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Unmasking the potential of secretory IgA and its pivotal role in protection from respiratory viruses

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ABSTRACT

Mucosal immunity has regained its spotlight amidst the ongoing Coronavirus disease 19 (COVID-19) pandemic, with numerous studies highlighting the crucial role of mucosal secretory IgA (SIgA) in protection against Severe acute respiratory syndrome coronavirus-2 or SARS-CoV-2 infections. The observed limitations in the efficacy of currently authorized COVID-19 vaccines in inducing effective mucosal immune responses remind us of the limitations of systemic vaccination in promoting protective mucosal immunity. This resurgence of interest has motivated the development of vaccine platforms capable of enhancing mucosal responses, specifically the SIgA response, and the development of IgA-based therapeutics. Recognizing viral respiratory infections as a global threat, we would like to comprehensively review the existing knowledge on mucosal immunity, with a particular emphasis on SIgA, in the context of SARS-CoV-2, influenza, and Respiratory Syncytial Virus (RSV) infections. This review aims to describe the structural and functional specificities of SIgA, along with its nuanced role in combating influenza, RSV, and SARS-CoV-2 infections. Subsequent sections further elaborate promising vaccine strategies, including mucosal vaccines against Influenza, RSV, and SARS-CoV-2 respiratory viruses, currently undergoing preclinical and clinical development. Additionally, we address the challenges associated with mucosal vaccine development, concluding with a discussion on IgA-based therapeutics as a promising platform for the treatment of viral respiratory infections. This comprehensive review not only synthesizes current insights into mucosal immunity but also identifies critical knowledge gaps, strengthening the way for further advancements in our current understanding and approaches to combat respiratory viral threats.

1. Introduction

In the ever-evolving landscape of infectious diseases, respiratory viruses constantly mutate, challenging current vaccination strategies. The global impact of the COVID-19 pandemic not only reshaped public health policies but also called for a reevaluation of vaccine development and approval processes. A significant outcome was the documented shift in the circulation of respiratory viruses like influenza and RSV. This prompted a dynamic change in our perception of respiratory viruses and emphasized the need to investigate vaccination strategies and better

prepare us for future pandemics to previously evolved or newly emerging pathogens.

Despite widespread vaccination efforts against SARS-CoV-2 infections, the emergence of breakthrough infections directs us to consider the limitations of current systemic vaccination route and focus our efforts to other vaccination strategies. Mucosal vaccination comes at the forefront of this new perspective and directs us to reanalysis the role of mucosal immunity in protection from respiratory infections. Current systemic vaccines, whilst effective against the disease, raise questions about their ability to generate sufficient mucosal immune responses involved in protection against viral respiratory infection and

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Abbreviations

SIgA	Secretory IgA
RSV	Respiratory Syncytial Virus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
GALT	Gut-Associated Lymphoid Tissue
NALT	Nasopharynx-Associated Lymphoid Tissue
BALT	Bronchus-Associated Lymphoid Tissue
MALT	Mucosal-Associated Lymphoid Tissue
HIV	Human Immunodeficiency Virus
SIgAD	Selective IgA Deficiency
SC	Secretory Component

M-cells	Microfold cells
HAI	Hemagglutinin Inhibition Assay
pIgR	Polymeric Ig Receptor
HA	Hemagglutinin
NA	Neuraminidase
COVID-19	Coronavirus Disease 2019
RBD	Receptor Binding Domain
ACE2	Angiotensin-Converting Enzyme
S-protein	Spike-Protein
LAIV	Live Attenuated Influenza vaccine
ASC	Antibody Secreting Cells

transmission. This review aims to address some important questions: Why is mucosal immunity crucial? Can conventional systemic vaccines adequately generate sufficient mucosal immune responses to protect against SARS-CoV-2, RSV and influenza infections? Do mucosal vaccines offer superior immune responses compared to systemic routes? In exploring these questions, this review will focus on the role of SIgA, a key molecule in mucosal immunity. While SIgA's significance in the Gut-Associated Lymphoid Tissue (GALT) is well-documented, its role in the respiratory tract remains less explored. Does SIgA play a protective role in preventing influenza, RSV and SARS-CoV-2 infections? Can vaccine strategies, including those inducing SIgA responses, enhance protection and help reduce or block viral transmission?

This review aims to fill the gaps in our current understanding of mucosal immunity, focusing on SIgA's structure, isoforms/subclasses, and its critical role in safeguarding against infections caused by SARS-CoV-2, RSV, and influenza viruses. By examining the potential of mucosal vaccines and IgA-based therapeutics, this review will help gain insights into improving protection against these respiratory viruses.

1.1. The fate of respiratory viruses

Respiratory viruses are the leading culprits behind human diseases, causing a substantial burden on global health. Common viruses causing respiratory infections are influenza viruses, parainfluenza virus, coronaviruses, RSV, metapneumovirus, adenovirus, rhinovirus and bocavirus. These are frequently encountered respiratory viruses and are well adapted for person-to-person transmission (Boncrisiani et al., 2009).

Acute respiratory infections (ARIs) are reportedly linked to one-fifth of all childhood deaths worldwide (Boncrisiani et al., 2009). Many frequently encountered respiratory viruses typically lead to minor cold and occasional hindrance in day to day activities. However, in infants, pregnant women, elderly and immunocompromised patients, these viruses can lead to severe disease related outcomes, including death. Given their ability to transmit through the respiratory system, newly emerging pathogens have the potential to spread on a global scale. Additionally, the recent COVID-19 pandemic has highlighted the long term symptomatic effects associated with SARS-CoV-2 infections, several months post-recovery (Davis et al., 2023). This is also well established for other respiratory viruses such as influenza viruses (Chen et al., 2017) and RSV (Fauroux et al., 2017) where long-term changes within the lung pathology, affecting several respiratory functions, have been well documented.

The World Health Organization (WHO) recently published an epidemiological alert which reported an increased circulation of respiratory viruses and cases of infection in the southern hemisphere along with a shift in the seasonal pattern of respiratory viruses (Meslé et al., 2023). This shift could be a direct consequence of the recent emergence of COVID-19 which impacted human hygiene practices, limited travel within and outside countries, restricted public and private gatherings, as well as the closure of schools and work places. This consequentially

lowered human to human viral transmission and contributed to the changes in the circulation of other respiratory viruses (Garg et al., 2022).

One such example was witnessed with the recent surge of RSV in 2022. After being undetectable in the circulation for the previous 2 years, RSV infections overwhelmed hospitals across the US and Europe with increased hospitalization rates for infants, particularly under the age of 2 and elderly above the age of 65 (Havers et al., 2023; Munkstrup et al., 2023). Some possible explanations for this surge might be related to the waning immunity in the vulnerable population due to the lack of RSV exposure during the COVID-19 pandemic, (Abu-Raya et al., 2023) whilst some other studies explored the additive effects on RSV virulence due to the possible interactions in hosts infected with both SARS-CoV-2 and RSV concurrently, a phenomenon known as co-infections (Kahanowitch et al., 2022; Li et al., 2021; Swets et al., 2022). This however, is not the only instance where RSV circulation has been impacted, due to other respiratory infection surges. A similar trend was witnessed in 2009, during the influenza pandemic, which delayed the seasonal RSV infection by roughly 3 months (Li et al., 2021).

This impact of COVID-19 on the epidemiology is not simply limited to RSV but has also affected the illness severity induced by influenza viruses in children under the age of 4 and population aged greater than 55 years of age. In addition, the circulation pattern of influenza viruses has also changed following SARS-CoV-2 infection waves. Unexpected surges in influenza were reported in unusual months across the globe (Lee et al., 2022).

Given respiratory viruses mainly use the respiratory epithelium and less commonly other mucosal routes (oral, conjunctival), their respiratory transmission makes mucosal immunity an essential first line of defense (Killingley and Nguyen-Van-Tam, 2013; Kutter et al., 2018). Understanding the role of mucosal immunity in protection against seasonal and emerging respiratory viral infections is crucial to develop the best intervention strategies to fight such viruses.

2. Mucosal immunity

The concept of "Common Mucosal System" or CMS was initially described in the early 1970's by Bienenstock. The author focused on the concept, that IgA arising at mucosal surfaces and the IgA extracted from the plasma must have a common "Pre-excretory" pool and must arise from an interconnected network of trafficking immune cells within the gut mucosa and Bronchial Associated Lymphoid tissue (BALT) (Bienenstock et al., 1974). For 50 years, several studies have further characterized this complex network that together makes up the largest mammalian lymphoid organ system called the Mucosal Associated Lymphoid Tissues or MALT (Bienenstock and Befus, 1980).

MALT consist of distinct lymphoid aggregates, including where the immune response is initiated, called the inductor sites. These sites, involve a network of mesenteric lymph nodes for communication at the systemic level. Another site, called the effector sites, occurs all across mucosa such as lamina propria of respiratory, gastrointestinal and

genitourinary tracts where IgA is also secreted as a potential defense molecule (Cesta, 2006; McGhee and Fujihashi, 2012).

2.1. Systemic and secretory IgA

A crucial part of immune response at mucosal surfaces is mediated by IgA. IgA production is the highest in humans and most mammalian bodies (Corthesy, 2013) compared to other immunoglobulins and is the second most dominant antibody after IgG in the serum (Patel and Jialal, 2023).

