Oral	✔ WHO-prequalified	Conjugate	RNA
Patch	⊘ Discontinued	Live-attenuated	Replicating viral vector
Intranasal	Ⓜ Mucosal immunity effect in humans indicated in the literature	Inactivated	Non-replicating viral vector
Aerosol	*Aluminium Hydroxide (AH) Aluminium Phosphate (AP) Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)	Not classified	

Recommendations

Expand the toolkit

- **Standardise mucosal sampling across studies.** Harmonise mucosal sampling protocols (e.g. stool, rectal swabs) and immune readouts (e.g. IgA, gut-homing T cells) to enable reliable comparisons across vaccine candidates and geographies.

Strengthen the evidence base

- **Apply systems biology to compare natural and vaccine-induced immunity.** Use systems biology tools (transcriptomics, proteomics) to identify mechanisms of protection and/or correlates of protection, as well as drivers of mucosal immunity. Compare responses to natural infection vs. different vaccine platforms in endemic vs non-endemic populations.

Improve foundational understanding

- **Distinguish mucosal vs systemic immune targets across NTS syndromes.** Design studies to differentiate immune mechanisms needed for protection against diarrheal vs. invasive disease. Evaluate whether mucosal immunity can prevent dissemination in iNTS and how systemic and mucosal responses differ across syndromes, potentially informing vaccine strategies.

Accelerate vaccine development

- **Advance mucosal vaccine platforms for iNTS.** Develop oral vaccines that induce robust gut-localised responses, such as sIgA, Th17, and resident memory responses. Evaluate candidate platforms in relevant animal models and early-phase trials, particularly in children under five years old.
- **Explore prime-boost approaches for dual protection.** Test combinations of mucosal and systemic vaccines to address both intestinal and systemic disease. Mucosal priming followed by parenteral boosting may yield broader protection across compartments and age groups.
- **Investigate environmental and microbial factors shaping vaccine response.** Understand how microbiome composition, gut inflammation, and environmental enteropathy impact mucosal immunity to NTS. Design interventions that restore gut integrity and enhance oral vaccine efficacy.

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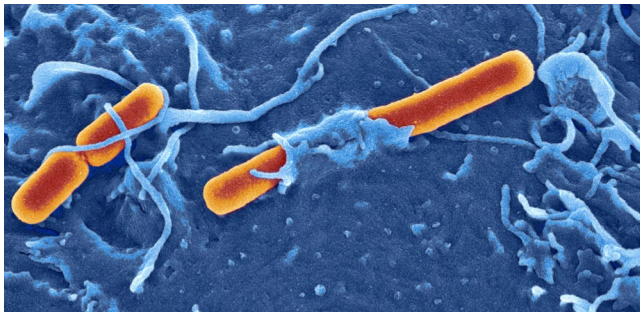
PATHOGEN

Shigella spp.



Overview

Shigella are gram-negative enteric bacterial pathogens that cause a significant portion of the global diarrhoeal disease burden, with ~117,000 deaths annually.[1] *Shigella* manifests clinically as shigellosis, which can vary from self-limiting diarrhoea to severe dysentery, including bloody stools and fever. There are an estimated 188 million cases of shigellosis annually, with a substantial impact on young children in LMICs.[2,3] Shigellosis causes an estimated 3.5 million cases of moderate-to-severe stunting,[2] and contributes to undernutrition and growth faltering, which are linked to impaired cognitive development, poor school performance and reduced economic potential.[3,4] *Shigella* thrives in areas with poor water, sanitation and hygiene conditions and high population density. Changing climates appear conducive to *Shigella* proliferation and transmission.[5]

Shigella is antigenically diverse, with four subgroups (*S. dysenteriae, S. flexneri, S. boydii* and *S. sonnei*) which are divided into more than 50 serotypes defined by components of the lipopolysaccharide O antigen.[2,3] *S. flexneri* (~ 15 serotypes) and *S. sonnei* (1 serotype) are responsible for most disease.[5] The WHO has called antibiotic-resistant *Shigella* a serious threat.[6]

Despite this disease burden and decades of development efforts, there are currently no licensed vaccines for *Shigella*.[7] Development challenges include broad antigenic diversity requiring multivalent vaccines targeting O-antigens, the fact that *Shigella* can persist intracellularly, evading some immune responses, the generation of immunity within the mucosal context, as well as challenges associated with generating protective immunity in children in LMICs.[7] Vaccine strategies have been hindered by reactogenicity, high number of doses, duration, immunogenicity and manufacturing issues. New approaches include nanoparticles, modified outer membrane vesicles (OMVs), the inclusion of adjuvants and novel protein-based subunit vaccines.[7]

Potential Role for Mucosal Immunity

Shigella is highly transmissible via the faecal-oral route; it invades the colonic mucosa, disrupting epithelial integrity and triggering inflammation.[3] *Shigella* has a complex life cycle, and multiple host immune mechanisms likely impact infection, intestinal invasion, and the severity or duration of disease.[8] Natural infection induces short-lived (2 years or less), serotype-specific protection; cumulative natural exposures contribute to increased immunity over time.[9] Protection is believed to rely on both mucosal and systemic immunity, including sIgA at the gut lumen, serum IgG, and cell-mediated responses,[10,11] though precise mechanisms of action and validated correlates of protection are lacking.[12] Oral candidate vaccines target mucosal surfaces and have been shown to elicit different immune responses than parenteral formulations.[8] *Shigella* is a human-restricted pathogen, increasing the importance of existing CHIM models. However, most CHIMs are conducted in high-income countries, which may not effectively model responses in those most at risk.[13]

Pathogen Dashboard

Shigella spp.

STRATEGIC INDICATORS	BARRIERS TO DEVELOPMENT				
NEED	KNOWLEDGE GAPS		VACCINE DEVELOPMENT LANDSCAPE		
	PATHOGEN TARGETS	MUCOSAL MECHANISMS & COPS	VACCINE PIPELINE	MUCOSAL VACCINE PIPELINE	CHIM AVAILABILITY
	LOW	MODERATE	FAIRLY HIGH	MODERATE	LOW
ANNUAL MORTALITY **117,000**	Good understanding of pathogen targets	Some knowledge gaps of mucosal mechanisms and correlates of protection	Limited vaccine pipeline	Moderate pipeline of mucosally delivered products	Established CHIM
ANNUAL INCIDENT CASES **188,000,000**					
DALYS **9,410,000**					

Gaps in understanding / progress: High | Fairly High | Moderate | Fairly Low | Low

Vaccine Pipeline

PHASE 1	PHASE 2	PHASE 3	LICENSED[10-11]
CVD 1208S-122[14] *(S. flexneri)*	**GSK 4001785A + AH**[15-17] *(S. sonnei; S. flexneri)*	**ZF0901 + AP**[18] *(S. sonnei; S. flexneri)*	
InvaplexAR-Detox + dmLT[19] *(S. flexneri)*	**SF2a-TT15 (GlycoShig3)**[22] **+ AH** *(S. flexneri)*		
ShigETEC[20] *(S. flexneri)* Ⓜ	**Shigella sonnei vaccine / 1790GAHB**[24-27] *(S. sonnei)* Ⓜ		
ShigOraVax[21] *(S. sonnei; S. flexneri)*	**S4V-EPA (Shigella4V)**[28,29] *(S. sonnei; S. flexneri)*		
WRSs2 / WRSs3[23] *(S. sonnei)* Ⓜ			

Mucosal product or mucosal effect

DELIVERY ROUTE		VACCINE TYPE
Parenteral	Purple text: Adjuvanted*	Subunit, Conjugate, DNA, RNA
Oral	✔ WHO-prequalified	Live-attenuated, Inactivated, Replicating viral vector, Non-replicating viral vector
Patch	⊘ Discontinued	Not classified
Intranasal	Ⓜ Mucosal immunity effect in humans indicated in the literature	
Aerosol	*Aluminium Hydroxide (AH) Aluminium Phosphate (AP) Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)	

Recommendations

Expand the toolkit

- **Standardise mucosal sampling and functional assays across trials.** Develop validated protocols for measuring faecal IgA/IgG and standardise mucosal functional assays to enable cross-platform immunogenicity comparisons.
- **Increase sampling in clinical trials.** Ensure prospective sampling in future clinical studies and retrospective analysis of samples from completed studies.

Strengthen the evidence base

- **Use an integrated approach.** Utilise CHIMs and systems-level -omics to assess systemic and mucosal functional responses, map protective mucosal signatures, and compare responses across vaccine platforms and age groups, including a head-to-head comparison of oral and parenteral Shigella vaccines.

Improve foundational understanding

- **Clarify mucosal correlates of protection in children.** Adapt scalable, child-friendly mucosal sampling protocols (e.g., optimised rectal swabs, stool sampling) for use in large paediatric trials in LMICs to identify protective immune markers.
- **Study immune imprinting and age-specific responses.** Investigate how early-life exposure to Shigella and other enteric pathogens influences long-term mucosal immunity and impacts vaccine responsiveness across different age groups.

Accelerate vaccine development

- **Support live oral and hybrid vaccine platforms.** Advance live-attenuated oral vaccine candidates with improved tolerability and explore protein–O-antigen conjugates to induce both local sIgA and systemic IgG, especially in young children.
- **Address enteropathy-associated barriers to mucosal vaccine efficacy.** Pair vaccination with interventions that improve gut health to enhance mucosal immune responses and vaccine efficacy in enteropathy-prone populations.

