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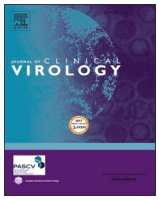

What have we learned from animal studies of immune responses to respiratory syncytial virus infection?

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A B S T R A C T

Respiratory syncytial virus (RSV) is a common cause of severe respiratory tract infection at the extremes of age and in vulnerable populations. However, it is difficult to predict the clinical course and most infants who develop severe disease have no pre-existing risk factors. With the recent licencing of RSV vaccines and monoclonal antibodies, it is important to identify high-risk individuals in order to prioritise those who will most benefit from prophylaxis. The immune response to RSV and the mechanisms by which the virus prevents the establishment of immunological memory have been extensively investigated but remain incompletely characterised. In animal models, beneficial and harmful immune responses have both been demonstrated. While only chimpanzees are fully permissive for human RSV replication, most research has been conducted in rodents, or in calves infected with bovine RSV. Based on these studies, components of innate and adaptive immune systems, cytokines, chemokines and metabolites, and specific genetic and transcriptomic signatures are identified as potential predictive indicators of RSV disease severity. These findings may inform the development of future human studies and contribute to the early identification of patients at high risk of severe infection. This narrative review summarises the factors involved in the immune response to RSV infection in these models and highlights the relationship between potential biomarkers and disease severity.

1. Introduction

Respiratory syncytial virus (RSV or human orthopneumonvirus) is a single-stranded, negative-sense RNA virus of the *paramyxoviridae* family. Approximately 100,000 infant deaths globally are caused by RSV each year [1] but identifying patients who will develop severe disease is challenging, even amongst those with known risk factors, such as prematurity.

Several animal models have been used to study RSV [2]. Most studies are in mice, benefitting from fast gestation times, low husbandry costs, the availability of genetically modified mice, many immunological reagents and a well-characterised immune system. Some mouse strains have a much greater susceptibility to viral infection and disease than others, influencing study outcomes [3]. The immune system and the response to RSV in other small animals is less well characterised.

Bovine disease can be induced by bovine RSV (bRSV), closely related to human RSV-B strains with broadly similar pathogenesis and epidemiology [2]. The utility of bovine models is limited by cost and logistical issues of conducting experiments in large animals. Chimpanzees are highly susceptible to human strains but are essentially no longer used as experimental animals for ethical and cost reasons [4]. Additionally, pneumonia virus of mice (PVM) is the murine homolog of RSV and has been used to infer features of RSV pathogenesis [5]. However, the PVM model is restricted by the high rate of transmission within animal facilities, presenting a welfare and biosafety challenge.

Severe RSV disease is variably defined in different model organisms. Severity scores using clinical parameters can be reliable in some models but are somewhat subjective and variable. Weight loss and histopathological changes in the lungs are more commonly used to determine severity in animal models.

Findings from animal studies may not be directly transferable to humans, but insights gained from animal studies can establish principles and inform the design and focus of human studies which we have reviewed recently [6]. This current review summarizes factors

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influencing disease severity in selected major animal RSV models, focusing on the immunological readouts that may act as biomarkers of disease severity.

2. Innate immune response

The innate immune system provides an immediate response to an encounter with RSV and aims to limit early RSV replication. The resident epithelial and antigen-presenting cells (APCs) express pattern recognition receptors (PRRs) including Toll-like receptors (TLRs) and RIG-like receptors (RLRs), which recognise pathogen-associated molecular patterns (PAMPs) and initiate inflammatory responses to RSV. Activated PRRs upregulate inflammatory cytokines and chemokines [1] and recruit eosinophils, monocytes and natural killer (NK) cells in a broad pattern that is similar across all prominent model organisms for RSV infection. The adaptor molecule MyD88 is a key component of TLR signalling that engages activation of NF-kB and subsequent inflammatory cytokine responses [7]. MyD88(-/-) mice exhibit exacerbated RSV pathophysiology, associated with enhanced Th2 cytokine expression [8] and reduced neutrophil recruitment to the lung [9]. Additionally, loss of RLR signalling in MAVS(-/-) mice resulted in a deficient early innate response to primary RSV infection, but also led to a weaker recall response by $CD4^+$ and $CD8^+$ *T* cells following re-infection, indicating that MAVS signalling is required for robust T cell memory responses to RSV [10]. Furthermore, MAVS signalling was later shown to be required for the formation of $CD8^+$ tissue resident memory T cell responses to RSV [11].