Two subclasses of IgA, IgA1 and IgA2, have been described in humans (Corthesy, 2013). In humans, IgA1 consist of a longer hinge region that can be recognized by specific bacterial proteases (Abokor et al., 2021) and is absent in IgA2, making it resistant to some bacterial proteases (Kilian et al., 1996).

The differential structure between secretory IgA at mucosal surfaces and IgA in serum has been revealed in a breakthrough study, by P. Brandtzaeg in 1973. Mainly dimeric (and some polymeric) forms of secretory IgA are present in mucosa instead of the monomeric forms mostly found in the sera (Brandtzaeg, 1973).

Secretory IgA is composed of two monomeric forms of IgA with a secretory component (SC) bound to IgA through a J chain (Li et al., 2020). This dimeric (polymeric) structure enhances its ability to bind to a larger repertoire of antigens and presumably enhancing antigen cross-linking capacity as well as its binding avidity (Kumar Bharathkar et al., 2020). Furthermore, the glycans of the SC region of SIgA confer structural resistance to the molecule from degradation by non-specific microbial and digestive proteases (Reinholdt and Husby, 2013).

Dimeric IgA2 immunoglobulin is less abundant in the serum ~10–20% (Bertrand et al., 2023) as oppose to the monomeric IgA1 ~90%. (Woof and Russell, 2011). In the mucosal secretions, this ratio varies depending upon the mucosal site. About 80–90% of IgA in nasal and male genital secretions and 60% of IgA in the saliva is of IgA1 monomeric isotype meanwhile 60% of IgA in the colonic and female genital mucosal surfaces is of IgA2 dimeric isotype (Woof and Russell, 2011). Furthermore, IgA2 is also present up to 25–30% in the bronchoalveolar fluid of the lung mucosa (Bertrand et al., 2023).

2.2. Secretory IgA production and transcytosis

Secretory IgA transcytosis and their functional roles have been widely studied in the GALT. In the GALT, production of IgA can occur in a T-dependent and independent pathway. Peyer's patches and lamina propria in the small intestine are key sites for T cell-dependent and -independent IgA production, respectively (Abokor et al., 2021).

T-dependent and independent pathways of SIgA production generate different types of SIgA. T-dependent pathways results in the production of high-affinity SIgA whereas T-independent pathways results in low-affinity SIgA production (Takeuchi and Ohno, 2022). The importance of affinity maturation of B-cells and the somatic hypermutation, with the involvement of AID or Activation-Induced Cytidine deaminase have been previously established in experimental settings and demonstrate the importance of high affinity SIgA in regulating and shaping the gut microbiota (Fagarasan et al., 2002; Takeuchi and Ohno, 2022; Wei et al., 2011).

It is also important to note that the glycosylation of SIgA contributes to its non-canonical microbial binding. These glycans provide multiple scaffolds for interaction with microbes (Pabst and Slack, 2020). This ability to be able to bind to a diverse range of microbiota can be termed as polyreactivity (Bunker et al., 2017) and these surface glycans are important for protective activity of SIgA in the intestines (Raskova Kafkova et al., 2021).

This polymeric SIgA, once produced, is transported to mucosal surfaces from their site of origin across the mucosal epithelium by Polymeric Ig Receptor (pIgR), which is expressed on the basolateral surface of epithelial cells lining the mucosal regions. Following the binding to

pIgR, the ectodomain of this receptor is cleaved and becomes the secretory component bound to dimeric/polymeric IgA (Stadmueller et al.). SC confers hydrophilic properties to dimeric/polymeric IgA along with a negative charge on the immune complexes created by SIgA molecules with pathogen(s) or their derivatives, which facilitate their elimination (Reinholdt and Husby, 2013). In addition, SC helps in protecting SIgA itself from enzymatic degradation in the mucosal secretions.

2.3. Functions of secretory IgA

2.3.1. Immune exclusion

SIgA protects the mucosal surfaces from invasive microbial attack with the help of a process called immune exclusion, where in, SIgA blocks the pathogen from attaching to the mucosal epithelial cells by binding to pathogenic epitopes or antigens on their surface, cross-linking them and thus preventing colonization and damage to the mucosal tissue (Corthesy, 2013).

This was demonstrated in the context of HIV viral entry via mucosal surfaces, where SIgA, specific to HIV conserved epitope, prevented interaction of HIV surface protein to epithelial cell receptors and thus prevented HIV-1 mediated transcytosis across the epithelial cell layer (Alfsen et al., 2001).

The immune exclusion activity of SIgA, is apparent not only on apical mucosal surfaces once its secreted by pIgR, but also established during their transcytosis across the epithelial cells. This form of immune exclusion has been previously reported for influenza and HIV viruses within the infected cells (Bomsel et al., 1998; Mazanec et al., 1995). Secreted IgA antibodies can co-localize with influenza surface proteins and prevent their intracellular propagation by excreting them back to the apical surface in form of non-pathogenic SIgA-viral particle immune complexes (Mazanec et al., 1995).

Furthermore, SIgA possess the ability to bind to and subsequently excrete antigens or possible pathogens that successfully breach the epithelial cell surfaces and gain access to the lamina propria have also been demonstrated as another mechanism of immune exclusion by SIgA (Gan et al., 1997; Kaetzel et al., 1991, 1994; Robinson et al., 2001).

2.3.2. Role of SIgA in homeostasis

Another crucial role SIgA, especially described in the gastrointestinal tract, is the controlled maintenance of homeostatic conditions by allowing for the development of immune tolerance to commensals.

Indeed, it is stipulated that SIgA aids M cells in the sampling of IgA-antigen immune complexes. This unique ability of SIgA to bind to M cells is not exhibited by IgG and IgM (Mantis et al., 2002) and is restricted to the mucosal compartment i.e. not exhibited by IgA in the serum (Kadaoui and Corthesy, 2007).

Interestingly, this ability of SIgA and its immunocomplexes with an antigen, to then later be preferentially transported over other free SIgA molecules, across the M cells in the Peyer's patches, and then to the underlying dendritic cells, is reportedly a result of structural modifications of IgA upon binding to antigens. This not only enhances its selective uptake but also confers higher resistance towards enzymatic degradation (Duc et al., 2010). Furthermore, this selective binding to M cells, although previously unknown, can be contributed to the Dectin-1 receptor, with the involvement of Siglec-5 as a possible co-receptor followed by the subsequent uptake of SIgA by Microfold cells (RocherEAU et al., 2013). These commensals, coated with SIgA, could possibly be recognized by DCs and can provide information in terms of the pathogenicity or potential danger associated with the bacteria. This essentially highlights the importance of SIgA to curb chronic stimulations of B-cells in the GALT, in response to commensal bacteria, thus, in essence contributing to homeostasis (Corthesy, 2007; Suzuki et al., 2004).

This property of SIgA contributing to gut homeostasis is termed as antibody-mediated immune selection, and involves both low affinity and high affinity SIgA molecules as described above in a T-independent

and T-dependent fashion respectively (Michaud et al., 2022). Furthermore, in the previous sections we highlighted the differences between IgA1 and IgA2 molecules. Another key difference between these molecules is also based on their glycosylation patterns which skews the type of immune response generated and makes an important contribution to their homeostatic function.

In humans, IgA1 is O-glycosylated (Novak et al., 2012) whereas IgA2 is mostly N-glycosylated (Steffen et al., 2020). The sialylation of IgA1 reduces the pro-inflammatory signalling (Steffen et al., 2020) whereas sialylation of SIgA2 promotes the reverse transcytosis of antigen-SIgA2 immune complexes to be up taken by M-cells (Rochereau et al., 2013).

Ultimately, secretory IgA (SIgA) facilitates immunological tolerance to commensal bacteria, which is important for preserving intestinal homeostasis. Its special capacity to attach to M cells helps to avoid persistent B-cell stimulation in response to commensals by enabling the selective uptake and delivery of SIgA-antigen immune complexes to underlying dendritic cells. In conclusion, SIgA plays a significant role in controlling immunological responses in the gut. This process, which is different for IgG and IgM, is mediated by structural changes of IgA upon binding to antigens and helps avoid autoimmune disorders and gut dysbiosis.

3. Dual role of SIgA in the respiratory tract

The dual role of SIgA in the modulation of inflammatory reactions is especially highlighted in the lung mucosal surfaces. IgA2, the dominant form of IgA in some mucosal surfaces (de Sousa-Pereira and Woof, 2019) exhibits pro-inflammatory characteristics in its interactions with neutrophils and macrophages (Bohländer, 2023; Steffen et al., 2020). This is mediated with the interaction of neutrophil IgA-Fc-receptor (Fc α RI) resulting in the release of a neutrophilic chemoattractant e.g. in the lungs during a lung infection (Mh and van E, 2017). The dual role of SIgA in inflammation becomes more apparent, however, during an acute allergic inflammation. Here, its ability to bind to IgA-specific Fc receptors on the mast cell prevent their degranulation and further block the binding of the allergen to the mucosal surfaces, thus limiting inflammation (Bohländer, 2023). These anti-inflammatory responses associated with SIgA are apparent upon analyses of the cytokine profile they induce. Under homeostasis, SIgA can inhibit the release of inflammatory cytokines from epithelial cells *in vitro*, as well as the pathogen-induced inflammatory cytokine response to maintain the tissue integrity (Diebel et al., 2005, 2010; Longet et al., 2014).