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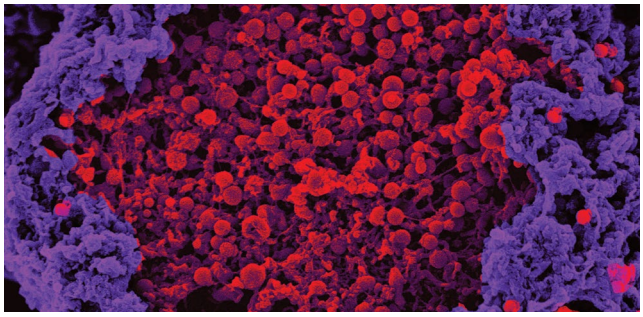
PATHOGEN

Chlamydia trachomatis



Overview

Chlamydia trachomatis is an obligate intracellular, Gram-negative bacterium with multiple serovars that infects mucosal epithelial cells of the cervix and upper genital tract, rectum, and conjunctiva. Chlamydia is the most commonly reported STI globally, with ~130 million new cases annually.[1] Most infections are asymptomatic, enabling persistent transmission and reinfection. If untreated, chlamydia can lead to severe reproductive complications in women, including pelvic inflammatory disease, infertility, and increased risk of ectopic pregnancy, prematurity, low birth weight, neonatal conjunctivitis and pneumonia through vertical transmission. In men, it can cause urethritis, epididymitis, prostatitis, and proctitis.[2] Deaths are rare, but may result from pelvic inflammatory disease or ectopic pregnancy.[3] Chlamydia enhances the acquisition of other STIs and is an independent risk factor for cervical cancer in women. While ~20% of chlamydia cases may resolve naturally, infection can persist if untreated.[4] Observationally, chlamydia is more prevalent in younger populations; older populations in high-incidence regions are less likely to acquire chlamydia, suggesting protection develops from natural infection and exposure. No vaccine is currently licensed.

Potential Role for Mucosal Immunity

C. trachomatis enters the body via the genital mucosa; bacteria enter columnar epithelial cells where they replicate intracellularly, leading to inflammation, epithelial damage, and potential complications. Limited evidence from natural immunity and animal studies suggests that inducing robust genital tract mucosal immunity, particularly TRM T cells, may offer protection.[5,6] The chlamydia vaccine pipeline is extremely limited and early stage, with current candidates targeting major outer membrane protein (MOMP) and containing B and T cell epitopes covering four serovars.[7] While no CHIM exists, models have been recently proposed,[8] and experts suggest that high chlamydia prevalence may offer opportunities for natural exposure cohorts.

Pathogen Dashboard

Chlamydia trachomatis

STRATEGIC INDICATORS	BARRIERS TO DEVELOPMENT				
NEED	KNOWLEDGE GAPS		VACCINE DEVELOPMENT LANDSCAPE		
	PATHOGEN TARGETS	MUCOSAL MECHANISMS & COPS	VACCINE PIPELINE	MUCOSAL VACCINE PIPELINE	CHIM AVAILABILITY
ANNUAL MORTALITY **1,030**	MODERATE	MODERATE	HIGH	FAIRLY HIGH	MODERATE
ANNUAL INCIDENT CASES **128,500,000**	Some knowledge of potential pathogen targets	Some knowledge gaps of mucosal mechanisms and correlates of protection	Sparse vaccine pipeline	Limited vaccine pipeline of mucosally delivered products	Natural exposure CHIM proxy
DALYS **5,600,000**					

Gaps in understanding / progress: High Fairly High Moderate Fairly Low Low

Vaccine Pipeline

*Fast track designation

Mucosal product or mucosal effect

DELIVERY ROUTE		VACCINE TYPE	
Parenteral	Purple text: Adjuvanted*	Subunit	DNA
Oral	WHO-prequalified	Conjugate	RNA
Patch	Discontinued	Live-attenuated	Replicating viral vector
Intranasal	Mucosal immunity effect in humans indicated in the literature	Inactivated	Non-replicating viral vector
Aerosol	*Aluminium Hydroxide (AH) Aluminium Phosphate (AP) Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)	Not classified	

Recommendations

Expand the toolkit

- **Use approaches from other disease areas.** Many approaches used for HIV and HPV vaccine research may have application for designing and testing *C. trachomatis* vaccines, including sampling methods, immunological tools, and vaccine platforms (including safe and effective mucosal adjuvant formulations).

Strengthen the evidence base

- **Leverage high-incidence populations.** Utilise regions with high chlamydia prevalence to establish natural exposure cohorts. Collect mucosal samples, including biopsies, to capture mucosal immune responses post-infection, linking local immune profiles to reinfection risk. Ensure that vaccine approaches would be acceptable in at-risk populations, including drawing relevant lessons from HPV vaccine roll-out.

Improve foundational understanding

- **Define protective immune signatures.** Prioritise research to quantify TRM B- and T-cell densities in the genital mucosa and immune signatures associated with protection against reinfection.

Continued on following page

Accelerate vaccine development

- **Evaluate mucosal routes for genital immunity.** Systematically assess intranasal, oral (including sublingual), and rectal vaccine delivery strategies compared with parenteral vaccines for their ability to elicit strong genital tract immunity, including intravaginal TRM and mucosal antibody responses.
- **Interrogate microbiome, hormonal, and environmental influences on vaccine efficacy.** Investigate how vaginal microbiota, hormonal variation, and baseline inflammation affect mucosal immune responses, including vaccine responses. Incorporate these factors into trial design and stratification, particularly in populations with high disease burden.
- **Determine how to generate broad-serovar coverage and long-term protection.** Utilise conserved antigens like major outer membrane protein (MOMP) and Outer Membrane Protein 2 (OMP2), as well as focused responses on vulnerable epitopes/targets. Confirm if systemic priming followed by mucosal boosting can enhance the quality, breadth and duration of the mucosal immune response,[7] and if innovative delivery systems (e.g. thermoresponsive gels and liposomal formulations) can facilitate uptake of immunogens at mucosal surfaces.
- **Adjuvants.** Explore additional adjuvants for safety and the promotion of required immune responses.

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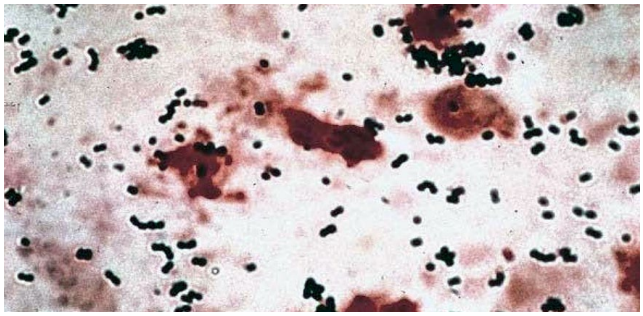
PATHOGEN

Group B streptococcus (GBS)



Overview

Group B streptococcus (GBS), *Streptococcus agalactiae,* is a major cause of neonatal sepsis, meningitis, and stillbirth globally. There are an estimated 20 million women colonised with GBS and 518,000 GBS-associated preterm births annually.[1] GBS can be transmitted in the womb, during birth, or in the early weeks of life; there are an estimated 390,000 infant cases annually (resulting in ~90,000 infant deaths and 57,000 still births).[2] Infants who survive GBS may suffer from long-term neurodevelopmental impairment. Early-onset disease (EOD) typically results from vertical transmission during delivery, while late-onset disease (LOD) occurs postnatally. Intrapartum antibiotic prophylaxis has reduced EOD in high-income countries, but is challenging to implement in low-resource settings and does not prevent LOD.[3] Because GBS infection occurs too early in life for infants to elicit an effective immune response, maternal

Potential Role for Mucosal Immunity

The reservoir for GBS in humans is the lower GI and GU tracts, where recto-vaginal colonisation is necessary for maternal-to-infant transmission.[1] Natural mucosal immunity at the genital mucosa, particularly IgG, has been shown to influence colonisation and transmission dynamics.[4,5] The limited number of early-stage maternal vaccine candidates focus on systemic delivery to induce antibodies for transplacental transfer to newborns; these antibodies have also been shown to influence maternal GBS colonisation at mucosal sites.[6] Understanding the mechanisms for systemic immunisation influencing mucosal immunity, and whether mucosal delivery or adjuvants might further reduce colonisation, is still evolving. The ability to collect genital samples from pregnant women presents a unique opportunity to explore these pathways.

Pathogen Dashboard

Group B streptococcus (GBS)

STRATEGIC INDICATORS	BARRIERS TO DEVELOPMENT				
NEED	KNOWLEDGE GAPS		VACCINE DEVELOPMENT LANDSCAPE		
	PATHOGEN TARGETS	MUCOSAL MECHANISMS & COPS	VACCINE PIPELINE	MUCOSAL VACCINE PIPELINE	CHIM AVAILABILITY
ANNUAL MORTALITY **147,000**	MODERATE	HIGH	HIGH	HIGH	HIGH
ANNUAL INCIDENT CASES **392,000**	Some knowledge of potential pathogen targets	Significant knowledge gaps of mucosal mechanisms and correlates of protection	Sparse vaccine pipeline	No mucosally delivered products in the pipeline	No available CHIM
DALYS **11,200,000**					

Gaps in understanding / progress: High Fairly High Moderate Fairly Low Low

Vaccine Pipeline

*Breakthrough Therapy Designation
**Fast track designation

Mucosal product or mucosal effect

DELIVERY ROUTE		VACCINE TYPE	
Parenteral	Purple text: Adjuvanted*	Subunit	DNA
Oral	✔ WHO-prequalified	Conjugate	RNA
Patch	⊘ Discontinued	Live-attenuated	Replicating viral vector
Intranasal	Ⓜ Mucosal immunity effect in humans indicated in the literature	Inactivated	Non-replicating viral vector
Aerosol	*Aluminium Hydroxide (AH) Aluminium Phosphate (AP) Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)	Not classified	

Recommendations

Expand the toolkit

- **Accelerate licensure via harmonised immune endpoints.** Support immunogenicity-based regulatory pathways by standardising and qualifying assays to measure mucosal antibody titers, specificities and subclasses. Develop serotype-specific functional assays such as OPA for carbohydrate-based responses and novel assays for protein antigens to validate maternal antibody–driven protection.[6,12]
- **Adapt trials and assays for LMIC and newborn contexts.** Scale assay platforms to low-volume neonatal and mucosal samples and build clinical research capacity in LMICs to support GBS vaccine trials and translational research studies.

Strengthen the evidence base

- **Leverage the GBS6 trial to evaluate mucosal immunity.** Use the upcoming GBS6 efficacy trial to assess mucosal antibody levels and colonisation in the GU tract. Genital and breast milk sampling during the trial offers a rare opportunity to connect systemic responses with local immunity.[5]

Improve foundational understanding

- **Strengthen immunoepidemiology across diverse maternal populations.** Expand sero-epidemiological monitoring and translational research studies in pregnant women, including women with HIV, preterm births, and different geographic regions, to refine dosing and scheduling[3,6] and contribute to next-generation vaccine design and immune correlates studies.