A deeper understanding of the functions associated with SIgA and its role in immune-mediated protection can potentially be elucidated in relation to respiratory viruses. The subsequent sections will focus on respiratory viruses such as SARS-CoV-2, influenza, and Respiratory Syncytial Viruses, exploring the impact of SIgA on the outcomes associated with these respiratory infectious agents.

3.1. Role of SIgA in respiratory infections: influenza viruses

Influenza viruses are one of the most widely spread respiratory viruses with the potential to cause pandemics and seasonal epidemics across the globe. Influenza viruses exist mainly as four strain types A, B, C and D (Bouvier and Palese, 2008). The A and B strains are the targets of the currently approved vaccines against influenza viruses in the market (Clem and Galwankar, 2009). Some of the most common influenza subtypes found in the general circulation during seasonal epidemics include A (H1N1) and A (H3N2) (Krammer et al., 2018). Despite the immune response generated against influenza infections, influenza drifting strains are able to evade this immunity due to the ongoing antigenic evolution of the hemagglutinin (HA) and neuraminidase (NA) surface proteins (van de Sandt et al., 2012). Studies have shown evidence that mucosal SIgA antibodies play a central role in protection against upper respiratory tract infections, while serum IgG antibodies are primarily responsible for defending against infections in the lower

respiratory tract (Ito et al., 2003; Ramphal et al., 1979). The mechanisms underlying the protective role of secretory IgA against the influenza virus infections is still not fully clear, particularly in pediatric population, which forms a high-risk group for influenza infections.

A recent study conducted on mouse models mimicking high risk individuals, tried to determine the importance of IgA production in mucosal secretions of the upper respiratory tract as first line of defense to prevent disease severity and morbidity upon influenza A (H₁N₁) virus infection (Zhao et al., 2020). Some mice groups were infected with influenza A virus via intubation to cause direct infection of the lower respiratory tract, thus ultimately disabling the involvement of SIgA interacting with the virus at the upper respiratory tract. A higher lung inflammation and tissue injury was witnessed in these groups as compared to the mice groups infected with influenza virus via nasal droppings i.e., allowing the involvement of the SIgA secreted in the upper respiratory tract, thus supporting its role in preventing disease severity, particularly in high risk populations (Zhao et al., 2020). Additionally, maintaining baseline levels of SIgA specific antibody secreting cells in the nasal mucosa or in the upper respiratory tract mucosa is essential for protection against influenza infections and a decrease below a certain threshold could render individuals susceptible to these infections (Brokstad et al., 2002). Furthermore, secretory IgA may be more broadly reactive, owing to the high avidity due to their multimeric state (Krammer, 2019). Where the neutralizing ability of an antibody is an important factor in protection against viral infection and transmission, non-neutralizing polymeric SIgA antibodies, (and not IgG or monomeric IgA antibodies), illustrated a higher ability to demonstrate cross-protection against infection caused by several influenza strains and significantly reduced viral progeny production from infected cells (Okuya et al., 2020b).

The challenge in identifying suitable correlates of protection associated with influenza infections are often due to the differential antibodies at play in the upper and lower respiratory tract (Ito et al., 2003). Mucosal IgA is often short-lived (1–2 years or less) (Johnson et al., 1985; Shvartsman and Grigorieva, 1979), whereas serum IgG antibodies transudate from the blood (Hettegger et al., 2019), also known to be neutralizing at a certain level and protective in influenza infections (McCullers and Huber, 2012) can last for several years and can be further boosted by memory B-cell stimulation (Bernasconi et al., 2002). Studies show that IgG antibody, particularly at the level of the lower respiratory tract are more important than IgA in protection from influenza related pneumonia (Ito et al., 2003). Drawing from these studies, it can be concluded that, for an effective protection, induction of a well-balanced immune response, comprising of both, effective IgG and IgA production would be good targets for an effective vaccine against influenza viruses (Tsunetsugu-Yokota et al., 2022).

The evident protective role of SIgA in combating influenza infections highlights its significance in advancing research on various respiratory viruses. The insights gained from these studies can serve as foundations for the development of targeted IgA therapies against other respiratory viruses. However, as elaborated in the next section, this becomes more complex when dealing with viruses like RSV. In contrast to the unequivocal support for IgA's protective role in influenza infections, the scenario is less conclusive for RSV. This discrepancy not only underscores the challenges in development of an IgA-focused strategies for RSV but also highlights a critical gap in our understanding of the immune responses that confer protection against RSV infections.

3.2. Role of SIgA in respiratory infections: Respiratory Syncytial Virus

Respiratory Syncytial Virus (RSV) is a virus of great concern, perhaps due to the limited number of established therapeutics in the market to tackle the ongoing surge of RSV infections. RSV infections have been associated with higher symptomatic severity compared to other respiratory viruses and have been extensively studied for their possible association with long term respiratory diseases (Barnes et al., 2022). A

higher inflammatory response in the respiratory airways have been correlated with disease severity indicating the involvement of immune responses in the clinical outcome associated with RSV infections (McNamara et al., 2004; Thwaites et al., 2018). RSV infections are often recurrent throughout the lifetime, with severe infections mostly occurring in the infant and elderly populations (Falsey et al., 2005; Nair et al., 2010). Detailed studies focusing on understanding the different immune responses generated in several age groups upon natural RSV infections are pertinent for effective therapeutic strategies.

So far, the role of IgA in protection from RSV infections has been conflicting. In a study published in 1997, focusing on children who developed bronchiolitis followed by an RSV infection, reported that the serum IgA antibody titers were higher in the group with RSV bronchiolitis than in the control groups (Strannegård et al., 1997). An interesting observation made, was that the children with previous RSV bronchiolitis infections and consequently developing allergic sensitizations, had higher levels of RSV IgA levels in the sera than children who did not develop these allergenic sensitizations following RSV bronchiolitis. This does not necessarily prove the direct involvement of IgA in allergic sensitization post RSV infections. This could possibly be a consequence of RSV infections itself, considering RSV infections are suggested to induce strong Th2 dominant immune responses (Monick et al., 2007) which could also induce IgA as a result of the Th2 chemokines produced (Xu-Amano et al., 1992).

In terms of the current antibody-based treatments approved for RSV, Palivizumab and Motavizumab are therapeutic monoclonal IgG1 antibodies that target RSV epitopes. To study the mucosal immunity, conferred by IgA in comparison to IgG during RSV infections, upon intranasal administration in mice, Palivizumab and Motavizumab antibodies were re-engineered to be of IgA isotype, but with the ability to recognize the same epitopes as the original antibodies. These re-engineered antibodies, when administered intranasally, were less protective during infection and had decreased effectiveness, as compared to the recombinant IgG1 palivizumab and motavizumab which were also administered intranasally (Jacobino et al., 2018).

However, there is still a silver lining for understanding the importance of IgA's protective role in the context of RSV infections. Adult populations have previously reported high titers of IgA and IgG against human RSV G and F proteins (Cortjens et al., 2017; Goodwin et al., 2018). Additionally, low titres of anti-RSV F and G nasal IgA i.e. a failure to induce nasal SIgA responses to RSV in healthy elderly population was associated with an increased disease severity, indicative of SIgA's protective role (Walsh and Falsey, 2004). Perhaps, the reason why SIgA, till date, has not been established as a clear correlate of protection against RSV, could be analyzed from a study published by Habibi et al. (2015). Habibi et al. conducted a study focusing on determining correlates of protection from infection by mucosal and serum antibody responses, induced after controlled RSV infection challenges in healthy adults. In addition to this, they further analyzed memory B-cell frequencies up till 28 days post challenge. They noted that higher RSV specific SIgA levels in nasal secretions prior to challenge conferred higher correlates of protection from infection as compared to IgA in the serum. Thus, highlighting a positive finding in favor of SIgA. However, during the convalescence period, only IgG memory B cells towards RSV were detected in the peripheral blood (Habibi et al., 2015). These findings might be suggestive of the fact that perhaps the reason for recurrent RSV infections could be due to the lack of sufficient IgA producing memory B cells post infection. Furthermore, in a RSV human challenge model, presence of pre-existing nasal SIgA antibody levels correlated with lower measures of viral replication but these did not provide any significant protective effect once RSV infection occurred (Bagga et al., 2015). Therefore, vaccines that focus on IgA specific memory B cell induction might be the key to producing effective vaccines against RSV infections.

Another significant issue here is the differential immune response generated against RSV based on age related factors. RSV infections occurring in infants mainly resulted in mucosal SIgA induction during

the convalescence period (Tsutsumi et al., 1995), meanwhile this convalescence period in adults, is associated with induction of RSV-specific IgG memory B-cell in circulation (Habibi et al., 2015). Considering that infants and elderly are severely impacted by RSV infections, studies have tried to compensate for the differential IgA production in different age groups using IFN- α administration prior to infectious challenge in neonatal mice and reported high SIgA production post IFN- α treatment and reduced RSV mediated inflammation post challenge (Hijano et al., 2018).

The study of RSV infections underscores the intricate relationship between SIgA's protective effects to combat this virus and the challenge of establishing a lasting immunity through the engagement of memory B cells. This complexity highlights the gaps in our understanding of respiratory viruses and how our immune system tackles them. As we move on to SARS-CoV-2 infections, the ongoing exploration of SIgA's role in preventing viral respiratory infections would also offers insights that may bridge our understanding between RSV and the complexities of the current COVID-19 pandemic.