Accelerate vaccine development

- **Advance multivalent and protein–conserved antigen vaccines.** Prioritise vaccines covering CPS serotypes Ia, Ib, II, III, IV, and V (e.g., GBS6) and incorporate conserved protein antigens (e.g. Alp family, Sip) to mitigate serotype replacement.[5,13]

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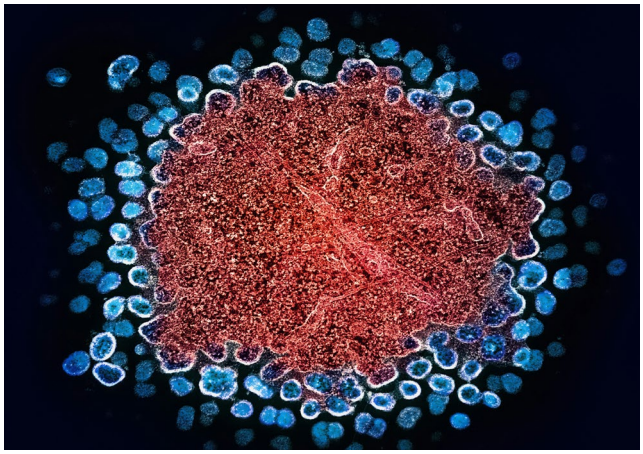
PATHOGEN

Human Immunodeficiency Virus (HIV)



Overview

HIV is a lentivirus that targets CD4+ T cells and other immune cells, resulting in progressive damage to the immune system. There are two main types, of which HIV-1 is responsible for the global pandemic. Without treatment, HIV progresses to AIDS, marked by severe opportunistic infections and malignancies. As of 2023, ~40 million people are living with HIV, and the virus causes over 1.3 million new infections and 630,000 deaths annually.[1] Vertical transmission during pregnancy, delivery, or breastfeeding results in ~120,000 infant cases a year.[2] Populations most affected by HIV include various demographic groups, including men who have sex with men, sex workers, HIV-discordant couples, intravenous drug users,[3] individuals affected by specific cofactors, e.g., STIs and certain geographic contexts. ART has transformed HIV from a fatal disease to a manageable chronic condition, and the recent introduction of long-acting antiretroviral therapy and pre-exposure prophylaxis has both meaningfully expanded the prevention toolkit and complicated the clinical trial landscape.

Despite decades of research, there is still no licensed vaccine. Challenges to vaccine development include HIV's genetic variability, immune evasion strategies, integration into host DNA, and limitations of animal models. Systemic vaccine candidates have shown limited or no efficacy and relatively poor immunogenicity in early phase I/II studies. Several vaccine candidates are in clinical development, focusing on eliciting broadly neutralising antibodies and broadly antiviral T-cell responses. However, to date, the generation of broadly reactive neutralising antibodies and cell-mediated immune responses, including but not limited to broadly reactive cytotoxic T cells, has proven to be very challenging. While theoretically, induction of broadly reactive mucosal immunity might enhance both local and systemic protection, there remains limited clinical evidence.

Potential Role for Mucosal Immunity

Sexual transmission drives the global HIV epidemic; the virus enters via the female genital tract, penis or rectal mucosa, where lesions, STI co-infections, local inflammation and immune cell activation play roles in promoting viral acquisition and establishment. Most infections are established by one or two viruses.[4] As mucosal tissues host early viral replication, they offer primary sites for prevention, and this is supported by the effective use of post-exposure prophylaxis within 3 days of exposure, and before virus dissemination. Once the virus disseminates systemically, it replicates and evolves rapidly during acute infection, with high viral loads and rapid immune destruction in the LN observed within a few days of the initial infection and in the GI tract within days to weeks. The virus continues to replicate, integrates into the host genome, and establishes latency in lymphoid reservoirs. Once this happens, there is no cure, as latent reservoirs remain resistant to highly effective treatments. A vaccine that could contain infection at the mucosa, and/or slow spread to the LN and GALT, might provide the host the chance to mount an effective immune response to limit immune destruction. However, most vaccine trials and epidemiology studies have measured only systemic responses, missing potentially protective mucosal correlates and clues.

Identifying correlates of protection remains a major challenge, as spontaneous clearance of HIV does not occur. However, most individuals resolve acute peak viraemia, albeit to different levels, and a minority remain symptom free with persistently low viral loads for decades without therapy;[5] these individuals tend to have highly effective functional CD8 T cell responses.[6] Genome-wide studies have consistently linked viral control with certain HLA class I alleles (e.g., HLA-B57, HLA-B27),[7] suggesting cytotoxic T cell responses are central to viral control. Further, some chronically infected individuals develop broadly neutralising antibodies (bnAbs) capable of neutralising diverse HIV strains in vitro. While passive administration of bnAbs has shown partial efficacy in blocking HIV acquisition in high-risk individuals, vaccines have failed to elicit the required breadth and potency to impact HIV acquisition, and only modest impact on viral load in some participants.[8] Targeting effective mucosal immunity might enhance both local and systemic protection.

Pathogen Dashboard

Human Immunodeficiency Virus (HIV)

STRATEGIC INDICATORS	BARRIERS TO DEVELOPMENT				
NEED	KNOWLEDGE GAPS		VACCINE DEVELOPMENT LANDSCAPE		
	PATHOGEN TARGETS	MUCOSAL MECHANISMS & COPS	VACCINE PIPELINE	MUCOSAL VACCINE PIPELINE	CHIM AVAILABILITY
ANNUAL MORTALITY **630,000**	HIGH	MODERATE	MODERATE	FAIRLY HIGH	HIGH
ANNUAL INCIDENT CASES **1,300,000**	Significant knowledge gaps of pathogen targets	Some knowledge gaps of mucosal mechanisms and correlates of protection	Robust vaccine pipeline	Limited pipeline of mucosally delivered products.	CHIM not suitable*
DALYS **40,300,000**					

Gaps in understanding / progress: High Fairly High Moderate Fairly Low Low

*HIV early treatment and treatment interruptions are the closest approximations of CHIM studies.

Vaccine Pipeline[9]

PHASE 1	PHASE 2	PHASE 3	LICENSED
AdC6-HIVgp140[10] AdC7-HIVgp140 CH505TF gp120 + GLA-SE			
VIR-138811[11]			
Ad26.Mos4.HIV + CH505 TF[12]			
GRAdHIVNE1[13]			
ChAdOx1.tHIVconsv1[14]			
Ad4-Env145NFL[15] Ad4-Env150KN VRC-HIVRGP096-00-VP + Alum			
BG505 MD39.3[16] BG505 MD39.3 gp151 BG505 MD39.3 gp151 CD4KO HIV trimer			
mRNA-1644[17] mRNA-1644v2			
CH505M5 N197D mRNA-gp160[18] CH505 TF mRNA-gp160			
eOD-GT8 60mer, coreg28v2 60mer, N332-GT5 gp151[19] DV700P-RNA + DV701B1.1-RNA[20]			

Continued on following page

Vaccine Pipeline

PHASE 1	PHASE 2	PHASE 3	LICENSED
V3G CH848 Pr-NP1 + V3G CH848 w/ 3M-052 AF21 + Alum[21]			
IHV01 A244/AHFG22 + ALFQ[22]			
16055 NFL Delta Gly4 Env Trimer + Trimer 4571 + 3M-052-AF[23] + Alum + Ad4-Env145NFL viral particles			
Stabilized CH505 TF chTrimer 3M-052-AF[24] + Alum			
426c.Mod.Core-C4b 3M-052-AF[25] + Alum			
A244/B.63521 HIV-1[26] + ALFQ			
SOSIP v8.2 763 vaccine[27] + MPLA			
BG505 SOSIP.664 gp140[28]			
HIV Env Trimer, N332- GT5 gp140[29]+ SMNP			
UVAX-1107 + UVAX1107[30] UVAX-1197 + CpG 1018/Alum UVAX-1107 + UVAX1197 with 3M-052-AF + Alum			
CD40.HIVRI.Env (VRIPRO)[31] + Hiltonol			
426c.Mod.Core-C4b + HxB2.WT. Core-C4b with 3M-052 AF[32] + Alum			

Mucosal product or mucosal effect

DELIVERY ROUTE

- Parenteral
- Oral
- Patch
- Intranasal
- Aerosol

Purple text: Adjuvanted*
- ✓ WHO-prequalified
- ⊘ Discontinued
- Ⓜ Mucosal immunity effect in humans indicated in the literature

*Aluminium Hydroxide (AH)
Aluminium Phosphate (AP)
Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)

VACCINE TYPE

- Subunit
- Conjugate
- DNA
- RNA
- Live-attenuated
- Inactivated
- Replicating viral vector
- Non-replicating viral vector
- Not classified

Recommendations

Expand the toolkit

- **Harmonise mucosal sampling and trial endpoints.** Establish standardised protocols for sample collection (e.g., nasal swabs, cervicovaginal cytobrushes and biopsies, colorectal biopsies) and standardised immune readouts (e.g., mucosal CD8+/CD4+ TRM, IgA/IgG ratios, dendritic cell activation), functional assays, and clinical measures (e.g., mucosal shedding, epithelial barrier integrity) to enable meaningful cross-trial comparisons and meta-analyses.
- **Use systems immunology to map and compare mucosal correlates.** Apply next-generation technologies (e.g., scRNA-seq, multiplex imaging) to characterise tissue-resident immune responses in the mucosa. Compare vaccine-induced mucosal responses (e.g., TRM, secretory IgA/IgG) with those from natural infection and elite controllers.

Strengthen the evidence base

- **Include sampling and assessment of mucosal immune responses across genital, rectal, GI and nasopharyngeal tissues** in both high-risk and general population cohorts. Evaluate common vs unique correlates across tissues and geographies to better understand the potential role for mucosal immunity in protection, or identify potential signatures in blood indicative of mucosal responses.
- **Include extensive mucosal sampling** in small numbers of vaccine recipients, and less invasive mucosal sampling routinely in larger ongoing vaccine trials.

Improve foundational understanding

- **Quantify antibody transudation kinetics in the mucosa.** Utilise passive immunisation studies to examine how systemically administered antibodies (bnAbs or IgG/IgA) penetrate mucosal tissues, including differences by tissue type, sex and inflammation state.
- **Characterise the cellular responses** in tissues derived from well-characterised cohorts from diverse risk groups and geographies. Utilise in vitro Imaging to better understand early transmission events and the complex interplay between virus and host mucosa.

Accelerate vaccine development

The recommendations below focus on strengthening the potential for induction of broadly reactive, and disease-controlling cell-mediated immune responses to complement ongoing efforts to elicit bnAbs.

- **Target TRM induction via novel vectors and prime-pull strategies.** Utilise vectors like CMV-based or influenza/adenovirus replicating platforms that sustain effector-memory T cell populations at mucosal sites. This systemic or mucosal priming can be paired with local “pull” strategies, e.g., topical chemokines like CCL19/CCL28 or mucosal cytokine adjuvants, to recruit and retain antigen-specific cells at the mucosal entry site.
- **Test mucosal routes and vectors in prime-boost regimens.** NHP studies show that intranasal or aerosol administration combined with systemic boosts can generate broad mucosal immunity in genital tissue, GALT and lung. Test various mucosal routes and complement assay tool kits with functional assays and next-generation systems biology capabilities to interrogate samples.
- **Refine rational design to co-induce antibody and T cell immunity.** Learn from effects observed in passive antibody and T cell-based prophylactic and therapeutic trials. Design immunogens and adjuvants to induce mucosal neutralisation and cellular control at the entry site, especially in GU and rectal tissues. Develop in vitro explant systems to enhance vaccine screening.

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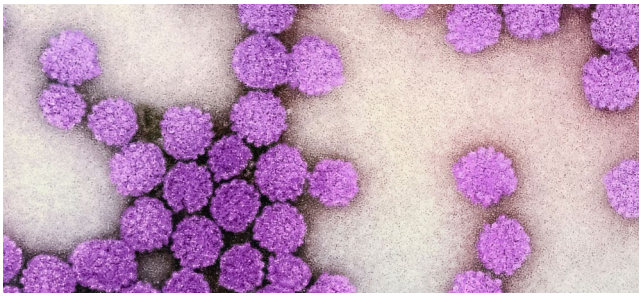
PATHOGEN

Human Papillomavirus (HPV)



Overview

Human papillomavirus (HPV) is a double-stranded DNA virus with over 200 genotypes. 85% of people will acquire an HPV infection in their lifetime;[1] 80-90% of these infections occur without symptoms and are cleared within 1–2 years by the host immune system.[2] Persistent infections with high-risk, oncogenic genotypes are highly associated with cancer of the cervix (>95% of cases), oropharynx (60%), anus (>90%), vagina and vulva (70%), and penis (60%).[3] There are an estimated 830,000 new cases of HPV-related cancers annually and over 420,000 deaths; HPV is the 4th leading cause of cancer in women globally.[4] As of 2025, there are seven highly efficacious HPV vaccines available globally, which have contributed to a profound reduction in the incidence of HPV-associated cancers in countries with high levels of access and uptake.[5] Yet, disparities in vaccine access exist, in part due to cost and cold chain requirements. Further, existing vaccines offer little therapeutic benefit to those already infected.

Potential Role for Mucosal Immunity

HPV initiates infection at mucosal surfaces, entering basal epithelial cells where, in a subset of individuals (10-20%), it evades immune detection and response.[6] Current prophylactic HPV virus-like particle (VLP) vaccines are administered intramuscularly. They are highly immunogenic, inducing strong antibody responses associated with high efficacy that are thought to reach genital and oropharyngeal mucosal sites through both direct exudation and transudation.[7]

Antibodies are thought to prevent infection effectively due to the very slow rate of virus entry, the highly localised nature of the infection and susceptibility of the virus to neutralisation. Robust local cellular immunity, particularly involving mucosal CD8+ T cells, is considered important for clearing existing HPV infections and preventing lesion progression, although an effector role for CD4+ T cells has not been ruled out.[2] The specific threshold of immune response that correlates with protection has not been formally established in humans.[7] More than 15 prophylactic candidates are currently in the pipeline, along with ~ 30 therapeutic candidates.[8]

Existing vaccines are highly effective and safe, setting an extremely high bar for demonstrating a mucosal advantage. While therapeutic HPV vaccines are beyond the scope of this review, experts suggest that mucosal immunity, including antigen-specific TRMs, is essential to their development. To date, therapeutic vaccines have focused overwhelmingly on parenteral administration.

Pathogen Dashboard

Human Papillomavirus (HPV)

STRATEGIC INDICATORS	BARRIERS TO DEVELOPMENT				
NEED	KNOWLEDGE GAPS		VACCINE DEVELOPMENT LANDSCAPE		
	PATHOGEN TARGETS	MUCOSAL MECHANISMS & COPS	VACCINE PIPELINE	MUCOSAL VACCINE PIPELINE	CHIM AVAILABILITY
ANNUAL MORTALITY **422,000**	LOW	MODERATE	FAIRLY LOW	HIGH	HIGH
ANNUAL INCIDENT CASES **830,000**	Good understanding of pathogen targets	Some knowledge gaps of mucosal mechanisms and correlates of protection	Robust vaccine pipeline	No mucosally delivered products in the pipeline	CHIM not suitable
DALYS **9,910,000**					

Gaps in understanding / progress: High Fairly High Moderate Fairly Low Low

Prophylactic Vaccine Pipeline[8]

PHASE 1	PHASE 2	PHASE 3	LICENSED[12-17]
Recombinant 15-valent[18]	Recombinant quadrivalent vaccines + AH	Recombinant quadrivalent vaccine[19,20] + AP	Gardasil + AAHS ✓ Ⓜ
AAVLP-HPV[21,22]	Recombinant nine-valent vaccine + novel adj	Recombinant nine-valent vaccine[23] + AP	Gardasil 9 + AAHS ✓ Ⓜ
HPVAX		Recombinant eleven-valent vaccines[23,24]	Cervarix + AS04 ✓ Ⓜ
Recombinant bivalent + Alum		Recombinant quadrivalent vaccines[26] + Alum	Cecolin + Alum ✓ Ⓜ
Recombinant quadrivalent vaccine[25]		Recombinant trivalent HPV vaccine[26] + Alum	WalrinVax + Alum
		Recombinant nine-valent HPV vaccine[23,26] + AH	Cervavac + A13 (India)
		Recombinant nine-valent HPV vaccine + Alum	Cecolin 9 + Alum (China)
		SCT1000[27,28] Recombinant 14-valent vaccine + Alum	
		Recombinant nine-valent HPV vaccine + Alum	
		9 valent subunit vaccine[23,29] + AP	

Mucosal product or mucosal effect

DELIVERY ROUTE

- Parenteral
- Oral
- Patch
- Intranasal
- Aerosol

Purple text: Adjuvanted*
✓ WHO-prequalified
⊘ Discontinued
Ⓜ Mucosal immunity effect in humans indicated in the literature

*Aluminium Hydroxide (AH)
Aluminium Phosphate (AP)
Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)

VACCINE TYPE

- Subunit
- Conjugate
- Live-attenuated
- Inactivated
- Not classified
- DNA
- RNA
- Replicating viral vector
- Non-replicating viral vector

Recommendations

Expand the toolkit

- **Standardise mucosal assays and trials.** Harmonise endpoints and sampling methods to enable reliable comparisons of mucosal immunogenicity across studies.

Strengthen the evidence base

- **Expand experimental medicine Studies to map mucosal response.** Leverage the existence of highly effective vaccines for evaluation of mechanisms and duration of local mucosal immune responses (e.g., transudative systemic IgG, actively induced local IgA and TRM responses), including correlates and mechanisms of protection between blood and mucosa.

Improve foundational understanding

- **Model antibody transudation and protection thresholds.** Develop quantitative models that relate systemic antibody levels to concentrations in mucosal compartments to support efforts to define thresholds of protection. Explore avenues to assess levels of exudated antibodies, ideally at the site of infection, to further explore correlates of protection.

Accelerate vaccine development

- **Investigate age and sex differences in vaccine response.** Explore why HPV vaccine efficacy possibly varies by age and sex, particularly better efficacy in younger women, and assess how hormonal, anatomical, or mucosal immune factors may contribute compared with virus exposure.

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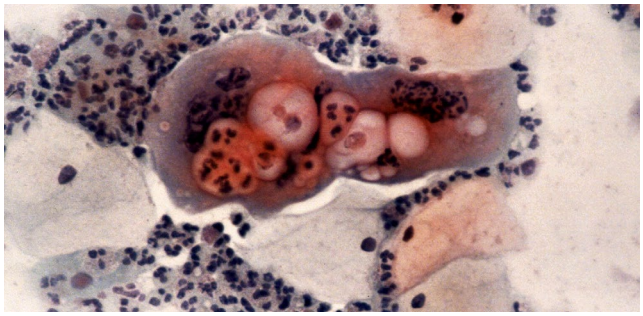
PATHOGEN

Herpes Simplex Virus (HSV)



Overview

Herpes Simplex Virus (HSV) is a double-stranded DNA virus that exists in two main types: HSV-1, commonly associated with oral lesions, and HSV-2, predominantly linked to genital infections.[1,2] Globally, almost 1 billion people are estimated to be living with HSV-2, with ~40M new infections occurring annually.[3] HSV establishes lifelong latency in sensory neurons, with periodic reactivation that can lead to recurrent symptoms and asymptomatic viral shedding, driving ongoing transmission even in the absence of clinical signs. While infection is often mild or subclinical, it can result in painful genital ulcers and has been associated with an increased risk of HIV acquisition. Neonatal herpes, though rare, can be severe and has a case fatality rate of ~60% if untreated.[4] Natural infection may induce immunity to stop subsequent infections with the same serotypes, but it does not provide protection against other serotypes or address latency.[5] Despite decades of research, no licensed vaccine exists, though multiple candidates targeting both prophylactic and therapeutic indications are in development. Challenges to vaccine development include latency, immune evasion, and induction of protective mucosal immunity.[6]

Potential Role for Mucosal Immunity

HSV-1 and 2 infections begin at the skin and mucosal epithelia, respectively, then ascend to sensory neurons, where the virus establishes latency through latency-associated transcripts. HSV has a complex genome and life cycle and has developed complex immune evasion mechanisms, including inhibition of pattern recognition receptor signalling and disruption of innate and adaptive immune responses.[7,8] Mucosal immune responses, including TRM T cells, locally produced antibodies, and innate signalling, play a critical role in controlling HSV reactivation and transmission,[2,8] but knowledge gaps exist surrounding molecular and cellular mechanisms. Despite decades of effort, there are no licensed therapeutic or prophylactic vaccines for HSV.