3.3. Role of SIgA in respiratory infections: SARS-CoV-2

The nasal mucosa is the primary site for entry of SARS-CoV-2 viruses before its entry into the lower respiratory tract. Studies based on the current vaccines developed against COVID-19, particularly the mRNA COVID-19 vaccines, highlight, the importance of durable IgA immune responses in preventing SARS-CoV-2 infections. Additionally, Tang et al. also demonstrate that systemic COVID-19 mRNA immunizations might not be sufficient alone to induce neutralizing antibodies in the mucosal secretions (Belyakov and Ahlers, 2009; Sheikh-Mohamed et al., 2022; Tang et al., 2022). Moreover, serum IgA responses dominate over other antibodies in the early phases of humoral responses associated with COVID-19 infections (Sterlin et al., 2021). In fact, peripheral activation of IgA secreting cells show mucosal homing characteristics and are detectable shortly after symptomatic onset of COVID-19, with neutralizing IgA antibodies in the saliva (secretory IgA) remaining detectable up to 78 days post symptomatic disease onset (Sterlin et al., 2021). Additionally, it is understood that IgA antibody levels specific for SARS-CoV-2 spike protein in the serum following vaccination against SARS-CoV-2, in the absence of known prior SARS-CoV-2 infection, are elevated (Montague et al., 2022).

However, recent publications have also started focusing on secretory IgA antibodies in mucosal surfaces following COVID-19 infections. The dimeric form of IgA in mucosal secretions are reported to be 15 times more powerful at SARS-CoV-2 viral neutralization as compared to their monomeric forms available in the sera (Wang et al., 2021). Furthermore, secretory IgA in the respiratory mucosa is linked with a greater SARS-CoV-2 virus neutralization capacity than IgG at this level (Sterlin et al., 2021; Wang et al., 2021). Secreted IgA antibodies, specific for SARS-CoV-2, have also been detected in the breast milk of infected mothers. Thus, highlighting the possible role of SIgA in passing immunity from infected mothers to neonates which might be protective in early COVID-19 infections (Fox et al., 2020). In fact, SARS-CoV-2-specific mucosal antibody titres after being measured in healthcare workers reported positively on SIgA levels, which were higher as compared to IgG levels amongst participants with previous SARS-CoV-2 infections as compared to individuals with no previous exposure to this virus (Havervall et al., 2022). Most participants at the time of enrollment in the study, with high levels of wild type spike specific SIgA were categorized as "low-risk" for subsequent omicron breakthrough infections (Havervall et al., 2022).

Additionally, patients with primary immune deficiency characterized with a lack of IgA, called Selective IgA Deficiency (SIgAD), were reported to have lower responses to SARS-CoV-2 vaccination and had prolonged COVID-19 infection and viral shedding periods (Meyts et al., 2021; Naito et al., 2020; Quinti et al., 2021).

A recent pediatric study also reported high levels of salivary IgA in

asymptomatic cases of COVID-19 when compared to symptomatic cases, suggesting the importance of SIgA antibodies in lowering disease severity associated with SARS-CoV-2 (Dobaño et al., 2021).

However, some studies do not report a similar picture. Persistent salivary SIgA antibodies have been previously associated with severe COVID-19 infections (Costantini et al., 2022). A recent publication in 2021, investigated the kinetics of antibody responses within the respiratory system in response to COVID-19 infections, along with their severity and responses post vaccination. Interestingly, the study reported high IgG and IgA levels targeting RBD of SARS-CoV-2 which also correlated positively to disease severity (Cagigi et al., 2021).

Much like in the case of RSV, SIgA responses against SARS-CoV-2 infections, although measurable in early convalescent period seem to slowly decline gradually after infection. However, IgG levels in the saliva are not only detectable, but also remain stable with a much slower decline in titers (Alkharaan et al., 2021). Spike protein specific memory B cells, although maintained to similar levels post-convalescence in patients with both severe and mild COVID-19 disease profile, are predominantly IgG⁺ and thus might be reflective of the dominant antibody isotype response upon virus reinfection (Cagigi et al., 2021). However, this does not entirely negate the potential importance of SIgA in their protective immune responses at mucosal surfaces. Although strong nasal SIgA responses are established in patients post SARS-CoV-2 infection, against both spike and nucleoproteins, and remain elevated for up to 9 months post infection, the levels are not further boosted after systemic COVID-19 vaccinations, despite a boost in serum IgG and IgA levels (Liew et al., 2023).

While emphasizing the crucial protective function of SIgA in disease prevention, we highlight the significance of employing a tailored approach to stimulate SIgA production. By adopting intranasal immunization techniques that mimic natural respiratory infections (Freitag et al., 2023), there is a potential to enhance the generation of nasal SIgA responses, thereby augmenting their effectiveness in defending against viral infections. This prompts an understanding of an often-overlooked aspect of mucosal immunity: do existing vaccines approved for human use against respiratory viruses effectively induce mucosal immunity? this question will form the core of our discussion in the next section. Fig. 1 summarizes the contrasting findings in current literature with respect to the differential role or potential impact SIgA has on SARS-CoV-2, Influenza viruses and Respiratory Syncytial Virus (Fig. 1).

4. Mucosal immunity after vaccination against respiratory viruses

The development of vaccines against SARS-CoV-2, represents a significant turning point in the global effort to stop the pandemic. These vaccines, which have been approved after extensive clinical trials and research, emerge as pivotal players in fortifying our body's defense mechanisms. Currently approved vaccines against SARS-CoV-2, have demonstrated, not only their efficacy in reducing COVID-19 associated disease severity and hospitalization, but also their impact on mucosal immunity. SARS-CoV-2, mainly transmitted via the respiratory tract, targets the abundant ACE2 receptors in the nasal mucosa for its entry and subsequent infection (Costa dos Santos et al., 2023). Thus, mucosal

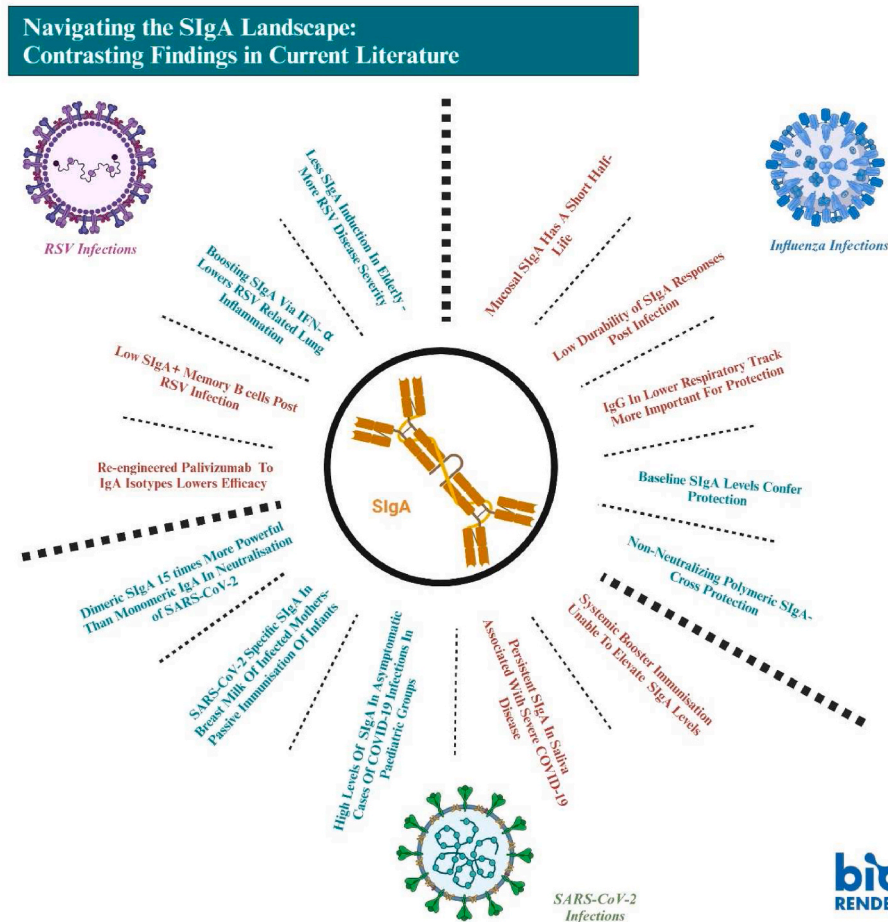


Fig. 1. Navigating the SIgA Landscape: Schematic representation summarizing the contrasting findings in current literature with respect to the differential role or potential impact SIgA has on respiratory viruses such as SARS-CoV-2, Influenza viruses and Respiratory Syncytial Virus. Turquoise blue statements highlight the benefits of SIgA responses in protection. Red statements pinpoint the limitations of SIgA responses in protection. Created with BioRender.com.

vaccinations are important to not only prevent possible binding of the virus to its entry receptors in the nasal epithelial cells, but also to stop serious complications associated with SARS-CoV-2 infections (Brüssow, 2023). Several recent studies have focused on understanding the impact of current vaccine platforms against SARS-CoV-2, on the induction of mucosal immunity to protect from severe infections associated with SARS-CoV-2 and the newly emerging variants of this virus.