There are numerous therapeutic products in the pipeline (outside the scope of this review), but only one prophylactic candidate is currently in the pipeline. Most clinical trials have focused on systemic responses, and relatively few include comprehensive measurements of mucosal endpoints. Natural infection studies and preclinical 'prime-pull' strategies in animal models suggest that targeted tissue-based immunity could improve both prophylactic and therapeutic vaccine outcomes.

Pathogen Dashboard

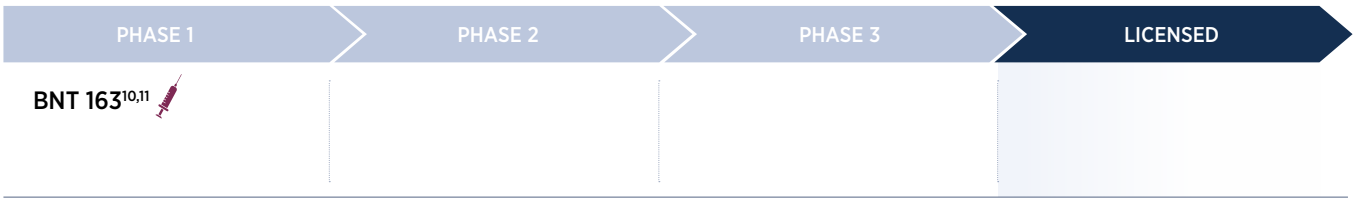
Herpes Simplex Virus (HSV)

STRATEGIC INDICATORS	BARRIERS TO DEVELOPMENT				
NEED	KNOWLEDGE GAPS		VACCINE DEVELOPMENT LANDSCAPE		
	PATHOGEN TARGETS	MUCOSAL MECHANISMS & COPS	VACCINE PIPELINE	MUCOSAL VACCINE PIPELINE	CHIM AVAILABILITY
ANNUAL MORTALITY* **8,554**	HIGH	HIGH	HIGH	HIGH	HIGH
ANNUAL INCIDENT CASES **40,200,000**	Significant knowledge gaps for rational immunogen design	Significant knowledge gaps in mucosal mechanisms and correlates of protection	Sparse vaccine pipeline	No mucosally delivered products in the pipeline	No available CHIM**
DALYS **300,000**					

Gaps in understanding / progress: High Fairly High Moderate Fairly Low Low

*Global estimated mortality for neonatal HSV infection.[4]
**No CHIM exists, but there are well-established natural history of infection studies.[9]

Vaccine Pipeline



Mucosal product or mucosal effect

DELIVERY ROUTE		VACCINE TYPE	
Parenteral	Purple text Adjuvanted*	Subunit	DNA
Oral	✔ WHO-prequalified	Conjugate	RNA
Patch	⊘ Discontinued	Live-attenuated	Replicating viral vector
Intranasal	Ⓜ Mucosal immunity effect in humans indicated in the literature	Inactivated	Non-replicating viral vector
Aerosol	*Aluminium Hydroxide (AH) Aluminium Phosphate (AP) Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)	Not classified	

Recommendations

Expand the toolkit

- **Standardise mucosal sampling and immunologic assays.** Harmonise swab protocols, tissue biopsy collection and processing, menstrual cup sampling, and antibody quantification to enable reliable comparisons across trials, especially in skin, vaginal and oral mucosa.

Strengthen the evidence base

- **Study immune correlates across natural infection and vaccine types.** Apply systems immunology to compare TRM T cell, and cytokine profiles in vaccine recipients vs. naturally infected individuals across endemic and non-endemic regions. Clarify the relationship between systemic antibody levels and mucosal protection, especially in light of prior vaccine failures.

Improve foundational understanding

- **Implement prime-pull or localised mucosal strategies in trials.** Design studies combining systemic priming with mucosal "pull" to induce TRMs and local antibodies. The female genital tract provides a uniquely accessible site for repeated sampling and biopsy to evaluate immune kinetics.
- **Integrate HSV-1/HSV-2 cross-reactivity and host factors into trial design.** Stratify and analyse by serostatus, sex, and HLA to understand response heterogeneity, and consider endpoints beyond lesions—like mucosal shedding or recurrence intervals.

Accelerate vaccine development

- **Advance rational adjuvant design for mucosal induction.** Evaluate TLR and STING agonists or cytokine adjuvants optimised for mucosal delivery and CD8+/TRM induction in humans.

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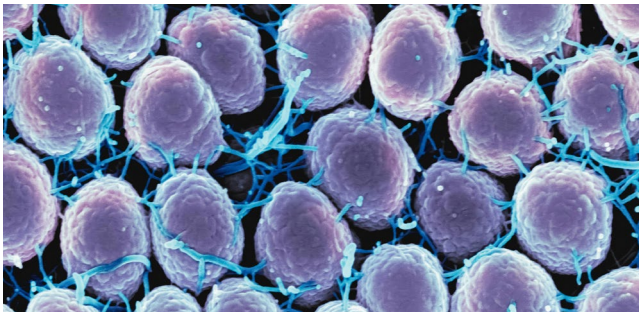
PATHOGEN

Neisseria gonorrhoeae



Overview

Neisseria gonorrhoeae is a Gram-negative diplococcus that causes approximately 86 million new infections each year.[1] Those most at risk include men who have sex with men, sex workers, transgender women and adolescents and young people in high-burden countries. Untreated gonorrhea can result in pelvic inflammatory disease, infertility, ectopic pregnancy, and potentially blindness in the baby if the infection is passed during delivery. It is associated with enhanced HIV acquisition.[2]

Natural infection fails to elicit protective immunity against subsequent infections, and repeat infections are common.[3] In many countries, AMR is a significant and growing concern, and the potential for gonorrhoeae to become untreatable has led to increased urgency to find preventive options.[4] While no licensed vaccine exists, data suggest that meningococcal serogroup B vaccines may induce cross-protection5 (~ 30-40% effectiveness with 4CMenB vaccine), and similar formulations using outer membrane vesicles from *N. gonnorrhoeae* are being explored.

Potential Role for Mucosal Immunity

N. gonorrhoeae is primarily transmitted through sexual contact and infects the mucosal epithelium of the genital tract, rectum, and oropharynx. It initiates infection at mucosal surfaces and exhibits a marked capacity to suppress both innate and adaptive immune responses, including inhibition of antigen presentation and induction of IL-105. The infection is usually localised (though untreated infections can ascend to the upper genital tract), suggesting mucosal antibody and T cell responses may be necessary for protection.[6]

While some vaccine approaches have focused on systemic vaccination and systemic responses, the importance of mucosal immunity is increasingly recognised, though there are no established mucosal correlates of immunity.[7] There is an extremely limited product pipeline, with the sole candidate, a fast-tracked Ph2 vaccine, recently halted. Strategies to elicit local antibodies and tissue-resident Th17/Th1 cells, especially via mucosal delivery or adjuvants, could be critical for effective protection.[6] A controlled urethral infection model of gonorrhea in men has been used to study pathogenesis and immunity.[8]

Pathogen Dashboard

Neisseria gonorrhoeae

STRATEGIC INDICATORS	BARRIERS TO DEVELOPMENT				
NEED	KNOWLEDGE GAPS		VACCINE DEVELOPMENT LANDSCAPE		
	PATHOGEN TARGETS	MUCOSAL MECHANISMS & COPS	VACCINE PIPELINE	MUCOSAL VACCINE PIPELINE	CHIM AVAILABILITY
ANNUAL MORTALITY **400**	MODERATE	HIGH	HIGH	HIGH	MODERATE
ANNUAL INCIDENT CASES **86,000,000**	Some knowledge of potential pathogen targets	Significant knowledge gaps in mucosal mechanisms and correlates of protection	Sparse vaccine pipeline	Limited vaccine pipeline of mucosally delivered products	CHIM in men only
DALYS **100,000**					

Gaps in understanding / progress: High Fairly High Moderate Fairly Low Low

Vaccine Pipeline

*Fast track designation from the US FDA

Mucosal product or mucosal effect

DELIVERY ROUTE		VACCINE TYPE	
Parenteral	Purple text: Adjuvanted*	Subunit	DNA
Oral	✔ WHO-prequalified	Conjugate	RNA
Patch	⊘ Discontinued	Live-attenuated	Replicating viral vector
Intranasal	Ⓜ Mucosal immunity effect in humans indicated in the literature	Inactivated	Non-replicating viral vector
Aerosol	*Aluminium Hydroxide (AH) Aluminium Phosphate (AP) Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)	Not classified	

Recommendations

Expand the toolkit

- **Standardise sampling and functional assays.** Implement harmonised genital and extragenital mucosal sampling protocols, standardise and qualify assays to precisely quantitate antibody titers, and further develop qualified functional antibody assays predictive of pathogen clearance, including serum bactericidal assays. Integrate these assays as endpoints into early-phase trials of current candidates such as Bexsero and OMV-based vaccines to enable direct comparison of mucosal immunogenicity.

Strengthen the evidence base

- **Investigate prime-boost strategies.** Explore combining systemic priming with mucosal boosting to promote transudated systemic antibody and local T cell responses. Examine the impact on mucosal imprinting and tissue-resident memory cell generation.
- **Expand controlled human infection and urethritis models.** Enhance the capacity and utility of CHIMs beyond the male urethra to include female and extragenital sites. Further develop the urethritis model in men to evaluate mucosal immunity and vaccine protection. Use these models to assess mucosal response specificity, quality and durability, including comparisons of Bexsero and OMV-based candidates.

Improve foundational understanding

- **Advance use of mucosa-directed adjuvants and delivery platforms.** Support development of mucosa-compatible adjuvants (e.g., TLR agonists, IL-12 analogues) with mucosal delivery routes (e.g., intranasal, intravaginal, or rectal). Evaluate capacity to recruit genital tract-resident T cells and promote mucosal IgA.
- **Explore longitudinal mucosal immunology.** Leverage the accessibility of the female genital tract for biopsy and sampling. Study prime-pull strategies, antibody transudation kinetics, and temporal evolution of mucosal immunity—including lessons from HIV AMP trials.

Continued on following page

Accelerate vaccine development

- **Interrogate microbiome, hormonal, and environmental influences on vaccine efficacy.** Investigate how vaginal microbiota, hormonal variation, and baseline inflammation affect mucosal immune responses, including vaccine responses. Incorporate these factors into trial design and stratification, particularly in populations with high disease burden.
- **Explore longitudinal mucosal samples** to identify correlates of clearance and translate these findings into next-generation immunogen design, vaccine delivery, and immunogenicity assays.

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Appendix B

Methodology

Methodology

This project utilised a multi-pronged methodology to assess the global state of mucosal vaccine development across 16 pathogens. The approach integrated a structured literature review, engagement with expert stakeholders and pathogen-specific analyses to provide an actionable evidence base to inform research and investment decisions in mucosal immunity.

1. Literature Review Approach

The literature review was conducted through three independent but interlinked evidence searches targeting:

- **Licensed vaccines:** Licensed human vaccines given parenterally and mucosally for protection against respiratory, enteric and genitourinary pathogens.
- **Pipeline vaccines:** The pipeline of vaccines targeting protection against human mucosal pathogens (from Ph 1 through marketed products, informed by data from human and advanced animal challenge models) in development, including their immunological and clinical outcomes and safety profiles.
- **Exploratory adjuvants:** The pipeline of exploratory adjuvants in development for human mucosal vaccines targeting respiratory, enteric and genitourinary pathogens, including the immunological and clinical outcomes and safety profile.

Searches were conducted December - April 2025, and followed PRISMA-aligned protocols, with tailored inclusion criteria and search strategies. Databases searched included PubMed, MEDLINE, Embase, Ovid, ScienceDirect, and medRxiv. Grey literature and publicly available sources (e.g., WHO databases, ClinicalTrials.gov, developer websites, press releases, and dashboards) were also systematically reviewed.

Each review used a standardised screening process; duplicates were removed before a two-phase search strategy was performed.

1. The eligibility of the title and abstract of every article was initially screened against the inclusion/ exclusion criteria. Studies with uncertain suitability were maintained at this stage of the search; a final decision was reached at the next phase to ensure that all relevant data were obtained.
2. Full articles were retrieved and assessed against the eligibility criteria. Additional articles were identified through hand searches and reference reviews, and the same process as above was followed.

Where vaccine pipelines were extensive (e.g., influenza, SARS-CoV-2), all mucosal candidates and a representative sample of parenteral ones were included. For underrepresented pathogens (e.g., group A streptococcus), high-potential preclinical candidates were added to ensure breadth.

Data were extracted and compiled into structured comparative tables. These data formed the empirical foundation for further synthesis and analysis. These reviews were complemented by expert interviews and targeted grey literature assessments (e.g., WHO, CDC, manufacturer websites). Specific details related to each of the three searches are detailed below.

1a. Review of Licensed Vaccines and Mucosal Immunity

Objective: To gain an understanding of the extent to which currently-licensed human vaccines for protection against respiratory, enteric, and genitourinary pathogens induce mucosal immunity, including a summary of the composition and kinetics of the mucosal response and its contribution toward vaccine efficacy and long-term protection.

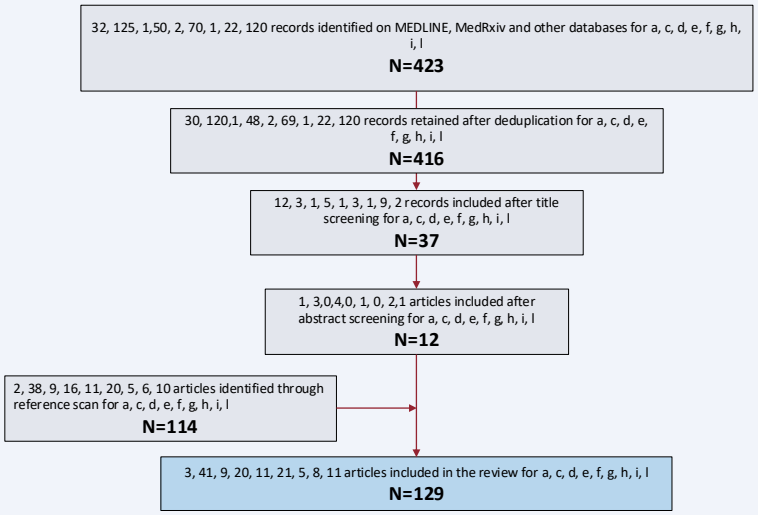
Representative Search Terms: (intradermal OR intranasal OR intramuscular) AND (human) AND (influenza OR measles OR SARS-CoV-2) AND (vaccine*) AND (mucosal*) AND (immune*)

The results from the published and pre-print literature were combined. An initial screening of all titles was performed to assess article relevance and exclude articles not relevant to the scope of the search. The full text review was performed for all published articles and pre-print articles identified as relevant, and key information was extracted and recorded in the table below.

Candidate vaccines for the following pathogens were studied:

- ***Respiratory:*** *Mycobacterium tuberculosis* (a); GAS (b); influenza (c); measles (d); SARS-CoV-2 (e); *S. pneumonia* (f)
- ***Enteric:*** *Vibrio cholerae* (g); Salmonella spp. (h); rotavirus (i); *Shigella* spp. (j)
- ***Genitourinary:*** HIV (k); HPV (l); NG (m); *Chlamydia trachomatis* (n); GBS (o); HSV (p)

Flow Diagram: Licensed Vaccines



Variables for the summary tables included:

- Pathogen
- Licenced vaccine / brand name / developer organisation / route of administration
- Type of vaccine / dose and schedule / adjuvant (if any)
- Composition and kinetics of the mucosal response (with sampling technique and assays mentioned where available)
- Contribution of mucosal response to vaccine efficacy and long-term protection

1b. Review of Vaccine Candidates in Clinical Development

Objective: To provide an overview of the clinical outcomes and immunological and safety profile of vaccine candidates in Phase I-III clinical trials for in-scope respiratory, enteric and genitourinary pathogens.

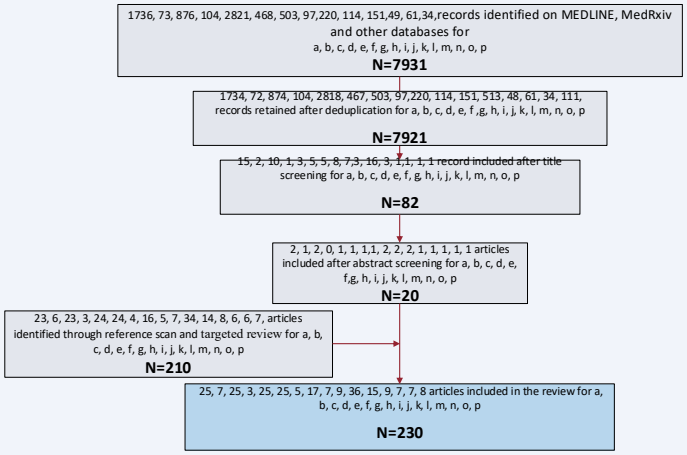
Representative Search Terms: (TB-specific): (human*[Title/Abstract]) AND (Mycobacterium tuberculosis*[Title/Abstract] OR (tuberculosis*[Title/Abstract] OR (TB[Title/Abstract]) AND (vaccin*[Title/Abstract]) AND (candidate*[Title/Abstract])

The full text review was performed for all published articles, pre-print and targeted review articles identified as relevant and key information was extracted and recorded in the document on the clinical, immunological and safety profile of prophylactic vaccine candidates in Phase I-III clinical trials (final document). If there were no recent reports of development identified for the vaccine candidates by targeted review, then they were not included in the final document. As the pipeline of candidates in Phase I-III trials was really large for Influenza and SARS-CoV-2, all candidates with mucosal administration and a representative sample of other candidates were included in the final document. If there are very limited candidates in clinical research (as seen for GAS), then the main preclinical vaccines were included.

Candidate vaccines for the following pathogens were studied:

- ***Respiratory:*** *Mycobacterium tuberculosis* (a); GAS (b); influenza (c); measles (d); SARS-CoV-2 (e); *S. pneumonia* (f)
- ***Enteric:*** *Vibrio cholerae* (g); Salmonella spp. (h); rotavirus (i); *Shigella* spp. (j)
- ***Genitourinary:*** HIV (k); HPV (l); NG (m); *Chlamydia trachomatis* (n); GBS (o); HSV (p)

Flow Diagram: Pipeline of Vaccines (GU, GI, Respiratory)



Variables for the summary tables included:

- Vaccine candidate, including vaccine platform and adjuvant information (where applicable)
- Developer organisation/s
- Phase of clinical research
- Route of administration
- Clinical outcomes
- Immunological outcomes
- Safety profile

1c. Review of Adjuvants Used in Mucosal Vaccines

Objective: Summarise adjuvants used in mucosal vaccine candidates, with a focus on safety, mucosal targeting, and immunopotentiation.

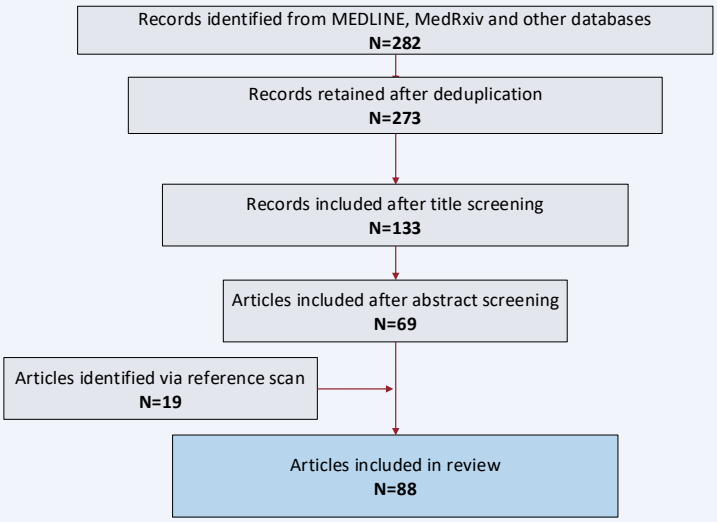
Approach:

- Literature and product review for mucosal vaccine formulations with adjuvants
- Targeted search of adjuvants (e.g., cholera toxin B subunit (CTB), MF59, MPLA, Poly(I:C), CpG)
- Sources included scientific literature, manufacturer pipelines, and clinical trial registries.