One such novel vaccine platform, which has been administered to millions worldwide, would be the mRNA vaccines against SARS-CoV-2. These vaccines can effectively induce IgG and IgA antibodies in the serum with the IgG level increasing even further after a booster dose. Although the same cannot be said about the IgA levels in the serum which decline quickly following the primary and booster immunisations (Wisniewski et al., 2021). Despite this, mRNA vaccines are still reported to be the highest inducers of serum IgA levels post immunization compared to other widely used COVID-19 vaccine platforms (Lafon et al., 2022).

Sheikh-Mohamed et al. reported presence of anti-Spike and anti-RBD IgG and IgA antibodies from serum and saliva samples of participants who received mRNA vaccines against SARS-CoV-2. They noted that following booster immunization, despite a rise in IgG levels, only 30% of the study population reported an increase in IgA response (Sheikh-Mohamed et al., 2022). Interestingly, the study cohort was further divided into two categories, participants with a breakthrough infection of SARS-CoV-2, and participants that did not experience an infection post vaccination. Surprisingly, the IgA levels in the former group were consistently lower at 2–4 weeks post booster dose as compared to the latter. Meanwhile the IgG levels were near comparable in both groups (Sheikh-Mohamed et al., 2022). This could be suggestive of a possible role of secretory IgA in protection from SARS-CoV-2 infections post systemic mRNA vaccinations. Spike specific IgG and IgA antibodies were also detected in saliva of those vaccinated with BNT162b2, but whether this came from mucosal secretion or systemically derived, could not be confirmed (Azzi et al., 2021; Longet et al., 2022). On the contrary, other studies demonstrated that SIgA in the saliva could be measured by estimation of their secretory component, and confirmed mucosal SIgA production, particularly in those who experienced natural infection prior to SARS-CoV-2 mRNA vaccination (Sano et al., 2021).

Some studies also utilized an intranasal administration strategy for one of the currently approved vaccines against SARS-CoV-2, in comparison to its usual intramuscular administration. The effectiveness of intranasal and intramuscular administration of the chimpanzee adenoviral vaccine (ChAd-SARS-CoV-2) encoding a stable SARS-CoV-2 spike protein, was conducted in mice. The intramuscular injection of the vaccine induced neutralizing antibodies and protected mice from infection, reducing viral levels and lung damage. However, it did not prevent upper respiratory infections or elicit IgA responses. In contrast, intranasal vaccination with the same vaccine generated strong IgA and neutralizing antibody responses, prevented both upper and lower respiratory track infections, and possibly achieved sterilizing immunity (Hassan et al., 2020).

Similarly, for influenza vaccinations, a total of 12 influenza vaccines have been approved for use in the European Union/UK/European Economic Area (2022) (Stuurman et al., 2023), one of them (Fluenz Tetra) is available as a nasal spray for protection of children aged 2 years or higher up to 18 years of age. In a recent comparative study for 8 out of 12 influenza vaccines involving several EU countries, Fluenz Tetra showed an estimated 65% influenza vaccine effectiveness amongst children which make up the recommended age group for this vaccine (Stuurman et al., 2023). LAIV's were first licensed as a trivalent vaccine (LAIV3). These LAIV3 formulation, are considered to be more effective than other injectable trivalent inactivated influenza vaccines in children (Ambrose et al., 2011; Jefferson et al., 2012) Furthermore, the ability of LAIVs to induce serum IgA1 responses, is demonstrated to be more in children as compared to adults (Manenti et al., 2017). LAIV are considered to be effective in the induction of mucosal immunity (Hoft

et al., 2017). Elaborating on this, intranasal immunization approach for influenza, induced elevated salivary IgA levels that correlated with serum Hemagglutinin inhibition (HI) activity (Mohn et al., 2016) with demonstrated ability to be one of the several key players in conferring protection from subsequent influenza infections and these IgA responses could be further boosted, following revaccination with mucosal LAIVs (Ambrose et al., 2012).

In a study conducted in ferrets, LAIVs induced influenza virus specific antibodies and T-cells responses in both naïve and previously seropositive models, thus indicating the ability of the vaccine to replicate even under conditions of pre-existing immunity, possibly challenging the long-standing disadvantage of LAIVs (Monto et al., 2009; Shannon et al., 2020). In contrast, inactivated influenza vaccine, which only produced an immune response in previously primed ferrets. LAIVs conferred significant protection in the upper respiratory tract against heterologous H1N1 influenza strains. Furthermore IgG and IgA secreting ASC, CD4⁺ and CD8⁺ T cells specific to influenza were also reported in peripheral circulation further confirming the ability of intranasal vaccines to induce systemic immune responses (Cheng et al., 2013).

This raises additional questions regarding the effectiveness of parenteral preparations against seasonal influenza infections and whether they contribute to induction of local or mucosal immunity against the pathogen in question, much like their intranasally administered counterparts. In a study published by Moldoveanu et al., (1995) aimed to compare a trivalent inactivated influenza vaccine via parenteral, oral or intranasal routes of immunization, in order to understand the impact on the humoral immune response generated at both systemic and mucosal levels in previously unimmunized individuals, for the influenza virus (Moldoveanu et al., 1995). Whilst oral vaccination induced predominantly SIgA antibodies in the nasal lavages and salivary sample, it was unable to induce significant antibody titres (for all isotypes) in the serum samples and had no influence on hemagglutinin inhibition (HAI) activity. On the contrary, intranasal vaccination resulted in dominant IgG producing cells, specific to the antigen in the sera, with significant HAI activity as well as IgA and IgG antibodies in the nasal and salivary samples, with the latter being more dominant (Moldoveanu et al., 1995). This could be due to the IgG producing B-cell population being dominant in the human NALT as compared to IgM and IgA producing B-cells (Boyaka et al., 2000). Influence of an intranasal inactivated influenza A (H5N1) virus-based vaccine on secreted IgA was also studied when administered to naïve human participants where strong neutralizing HA-specific SIgA antibodies were present in the nasal samples collected from the participants. The vaccine also utilized a mucoadhesive adjuvant which reportedly enhanced IgA nasal production but had no impact on the serum IgG production (Ainai et al., 2020).

Some studies have also been focusing on enhancing immune responses to currently existing influenza vaccines in selective populations, e.g. researchers hypothesis that in specific populations suffering from vitamin A deficiencies, immune response generated to intranasal vaccines against influenza such as Flumist (equivalent to Fluenz Tetra in USA/Canada), are limited (Surman et al., 2014). Since these vaccines focus on generation of mucosal immune responses, particularly SIgA, (Barría et al., 2013) the patients show limited SIgA development due to the lack of retinoic acid or vitamin A which is known to be involved in IgA synthesis. Thus, oral doses of retinoic acids, given prior to intranasal immunization in vitamin A deficient mice models results in higher IgA responses post intranasal vaccination with Flumist (Surman et al., 2014).

Therefore, although conflicting results from studies highlights the gaps in knowledge. What is clear, is that IgA responses are well established and documented following influenza mucosal vaccinations in the nasal samples and could be contributing to protective effects at the mucosal level.

Another important virus discussed within this article is the Respiratory Syncytial Virus or RSV. In 2023, FDA approved two vaccines against RSV namely, Abrysvo and Arexvy, for systemic immunization

(<https://www.fda.gov/consumers/covid-19--flu-and-rsv/respiratory-syncytial-virus-rsv>, 2023; Venkatesan, 2023), in adults aged 60 years and older. Since this vaccine is recently approved, data in regards to the mucosal antibody responses induced by these vaccine are not yet available. Therefore, we will discuss other novel mucosal vaccination strategies being developed against RSV infections in section 5.3.

In summary, while systemic vaccination has been a cornerstone in the field of immunization, there is an overwhelming need to focus on mucosal vaccination approaches that could further enhance the production of SIgA. The ongoing developments in mucosal vaccine strategies hold promise for more targeted and robust defenses and the same will be discussed in the next section.

5. Rationale to develop mucosal vaccines

In the pursuit of more effective approaches to vaccination, the development of mucosal vaccines presents a key solution to several challenges encountered with traditional systemic vaccination routes. From an immunological standpoint, mucosal vaccines not only stimulate systemic immunity but also generate a robust immune response at several mucosal sites, strategically inducing immunity at the focal points of pathogen entry. As mentioned in the earlier sections, the "common mucosal systems" allows immune responses to take place at not only the primary site of immunization but also at adjacent or interconnected mucosal sites (Holmgren and Czerkinsky, 2005).

Focussing on a more practical approach, vaccination via mucosal surfaces such as oral or nasal immunization would offer ease of administration, often without the need of medical supervision. Additionally, these could be administered at a much lower dose and is a better vaccination alternative in children or individuals with a fear of needles. Risk of disease transmission, involving use of non-sterile injections is dramatically reduced and mucosal vaccinations can be particularly useful for implementation of immunization programs in economically developing countries.

This dual benefit positions mucosal vaccines as a practical choice for global vaccination initiatives, eliminating the reliance on specialized professionals for administration and mitigating concerns associated with the sterility as seen with systemic vaccination routes. The simplicity and accessibility of mucosal vaccination makes it a compelling rationale for the evolution of immunization strategies worldwide. Some completed and ongoing clinical trials of mucosal vaccine candidates for SARS-CoV-

2, Influenza and RSV infections can be found in the summary Table 1.

5.1. Mucosal vaccines in clinical and pre-clinical development against SARS-CoV-2 infections

Intranasal vaccination approaches induce protective local and systemic immune responses in the respiratory tract (Kuroono et al., 1999) and the genitourinary tract (Imaoka et al., 1998). Therefore, use of the nasal mucosa could be an effective approach to administer vaccines against several infectious viruses gaining entry via respiratory surfaces.

One of the latest development for mucosal vaccinations against SARS-CoV-2 respiratory viruses, which have now entered clinical trials, are the adenovirus vector vaccine (Ad5-nCoV) administered via aerosol inhalation and has been proven to be as effective as its injectable counterpart in terms of inducing systemic neutralizing antibody titer against SARS-CoV-2 at only one fifth of its injectable dose (Wu et al., 2021). These have now been approved for immunization as a booster dose in China (Wang et al., 2023).

Bharat Biotech's iNCOVACC vaccine got approval for their intranasal recombinant chimpanzee adenovirus vector based-vaccine as a booster in India and expresses a pre-fusion SARS-CoV-2 spike protein, known to induce Anti-S IgA in nasal secretions (Singh et al., 2023; Hassan et al., 2020).

Several other novel intranasal vaccine approaches are now being explored in preclinical studies and some have even moved into clinical trials. A live attenuated influenza virus based intranasal vaccine encoding SARS-CoV-2 RBD (Receptor binding domain), reported an increase in RBD specific SIgA and IgG levels post vaccination. Interestingly, this approach also resulted in influenza-specific IgG antibodies in the lungs of immunized hamsters, suggesting a dual function for these vector-based vaccines (Chen et al., 2022). This vaccine then further moved into phase 3 clinical trials but showed limited induction of SIgA and limited protection, particularly in participants with a history of COVID-19 infections despite being well tolerated amongst the participants (Zhu et al., 2022, 2023). A similar concern surrounding intranasally administered influenza vaccine is the effect of pre-existing immunity which can lower the replication of such viruses and thus render the vaccine ineffective (Roy et al., 2020).

In another such unique approach, human RSV-based viral vector encoding SARS-CoV-2 spike protein in a live attenuated intranasal vaccine formulation (Tioni et al., 2022) was also developed and reported an 8-fold increase in SIgA levels in the nasal passage of non-human

Table 1

Summary of some completed and ongoing clinical trials of mucosal vaccine candidates for SARS-CoV-2, Influenza and RSV infections.

Vaccine Platform	Route of Administration	Name	Vaccine Description	Target Pathogen	Development Phase	Source
Live Attenuated Viral-Vector	Intranasal	DelNS1-2019-nCoV-RBDOPT1	Influenza Virus based vectored vaccine encoding SARS-CoV-2 RBD Spike protein	SARS-CoV-2	Phase 1, Phase 2 and 3	ChiCTR2100051391 PACTR202110872285345
Live Attenuated Viral Vector	Intranasal	MV-014-212	Recombinant Human Respiratory Syncytial virus vector encoding a chimeric SARS-CoV-2 spike	SARS-CoV-2	Phase 1	NCT04798001
Live attenuated	Intranasal	Sing2016 M2SR Bris10 M2SR and Sing2016 M2SR	M2-deficient single replication (M2SR) H3N2 influenza vaccine	H3N2 influenza	Phase 1b	NCT04960397 NCT03999554
Inactivated, Whole-Virus	Intranasal or Intramuscular	BPL-1357	Beta-propiolactone (BPL)- inactivated quadruple influenza virus cocktail (BPL-1357), -Inactivated, Whole-Virus vaccine	Universal influenza Vaccine	Phase 1b	NCT05027932
Adjuvanted Quadrivalent inactivated vaccine, split virion	Intranasal	NB-1008	The vaccine is composed of a licensed vaccine Fluzone, and an adjuvant, W805EC.	Seasonal Influenza	Phase 1	NCT01354379 NCT01333462
Non-Replicating subunit vaccine	Intranasal	SynGEM	RSV F protein vaccine linked to an immunostimulatory bacterium-like particle (BLP)	RSV	Phase 1	NCT02958540

primates. It also reported nasal IgA levels comparable to natural infection in Phase 1 clinical trials.

In terms of the vaccines currently under pre-clinical investigation, several different platforms have come forward with unique and novel approaches to tackle SARS-CoV-2 infections.

After years of investigation, it has been demonstrated that mucosal adjuvants have the capability to trigger defensive immune responses both locally and systemically. This is crucial for the success of mucosal vaccinations against a variety of infectious diseases (Lycke, 2012).

In one such approach, the SARS-CoV-2 spike proteins were combined with LP-GMP adjuvant. This combination was designed to activate TLR2 receptors and C-di-GMP, a synthetic STING agonist. When administered through the nasal route in mouse models, it elicited robust IgA responses in the serum, lungs and nasal secretions. Intriguingly, this significant IgA production was not observed in mice that received the same vaccine through intramuscular injection (Diallo et al., 2023).

In the dynamic field of mucosal vaccine development, nanoparticle-based adjuvanted mucosal vaccines have also been explored for their potential in the development of protective mucosal immunity. Studies have investigated several intranasal nanoparticle based vaccines by combining components like stabilizing adjuvants such as mannan and the receptor-binding domain (RBD) of SARS-CoV-2 with polyarginine and 2,3'-cGAMP which facilitate antigen transportation across nasal epithelial cells (Xiao et al., 2023).

Similar vaccine platforms have utilized other vaccine adjuvants such as peptide-poloxamine nanoparticles combined with the SARS-CoV-2 DNA based vaccine (Sun et al., 2023) and chitosan nanoparticles loaded with the RBD of the SARS-CoV-2 spike glycoprotein which are known for their mucoadhesive properties, thus allowing the vaccine to be retained longer in the nasal epithelium (Jearanaiwitayakul et al., 2021). These nanoparticles-based SARS-CoV-2 specific vaccines resulted in local IgA and IgG responses in nasal and bronchoalveolar lavages along with prominent neutralizing systemic antibody responses against the virus.

Other studies have also demonstrated the ability of viral vector-based vaccines to be adaptable in a mucosal vaccination approach. This includes comparison of intranasal vaccination of chimpanzee adenovirus vectored vaccine, encoding SARS-CoV-2 spike protein in hamster models. This demonstrated a higher ability to induce neutralizing antibody titers in the serum as well as significantly reduce the lung pathology associated with COVID-19 symptomatic inflammation when compared to its intramuscularly injected counterpart (Bricker et al., 2021). Similarly, lentiviral vectors also demonstrated successful decrease in SARS-CoV-2 viral load in the lungs of mice, when administered as an intranasal boost (Ku et al., 2021). Another strategy utilized parainfluenza viruses (Le Nouën et al., 2022) encoding SARS-CoV-2 spike glycoprotein in Rhesus macaques in an intranasal vaccination approach. A single-dose immunization resulted in elevated levels of IgA and IgG, not only in the mucosal secretions but also in the systemic circulation (Le Nouën et al., 2022).

This demonstrates that mucosal vaccines possess the ability to generate SIgA in mucosal secretions, which is associated with protection from SARS-CoV-2 infections. This is not only evident from the recently approved mucosal vaccines but also the newer strategies moving into human clinical studies. Of course, it is important to address the disadvantages associated with previous history of natural infection, particularly in the context of live attenuated vaccines. However, despite these considerations, the growing success of mucosal vaccines, both in approved formulations and those advancing through human clinical studies, offers a promising area for the development of vaccines against SARS-CoV-2 infections.

5.2. Mucosal vaccines in clinical and pre-clinical development against influenza viruses

Several mucosal influenza vaccines are currently in clinical trials,

including a single replication based LAIVs for intranasal immunization, currently in the phase 1 of clinical trial and holds promise (NCT04960397) along with another currently ongoing phase 1 clinical trial for intramuscular or intranasal immunization with a quadrivalent inactivated whole virus based vaccine (NCT05027932).

In a prime-pull strategy, LAIV given intranasally as prime followed by an AS03 adjuvanted or unadjuvanted inactivated influenza vaccination administered intramuscularly as boost, was recently tested in phase 1 clinical trial (Nachbagauer et al., 2021). Interestingly, the LAIV prime intranasally itself could not generate substantial mucosal antibody responses. This could be due to the low doses or the avian Influenza H8 head used in the LAIV8 formulation, could have reduced the replicative capacity of the vaccine in the nasal mucosa (Nachbagauer et al., 2021).

Viral vectors, specifically, adenoviral (Ad) vectors have been implicated in the development of protective immunity when administered mucosally. Ad vectors 19a encoding influenza A hemagglutinin (HA) and nucleoprotein (NP) were tested. The study involved comparison of Ad5 encoding the same influenza antigen, in a comparative analysis since Ad5 have previously reported a decrease in vaccine efficacy due to pre-existing immunity to the Ad5 vectors (Harro et al., 2009; Fitzgerald et al., 2003). The Ad19a and Ad5 based vaccines were given intranasally as one dose immunization or as a booster to intramuscular vaccination with a plasmid DNA vaccine encoding the same antigens. Vaccination with Ad5, whether as an intranasal prime or an intranasal boost following plasmid DNA vaccination, in general resulted in higher IgA levels in the mucosa and higher neutralizing antibody responses in the sera of vaccinated mice, thus establishing the superiority of Ad5 as a vector (Lapuente et al., 2018).