Search Terms: (adjuvant*[Title/Abstract]) AND ("mucosal*"[Title/Abstract]) AND (vaccin*[Title/Abstract]) AND ("clinical research*"[Title/Abstract] OR "clinical trial*"[Title/Abstract] OR "clinical stud*"[Title/Abstract] OR "non-human primate*"[Title/Abstract] OR "nonhuman primate*"[Title/Abstract] OR "NHP")

The results from the published and pre-print literature were combined. An initial screening of all titles was performed to assess article relevance and exclude articles not relevant to the scope of the search. The full text review was performed for all published articles and pre-print articles identified as relevant, and key information was extracted and recorded in the table below.

Flow Diagram: Adjuvants



Adjuvants/delivery systems included:

- Bacterial toxins and their derivatives
- TLR ligands
- Lipid-based or lipid-containing
- Nanoparticles and microparticles
- Others

Variables for the summary tables included adjuvant, phases of trials, population, mode of administration, doses, vaccines used, clinical outcomes, immunological outcomes and safety profile.

2. Key Opinion Leader (KOL) Engagement

To complement and contextualise our research, the team engaged over two dozen global experts through virtual and in-person consultation.

Expert Interviews: A total of 18 semi-structured virtual interviews were conducted with specialists in mucosal immunology, vaccine development, clinical trial design, adjuvant research, regulatory science, and delivery platforms. Questions were tailored to each domain and circulated in advance to the experts to encourage depth. Interviews were recorded, transcribed, and analysed for key insights, themes, and areas of divergence.

In-Person Expert Meeting: An in-person consultation was held on May 6–7, 2025, at the Wellcome Trust offices in London. The meeting brought together global scientific leaders to:

- Validate preliminary findings from literature and interviews
- Identify critical scientific and translational bottlenecks
- Develop consensus on key investment opportunities and research directions
- Provide input into pathogen-specific prioritisation

Facilitated sessions included presentations, panel discussions, and structured working groups organised by pathogen class (respiratory, enteric, genitourinary). Outputs from this meeting were critical in shaping the final analysis and recommendations.

3. Pathogen-Specific Analysis

Building on the literature review and expert engagement, a structured process was developed to synthesise findings for each of the 16 target pathogens:

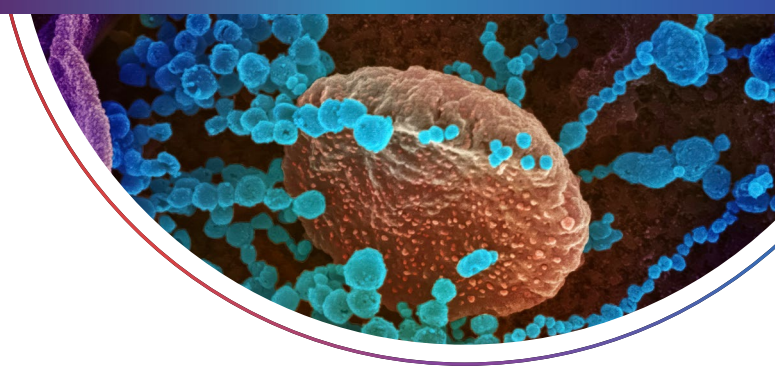
1. **Evidence Compilation:** Literature and recent reviews were consulted to extract relevant data on vaccine development, mucosal immunity, and scientific barriers for each pathogen.
2. **Snapshot Development:** For each pathogen, a standardised "snapshot" was created summarising pathogenesis, global burden, development pipeline, and innovation highlights.
3. **Dashboard Creation:** Findings were compiled into a cross-pathogen dashboard to enable comparative analysis across multiple metrics, including medical need, knowledge gaps and vaccine development landscape (see 'Scoring System' for details).
4. **Expert Review:** Draft snapshots were reviewed internally and validated by domain experts. Feedback was used to refine the snapshots and prioritise investment and research recommendations tailored to the needs and opportunities associated with each pathogen.

4. Use of AI Tools

AI was employed strategically to enhance the speed, consistency, and depth of insight generation, particularly for analysing qualitative inputs from expert interviews and discussions. Specific elements of NFA's approach to AI utilisation include:

- **Corpus Development:** Full transcripts of all KOL interviews and meetings were collected. These were summarised using AI-powered Natural Language Processing tools and reviewed by the project team for accuracy. Human-edited summaries were fed back into the corpus, enriching the dataset and enabling structured querying.
- **Model Training:** The AI model was trained on this enriched dataset to develop fluency in domain-specific language and concepts. This allowed the model to recognise patterns, recurring ideas, and relationships unique to mucosal immunology and vaccine development.
- **Insight Extraction:** The AI system conducted thematic analysis across the corpus, categorising information into themes. Outputs included both raw insight clusters and a consensus map identifying areas of broad agreement or divergence among experts. AI insights were considered as drafts and heavily reviewed and modified as appropriate. In addition, it should be noted that the vast majority of insights were human-initiated, from KOL/EAG commentary and/or NFA experience in concert with Wellcome and NNF discussion.
- **AI Notebook:** A custom AI notebook interface was developed to enable the team to query the corpus and retrieve structured, traceable responses to targeted questions. Four notebooks were developed: Respiratory pathogens, GI pathogens, GU pathogens and KOL feedback. The system included:
  - **Accuracy guardrails:** Human oversight at all output stages
  - **Traceability:** Each AI-generated insight was linked to source transcripts
  - **Domain alignment:** Outputs were reviewed to ensure contextual relevance

This AI-enhanced process enabled rapid synthesis across dozens of hours of expert engagement, significantly accelerating thematic distillation and reducing the risk of oversight.



Cross-Pathogen Heat Map

PATHOGENS	STRATEGIC INDICATORS				VACCINE DEVELOPMENT BARRIERS				
	MEDICAL NEED				KNOWLEDGE GAPS		VACCINE DEVELOPMENT LANDSCAPE		
	Annual Global Mortality	Annual Incident Cases	Disability Adjusted Life Years	Licensed Vaccine	Gaps in understanding of Pathogen Targets	Gaps in understanding of Mucosal Immunity	Vaccine Pipeline: Volume and maturity	Mucosally delivered vaccines and candidates	CHIM Availability
Group A Streptococcus									
Influenza virus									
Measles virus									
Mycobacterium tuberculosis									
SARS-COV-2									
Streptococcus pneumoniae									
Vibrio cholerae									
Rotavirus									
Typhoidal Salmonella									
Non-Typhoidal Salmonella									
Shigella spp.									
Chlamydia trachomatis									
Group B Streptococcus									
HIV									
HPV									
HSV									
Neisseria gonorrhoeae									

Scoring System

	CRITERIA	DEFINITION	SCORE	SCORING SYSTEM
STRATEGIC INDICATORS	**Mortality**	Total annual deaths were estimated using data from the IHME Global Burden of Disease (GBD) 2021 study; supplemented with earlier data or WHO sources where necessary.	HIGH	>500K
			FAIRLY HIGH	250 - 500K
			MODERATE	100 - 249K
			FAIRLY LOW	50 - 99K
			LOW	0 - 50K
	Incident Cases	Total annual incident cases (millions) were estimated using IHME GBD 2021 data, supplemented with earlier data or WHO sources where necessary.	HIGH	>100M
			FAIRLY HIGH	10 - 100M
			MODERATE	5 - 9.9M
			FAIRLY LOW	.5 - 4.9M
			LOW	0 - .49M
	Morbidity	Total annual disability-adjusted life years (DALYs, in millions) were used to reflect overall disease burden. Data were primarily drawn from IHME GBD 2021, and supplemented with earlier data or WHO sources where necessary.	HIGH	>35M
			FAIRLY HIGH	10 - 34.9M
			MODERATE	5 - 9.9M
			FAIRLY LOW	.5 - 4.9M
			LOW	0 - .49M
	Licensed Vaccines	Availability of preventive licensed vaccines. Vaccines were qualitatively evaluated based on efficacy and durability. Regional and population-specific variability was considered.	HIGH	NO VACCINE
			MODERATE	MODERATELY PROTECTIVE
			LOW	HIGHLY PROTECTIVE
VACCINE DEVELOPMENT BARRIERS	**Understanding of Pathogen Targets**	**Vaccine-induced immunity:** Evaluation was based on a review of the published literature and expert input, and considered the extent to which immune responses elicited by vaccination (systemic and mucosal) have been defined and correlated with protection in human populations.	SIGNIFICANT KNOWLEDGE GAPS	Each category ranked on a three point scale and scores averaged.
			SOME KNOWLEDGE GAPS	
			GOOD UNDERSTANDING	
		Natural immunity: Evaluation was based on a review of the published literature and expert input, and considered the extent to which immune responses following natural infection have been characterized and linked to reduced susceptibility or disease severity in humans.	SIGNIFICANT KNOWLEDGE GAPS	
			SOME KNOWLEDGE GAPS	
			GOOD UNDERSTANDING	
	Understanding of Mucosal Immunity	**Mucosal mechanisms of protection:** Based on a review of the published literature and expert input, and considered the extent to which key protective mechanisms (e.g., local antibody responses, cellular immunity, and mucosal barrier function) have been defined and linked to protection in humans.	SIGNIFICANT KNOWLEDGE GAPS	Each category ranked on a three point scale and scores averaged.
			SOME KNOWLEDGE GAPS	
			GOOD UNDERSTANDING	
		Mucosal correlates of protection: Based on a review of the published literature and expert input, and considered the extent which specific mucosal immunologic markers (e.g., antibody titers, cellular responses, or other biomarkers) have been identified and validated as correlates of protection against infection or disease in humans.	SIGNIFICANT KNOWLEDGE GAPS	
			SOME KNOWLEDGE GAPS	
			GOOD UNDERSTANDING	
	Pipeline Robustness	Assessment was based on a count of vaccine candidates across the development lifecycle, which was weighted by age (Ph1, Ph2, Ph3, licensed) with later-stage candidates weighted more heavily, to evaluate the depth and maturity of research efforts.	SPARSE	1 – 5
			LIMITED	6 – 20
			MODERATE	21 – 40
			ROBUST	41 – 80
			VERY ROBUST (OUTLIERS)	> 80
	Mucosal Candidates	Assessment was based on a count of candidates delivered via mucosal routes. Candidates were weighted by stage (Ph1, Ph2, Ph3, licensed) with later-stage candidates weighted more heavily, to evaluate the depth and maturity of research efforts.	NONE	0.00
			LIMITED	1 - 2
			MODERATE	3 - 6
			ROBUST	7 - 20
			VERY ROBUST (OUTLIERS)	> 20
	CHIM	Controlled human infection model availability was assessed using a three-point scale based on literature review and expert input.	NO CHIM	Qualitative assessment
			CHIM IN DEVELOPMENT AND/OR PROXY AVAILABLE	
			CHIM IN USE	

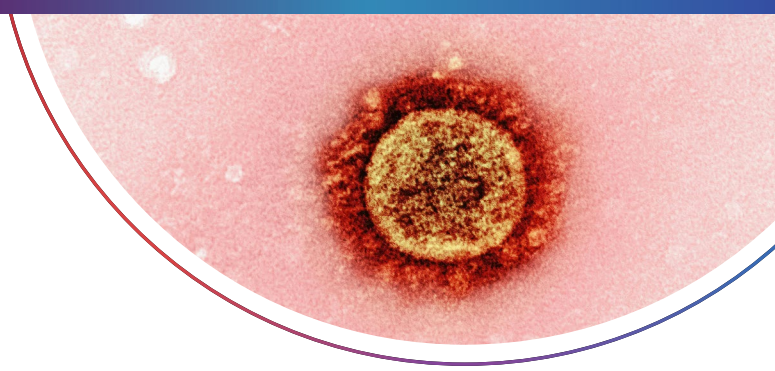


Photo Credits

Cover: Human macrophage rupturing after infection with *Chlamydia*. David Goulding, Wellcome Trust Sanger Institute. Source: Wellcome Collection

Page 13: *Neisseria gonorrhoeae* bacteria. Captured by the Research Technologies Branch (RTB) at the NIAID Rocky Mountain Laboratories (RML) in Hamilton, Montana. NIAID https://www.flickr.com/photos/niaid/53412697049/

Page 18: Electron micrograph of HIV-1 virus particles (colorized red) replicating from an HIV-infected H9 T-cell (blue). Image captured at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. NIAID. https://www.flickr.com/photos/niaid/52955756878/

Page 21: Colorized scanning electron micrograph of an apoptotic cell (blue) heavily infected with SARS-COV-2 virus particles (yellow), isolated from a patient sample. Image captured and color-enhanced at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. NIAID. https://www.flickr.com/photos/niaid/49680384281/

Page 22: SEM of *Streptococcus pneumoniae* colony. Source: Debbie Marshall / Wellcome Collection.

Page 29: Color-enhanced scanning electron micrograph showing *Salmonella Typhimurium* (red) invading cultured human cells. Rocky Mountain Laboratories, NIAID. https://commons.wikimedia.org/wiki/File:SalmonellaNIAID.jpg

Page 36: Florid human papillomavirus (HPV) infection of the ectocervix. Source: Wellcome Collection

Page 45: Electron microscope image shows SARS-CoV-2 (round gold particles) emerging from the surface of a cell cultured in the lab. Image captured and colorized at Rocky Mountain Laboratories in Hamilton, Montana. Credit: NIAID. https://www.flickr.com/photos/niaid/51269160975/

Page 62: Colorized scanning electron micrograph of Group A Streptococcus (*Streptococcus pyogenes*) bacteria (yellow) and a human neutrophil (blue). NIAID. https://www.flickr.com/photos/niaid/52602981880/

Page 65: Digitally-colorized, negative-stained transmission electron microscopic (TEM) image depicted a number of Influenza A virions. Centers for Disease Control and Prevention (CDC). https://phil.cdc.gov/

Page 69: Colorized transmission electron micrograph of a measles virus particle (red). Credit: Microscopy by CDC; layout, colorization and visual effects by NIAID. https://www.flickr.com/photos/niaid/53588626082/

Page 73: Electron micrograph of *Mycobacterium tuberculosis* particles (colorized pink). NIAID. https://www.flickr.com/photos/niaid/52765697672/

Page 77: Electron micrograph of SARS-CoV-2 virus particles (teal) within endosomes of a heavily infected nasal olfactory epithelial cell. Image captured at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. NIAID. https://www.flickr.com/photos/niaid/51484223894/

Page 81: SEM of *Streptococcus pneumoniae colony*. Debbie Marshall. Source: Wellcome Collection.

Page 81: *Vibrio cholerae*. nobeastsofierce / Adobe Stock

Page 89: Rotavirus. CDC/ Dr. Erskine L. Palmer. Centers for Disease Control and Prevention (CDC). https://phil.cdc.gov/

Page 89: Salmonella enterica serovar *Typhi* flagellar stain. Microbewriter. CC BY-SA 4.0.

Page 97: Color-enhanced scanning electron micrograph showing *Salmonella Typhimurium* (red) invading cultured human cells. Rocky Mountain Laboratories, NIAID. https://commons.wikimedia.org/wiki/File:SalmonellaNIAID.jpg

Page 101: *Shigella flexneri* invading embryonic stem cell. David Goulding, Wellcome Trust Sanger Institute. Source: Wellcome Collection.

Page 108: *Streptococcus agalactiae* gram stain. Centers for Disease Control and Prevention (CDC). https://phil.cdc.gov/

Page 111: Colorized transmission electron micrograph of numerous HIV-1 virus particles (blue) replicating from a segment of a chronically infected H9 T cell (red). Image captured at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. NIAID. https://www.flickr.com/photos/niaid/52532878449/

Page 117: Human Papillomavirus (HPV). Colorized electron micrograph of HPV virus particles (magenta) harvested and purified from cell culture supernatant. Captured at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. NIAID. https://www.flickr.com/photos/niaid/53511251469/

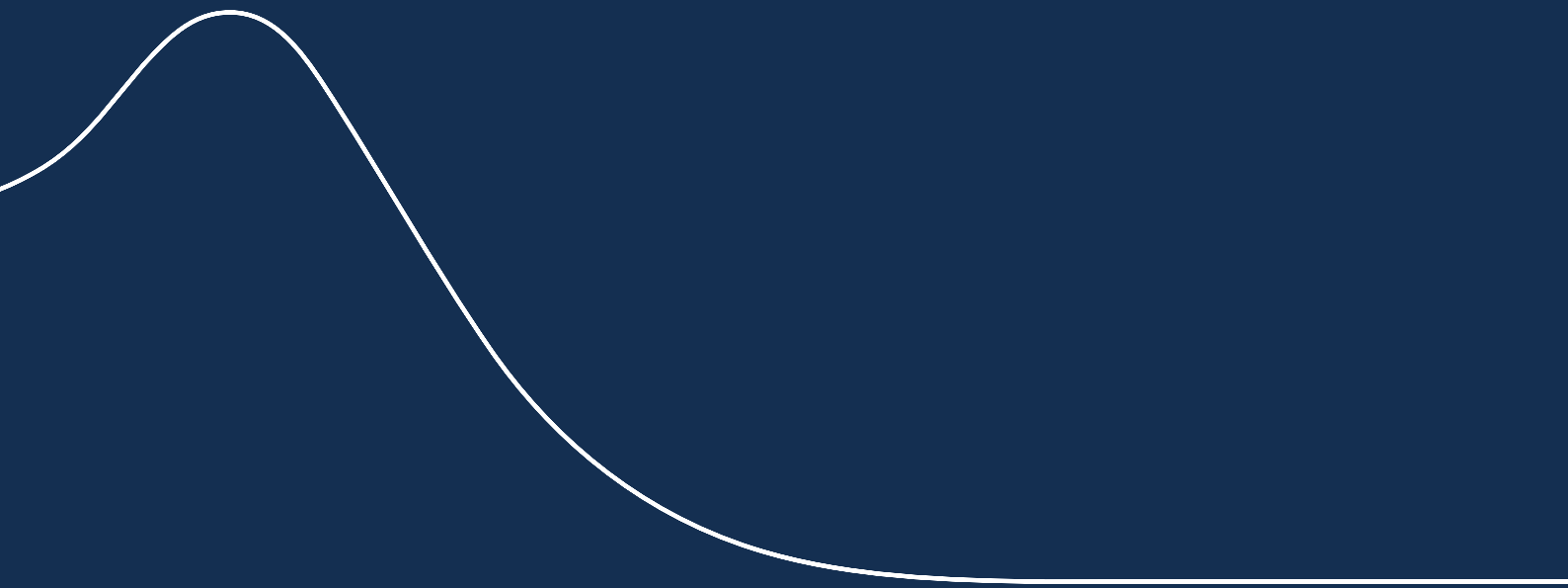
Page 121: Herpes simplex virus infection. Wellcome Collection. Source: Wellcome Collection. Licence: CC0 1.0 Universal.

Page 124: *Neisseria gonorrhoeae* bacteria. Captured by the Research Technologies Branch (RTB) at the NIAID Rocky Mountain Laboratories (RML) in Hamilton, Montana. NIAID https://www.flickr.com/photos/niaid/53412697049/

Page 128: Electron microscope image of Group A Streptococcus (orange) during phagocytic interaction with a human neutrophil (teal). NIAID. https://www.flickr.com/photos/niaid/52606801786/

Page 133: Electron microscope image shows SARS-CoV-2 (round blue objects) emerging from the surface of cells cultured in the lab. Image captured and colorized at NIAID's Rocky Mountain Laboratories (RML) in Hamilton, Montana. NIAID. https://www.flickr.com/photos/niaid/49557550751/

Page 134: Electron micrograph of a SARS-CoV-2 virus particle (UK B.1.1.7 variant), isolated from a patient sample and cultivated in cell culture. Image captured at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. NIAID. https://www.flickr.com/photos/niaid/50997709387/



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