Based on the same Ad5 vector, a phase I and II clinical trial was conducted using Ad5 based viral vector encoding for HA from influenza A strain as an oral capsule based vaccine (Liebowitz et al., 2015). The study established safety and tolerogenicity of the vaccine with a four-fold increase in neutralizing HA titres post vaccination in the serum of the participants, thus demonstrating oral vaccination route as a possible success.

Further motivated with the development of a universal influenza vaccine, Wang et al. utilized pulmonary surfactants to develop a heterosubtypic influenza vaccine by combining them with cGAMP, a STING agonist, to develop a Nano-emulsion based vaccine which, when administered with antigens derived from inactivated H1N1 influenza viruses, induced cross-protection in mice and ferret models and demonstrated a 60-fold increase of IgA levels in Bronchoalveolar Lavages when compared to their unadjuvanted counterpart (Wang et al., 2020).

Similarly, clinical trials with a nano-emulsion formulation, combining FluZone, a previously approved systemic influenza vaccine, and W805EC adjuvant, when administered intranasally, observed higher IgA levels specific to influenza antigen in mucosal secretions and were protected from infection and demonstrated lower viral shedding, particularly, in participants with prior influenza infections. This indicates the role of prior memory immune responses at play in protecting against influenza infection as well as the effectiveness of nano emulsion based adjuvants to deliver antigens to the nasal epithelium (Stanberry et al., 2012).

Besides intranasal immunization, other mucosal routes for vaccine administration, such as sublingual routes are also under development in pre-clinical mice models. Such approaches would be useful since this route does not encounter the possible CNS related side effects reported with the intranasal immunizations of LAIVs (Lewis et al., 2009). A sublingual vaccine, combined with the mucosal adjuvant LTK63 was able to illicit comparable systemic immune responses to intramuscular immunization but unlike the latter, also generated mucosal IgA and Th17 responses (Gallorini et al., 2014).

In summary, the ongoing trials are exploring several mucosal vaccine strategies, demonstrating potential correlates of protection. While viral vectors and LAIV based formulations are at the forefront, the preclinical

landscape suggests the efficacy of intranasal approaches (Asahi et al., 2002; Hodge et al., 2001). Innovative strategies, including Nano-emulsion-based vaccines, show promise, however, the most prominent challenge in influenza immunization remains the need for repeated yearly immunization. Developing a universal influenza vaccine candidate is therefore, crucial to address this challenge and achieve long term protection against influenza infections.

5.3. Mucosal vaccines in clinical and pre-clinical development= against Respiratory Syncytial Virus (RSV)

In a breakthrough news for RSV prevention, world's first vaccine against RSV, administered intramuscularly, was approved in the year 2023, for use in Europe and the USA. Arexvy, targeted for elderly population, <60 years old older in the European union and Abrysvo, approved by FDA for use in the same population (Venkatesan, 2023), comes as a huge respite after years of RSV research and vaccine development.

Most current RSV vaccines in development focus on induction of serum neutralizing antibodies, which, although associated with lowering RSV infection related hospitalizations (Habibi et al., 2015), do not prevent infection. Therefore, mucosal vaccination strategies and their further exploration is required to tackle the increasing burden of RSV infections.

Several mucosal vaccines against RSV have been tested in phase I clinical trials (Karron et al., 1997; Wright et al., 2000), including a novel intranasal RSV derived F protein containing vaccine, linked to an immunostimulatory bacterium-like particle (BLP) (Ascough et al., 2019). Despite persistent antibody response in the sera, anti-RSV nasal IgA responses were heterogeneous, with strongest response in participants having pre-existing antibodies (Ascough et al., 2019).

Two intranasal RSV live attenuated vaccines have been tested in phase I clinical trials, amongst adults, children and infants. Between these live attenuated vaccine candidates, one caused nasal congestion in seronegative infants (Pf et al., 2000) and the other candidate, despite the induction of antibodies in infants, showed limited replication in the nasal passage following a second dose (Karron et al., 2005). Another vaccine candidate with deletion of NS2 gene of RSV, responsible for inhibiting host innate immune responses, was tested in intranasally in adults and children, and demonstrated promising results (Wright et al., 2006). This however, does not take away from a very apparent lack of new potential mucosal vaccine candidates in clinical trials targeting RSV infections. Despite this, several preclinical studies are ongoing and show a potential for translation into clinical phases.

In preclinical studies for RSV-specific mucosal vaccine candidates, adenoviral vector based RSV fusion protein (Ad-F) vaccine have been demonstrated to be effective in the induction of mucosal IgA antibodies in combination with Interleukin (IL)-1 β upon intranasal administration and illustrated higher protection from RSV infection than prior natural infection in mice (Maier et al., 2022).

Another viral vector, encoding RSV fusion (F) or glycoprotein (G) protein utilized for an intranasal RSV vaccine in rodent models was Venezuelan equine encephalitis virus replicon particles (VRPs) (Mok et al., 2007). F-VRP vaccinated mice showed substantive F-specific SIgA in nasal and BAL secretions. Interestingly, VRP based immunizations via non-mucosal routes have been reported to generate IgA secreting cells in the mucosa of vaccinated animals (Mok et al., 2007). Perhaps studies identifying the mechanism of mucosal immune response induction by VRPs and other such viruses could be interesting to unlock their full potential.

Utilizing bacterial derived proteins as adjuvants also brought forth positive results. An adjuvanted intranasal RSV vaccine using outer membrane proteins (OMP) of *Neisseria* species as adjuvants, in conjunction with RSV subunit vaccine, for intranasal immunization in mice, reported a strong anti-RSV mucosal SIgA induction with complete protection from subsequent RSV challenge (Cyr et al., 2007). Another study

utilized BLPs or bacterium-like-proteins derived from *Lactobacillus* sp. combined with RSV prefusion F protein resulted in a substantive increase of SIgA levels in the nose, after intranasal administration in rodent models and demonstrated significant decrease in viral titers in the lungs post challenge (Rigter et al., 2013). A unique approach tackling, both influenza and respiratory syncytial viruses together in form of recombinant LAIV-RSV based intranasal vaccines, also induced combined protection in mice models (Matyushenko et al., 2020).

The recent approval of intramuscular RSV vaccines marks a significant breakthrough, yet the exploration of mucosal vaccination strategies, demonstrated in clinical and preclinical studies, highlights the ongoing development for a more comprehensive approach. Advances in adenoviral vectors, bacterial-derived adjuvants, and unique combined vaccines paints a promising picture for a mucosal vaccine candidate against RSV.

6. Challenges associated with mucosal vaccine development

In the context of the COVID-19 pandemic, a significant challenge posed, is the durability of mucosal immune responses induced. Studies demonstrate rapid decline of SIgA within 3–9 months post infection in severe cases of COVID-19 infections (Kryukova et al., 2023; Ren et al., 2022). A question then arises, can vaccines induce a desired immune response in recipients greater than the one induced by natural infections? This is true for vaccines developed against diseases such as Human Papilloma virus (HPV) (Pattyn et al., 2019), and Hib vaccines in infants (McVERNON et al., 2008). Furthermore, some intranasal vaccine designed for preclinical studies in animals with prior immunization, have also demonstrated the ability to induce SARS-CoV-2 specific immunity in the lungs, superior to natural infections (Mao et al., 2022). Thus, induction of mucosal immunity via vaccines with superiority over immunity induced by natural infections could be a possibility. This could also be achieved with the help of mucosal adjuvanted formulation, as demonstrated by several studies mentioned in this article.

When we talk about adjuvanted mucosal vaccines, another significant challenge presents itself. There are only a limited number of adjuvants that are approved for human use, with an even further limitation on adjuvants approved for mucosal vaccinations (Rhee et al., 2012). Therefore, another reason for the lack of substantive mucosal vaccines in the market, despite the immense research in preclinical studies, could also be due to the obvious lack of approved adjuvants that can be utilised for mucosal vaccine candidates (Verma et al., 2023).

Additionally, some mucosal approaches have utilized LAIVs or easily manipulated adenoviral vectors as antigen carriers. However, adenoviral based vectored vaccines have previously been demonstrated as inefficient in some clinical trials (Carvalho, 2022; Sekaly, 2008). Furthermore, LAIV's have been shown to be less protective in the past few flu seasons when compared to inactivated influenza vaccines delivered systemically (Chung et al., 2019; Zimmerman et al., 2016). The former could be denoted to pre-existing baseline immunity against the viral vector which could make it replication incompetent and thus raises a question of whether pre-existing mucosal immunity against SARS-CoV-2 viruses in the population, owing to its several outbreaks, could potentially limit the development of a live attenuated SARS-CoV-2 mucosal vaccine candidate. Moreover, the dearth of novel mucosal vaccine candidates based on vaccination platforms such as subunit, RNA or DNA vaccines could be due to the several challenges including questions regarding antigens of choice and their stability, mucosal barriers such as the mucus or the harsh digestive enzymes at mucosal surfaces e.g. salivary enzymes hindering vaccinations via oral routes (Kraan et al., 2014) as well as barriers presented by several commensal bacteria such as *Lactobacillus* at vaginal mucosal surfaces for an intravaginal vaccine design. Reversibly, researches have also tried to utilize these barriers to their advantage (Medaglini et al., 1997) and developed novel approaches such using *Lactobacillus* vectored mucosal vaccines against HIV infections (LeCureux and Dean, 2018) and utilizing barrier

properties of mucosal surfaces to design effective vaccines (Hartwell et al., 2022; “Hitchhiking the mucosa,” n. d.).

From an immunological standpoint, steering the mucosal immune response from tolerant to a protective one also presents an additional challenge. (Baker et al., 2022). Furthermore, while certain studies emphasize the protective role of SIgA, others present a divergent narrative. Indeed, it's important to recognize that, much like different components of the immune system, safeguarding against diseases relies on the combined efforts of various elements working together to keep the immune system functioning effectively. Therefore, it is essential to recognize the significance of tissue-resident memory T and B cells, along with other immunoglobulins present in mucosal secretions, particularly IgG1, which has been substantiated as crucial in the context of RSV infections. Hence, adopting a balanced approach necessitates not only considering both mucosal and systemic aspects of immunity but also recognizing other key components that contribute to mucosal immunity as integral factors for designing effective strategies against respiratory infections caused by SARS-CoV-2, influenza viruses, and RSV.

Additionally, the device use of the administration of a mucosal vaccine is of high importance and can significantly impact the immune response generated and also defines the ease of administration. Despite the lack of studies focusing on the mucosal vaccine administration devices, our knowledge of development of instillation devices for liquid drug formulations via mucosal surfaces can be extrapolated in the context of mucosal vaccines. Using catheters or micropipettes, or perhaps more complex metered spray pumps or nebulizers for pulmonary focused deliveries have been described in great depth in literature (Dugernier et al., 2019; Spence et al., 2019) and yet their adaptation for a vaccine platform presents a significant challenge.

More recent vaccine developments have been focused on tackling vaccine distribution and cold-chain maintenance concerns by developing a powdered influenza vaccine to be delivered intranasally. Not only would this vaccine benefit from the advantages of intranasal vaccinations established earlier in this section but also would be more stable than liquid preparations which often require expensive cold chain conditions that are not feasible in developing countries. Juan Huang et al. establish a novel powder based intranasally administered influenza vaccine candidate that was demonstrated to be as potent in generating an immune response, including nasal IgA titers, as its liquid formulation counterpart when both were administered intranasally in rat models (Huang et al., 2004).

7. IgA-based therapeutics

Immunoglobulins, as vaccination platforms, either in form of passive immunization or recombinant molecules have also underwent extensive research. Use of these immunoglobulins such as IgA in its secretory form is limited in current therapeutic settings, despite its established importance in combating infections, which might be due to the challenges associated with their isolation and purification (Longet et al., 2013).

Despite this, the ability of these immunoglobulins to act as effective antigen carriers and induce potent as well as effective immune responses have been previously explored in the context of HIV (Rochereau et al., 2015). Building on this versatility of immunoglobulins, monomeric forms of IgG, conjugated with spike protein from SARS-CoV-2 has been investigated in generating prominent immune responses following intranasal immunization, due to its ability to cross epithelial cell barriers via neonatal Fc receptors and induce an immune response against the conjugated antigen (Li et al., 2023). Other unique approaches such as passive immunization using “hyperimmune milk” from maternally vaccinated bovine animals against respiratory viruses are also being explored as potential means of protection from respiratory infections in animals and humans alike (Nili et al., 2022).

Use of secretory IgA isolated from human colostrum following intratracheal administration in murine models has been previously demonstrated to induce protection against *Mycobacterium tuberculosis*

challenge and reduced bacterial load in the lungs (Alvarez et al., 2013). This supports the idea of utilizing secretory IgA or monoclonal IgA antibodies, whether administered systemically or via mucosal surfaces, to induce protective immune responses against infection caused by several respiratory viruses.

Guinea pigs and ferrets were parenterally administered neutralizing mouse monoclonal IgG antibodies against H1N1 hemagglutinin and despite high titers, IgG did not prevent viral transmission post challenge. However, intramuscular administration of monoclonal IgA prevent up to 88% transmission in guinea pigs (Seibert et al., 2013), suggesting their importance in blocking influenza viral transmission and also draws upon the possibility of testing these IgA formulations for mucosal administration. Furthermore, mice injected with polymeric or monomeric forms of IgA specific for H1 hemagglutinin of influenza virus were compared with monomeric IgG upon parenteral administration with the same specificity. The polymeric IgA was demonstrated to transport more to the nasal secretions with respect to monomeric IgA (and IgG) and was further able to protect mice following nasal Influenza challenge. This further potentiates the possibilities of utilizing polymeric IgA antibodies in an intranasal approach to confer protection against infection (Kb and Pa, 1991).

Intranasal instillation of monoclonal IgA has been previously reported to be efficient in protecting non-immunized mice against other infectious diseases (Mazanec et al., 1987; Renegar and Small, 1991). In fact, IgA neutralizing activity is heavily determined by their differential glycosylation properties, (Ding et al., 2022) and IgA demonstrated to effectively inhibit the extracellular release of influenza viruses from infected cells at a much greater capacity than monoclonal IgG (Muramatsu et al., 2014).

Similarly, engineered tetrameric IgA antibodies, specific to mouse influenza A virus matrix-2 protein were compared with other recombinant monomeric IgA, dimeric IgA and IgG molecules with the same specificity *in vitro*, for demonstrating their ability to bind to the influenza M-2 protein. Polymeric IgA showed the highest ability to bind to these M-2 proteins and significantly reducing influenza A virus plaque size compared to the other molecules, demonstrating the potential of IgA antibodies in protection from influenza infections (Okuya et al., 2020a).

Conflicting results exist in regarding the efficacy of therapeutic IgA treatment against RSV infections. A study conducted in Rhesus monkeys, used intranasal administration of mouse dimeric and polymeric monoclonal IgA specific for RSV F glycoprotein demonstrated reduction in viral shedding in the throat and the lungs, in addition to RSV neutralizing antibodies in the serum (Weltzin et al., 1996). However, this strategy was not compared with other therapeutic interventions. Contrary to this, in another study, a monoclonal IgA antibody specific to RSV F-protein was compared with monoclonal IgG antibody with the same specificity, administered in mice intranasally. Monoclonal IgG antibody was more effective in reducing RSV lung titers as compared to IgA. This was further compared to parenteral administration where there was a further reduction of RSV titers in the nose, but only via parenteral administration of IgG (Fisher et al., 1999).

In conclusion, the therapeutic potential of IgA antibodies to combat respiratory viral infections such as those caused by SARS-CoV-2, influenza viruses, and RSV, whilst holds promise, calls upon the need of substantial research to reach its full potential. It is, however, essential to acknowledge certain limitations to therapeutic use of IgA.

The challenges posed by mucosal barriers to mucosal vaccines, as mentioned in the former sections, also apply to therapeutic IgA treatments. Furthermore, the kinetics of SIgA in terms of stability and possible risk of degradation in the mucosal environment, pose challenges to the development of these therapeutic approaches. Moreover, balancing the pro-inflammatory versus anti-inflammatory responses calls for a nuanced approach in IgA based therapeutic developments. Despite these limitations, the continued exploration of IgA-based therapies and innovative strategies further aids the advancement of therapeutics to improve mucosal immunity against respiratory viruses.

8. Conclusion

This review has synthesized current knowledge about the roles of mucosal SIgA in the context of SARS-CoV-2, influenza and RSV infections. The beneficial role of mucosal SIgA in protection from SARS-CoV-2 infections is now quite well-documented. Given that the current systemic vaccines targeting SARS-CoV-2 are not very efficient in inducing mucosal immunity, intranasal or inhaled COVID-19 vaccines aiming to boost SIgA responses are under development. Furthermore, a couple of these have now been licensed in specific countries. Regarding influenza, the protective role of SIgA in influenza infections has been described. However, some studies highlighted the low durability of SIgA responses and underlined a complementary role of IgG. An approach based on systemic and mucosal vaccination might be appropriate to enhance protection against influenza. So far, one licensed intranasal flu vaccine aiming to improve mucosal immunity has been approved in Europe and North America even though systemic vaccination remains the most common approach for the seasonal influenza vaccines. The ongoing advancements in mucosal vaccination strategies, particularly those targeting SIgA responses, ensure a promising view for enhancing respiratory immunity against SARS-CoV-2 and influenza infections. However, the durability of mucosal humoral responses, the need for efficient delivery systems, the exploration of adjuvants, and the understanding of cellular memory responses remain critical areas of research. Finally, tailoring vaccine formulations to induce a balanced inflammatory response at mucosal surfaces is extremely essential for inducing protective immunity. Regarding RSV, SIgA's role in protection from infection is currently less conclusive. Some evidences suggest a protective role but there are still significant gaps in knowledge. The potential benefit of mucosal vaccination to induce robust protection against RSV remains to be demonstrated. Current licensed therapeutic monoclonal antibodies against RSV administered by systemic routes are all based on IgG isotypes. The interest of using IgA-based therapeutics administered by mucosal routes could further be explored.

In summary, SIgA's protective role is nuanced based on the current literature and likely depends on the specific characteristics of the pathogen and the desired outcomes of vaccination.

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Divya Sinha: Writing – original draft. **Melyssa Yaugel-Novoa:** Writing – original draft. **Louis Waeckel:** Writing – original draft. **Stéphane Paul:** Writing – original draft, Conceptualization. **Stéphanie Longet:** Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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