2.1. Resident cells of the respiratory tract

While human studies of immune responses to RSV have largely depended on peripheral sampling, there is a clear need to focus on the local responses in the lung [12]. Alveolar macrophages and dendritic cells (DCs) are major phagocytic cells in the lung and play a key role in presenting antigen to T cells. One study found that alveolar macrophage depletion in RSV infection was associated with reduced inflammation in BALB/c mice [13], possibly as macrophage depletion reduces the initial cytokine response to RSV in the murine model [14]. Similarly, it has been reported that "M2 type macrophages" mediate resolution of pulmonary pathology in RSV infection in mice [15]. While this exact role has not been noted in humans, macrophages do play a role in immune regulation and antigen presentation [16]

Two murine studies found DCs were involved in viral clearance and were protective against RSV disease pathogenesis [17,18]. In humans and mice, DCs are the primary antigen-presenting cells in RSV infection, with low numbers of DCs being associated with the development of RSV bronchiolitis in humans [13]. Defects in DC function result in non-specific immunodeficiencies that might predict more severe infections from a wide range of pathogens including RSV. Therefore, DCs may not represent useful biomarkers specifically for RSV infection.

2.2. Recruitment of cells to the respiratory tract

Recruited inflammatory cells promote RSV clearance but can cause immunopathology. NK cells are innate lymphoid cells exhibiting perforin-dependent cytotoxic activity against RSV-infected cells and production of cytokines and chemokines [19]. In a study of perforin knockout mice, RSV clearance was delayed, with prolonged illness and overproduction of IFN-γ and TNF-α compared with controls [20]. However, it has also been reported that NK cell depletion significantly limits lung immune injury in RSV-infected mice, and that production of excessive IFN-γ by NK cells may result in acute injury [21]. While NK cells are important in the clearance of infection, this suggests that they may also be involved in RSV pathogenesis. Markers of NK cell over-activity could be studied in future biomarker research.

Eosinophils have been shown to protect against RSV in vivo, promoting virus clearance and limiting virus-induced lung dysfunction [22]. However, transferring eosinophils from RSV-infected mice into naïve mice resulted in airway hyper-responsiveness (AHR) [23], similar to their ambiguous role in human infection, where some contribution to recovery is observed, despite the association of eosinophils with a generally deleterious Th2 immune response [16].

In the early stages of RSV infection, neutrophils are also recruited to the respiratory tract but recent studies show that neutrophils have no protective role in primary infection of mice, but are also not pathogenic [9]. While neutrophil and eosinophil recruitment have been associated with RSV disease severity in humans, with neutrophils being by far the most prevalent cells recruited to the respiratory tract in humans with a definite role in disease pathogenesis [16], they play little role in primary infection of mice. Markers of neutrophil activity are excellent human biomarker candidates, there is, however, limited evidence from animal models [24].

3. Soluble immune mediators

3.1. Interferons

Type I and type III interferons (IFN) are induced by almost all nucleated cell types following PRR activation by infecting respiratory viruses. These IFNs act to suppress RSV replication through autocrine and paracrine signalling that induces the expression of IFN stimulated genes (ISGs) that underpin innate antiviral immunity [25,26]. RSV infection reduces IFN expression [27], and several studies have focussed on the role of the cytokine IFN-γ (type II IFN) in RSV disease severity [28]. One study of IFN-γ (-/-) mice challenged with RSV found that viral load in the lungs was significantly higher than in wild-type mice, with increased airway hyperresponsiveness (AHR). In studies of IFN-γR(-/-) mice, IFN receptor deficiency resulted in aggravated pulmonary pathology, enhanced disease and reduced viral clearance [29,30], leading to a shift towards a Th2-dominant response [29]. It has therefore been suggested that IFN-γ contributes to protection from AHR and lung histopathology [31].

However, another study demonstrated less severe obstructive airways disease during RSV infection in IFN-γ(-/-) mice compared with wild-type controls, and treatment with IFN-γ in IFN-γ(-/-) mice resulted in greater AHR [32]. These conflicting reports suggest there is no clear relationship between IFNs and RSV disease severity, and that observed effects are likely a result of beneficial effects on viral suppression alongside pathologic effects on exacerbating inflammation.

There have been many studies of cytokines and interleukins in animal models, recently summarised in an extensive review [33]. For example, studies of IL-12 in mice indicate enhanced disease *via* NK cells, an effect similar to that seen with IL-18, [34,35]. Treatment of RSV-infected mice with anti-IL-12 antibody resulted in increased AHR and mucus production [36]. It was found that IL-2 priming in mice reduced weight-loss and illness severity [37], while treatment of $CD8^+$-depleted mice with IL-5 resulted in lung eosinophilia and AHR [38].

TNF-α is a mediator of RSV-induced illness [39], and one study of various knockout mice found reduced disease severity with TNF-α depletion [40]. Age-dependent differential expression of TNF-α is also associated with disease severity in cattle [41], with older cattle experiencing more severe infection and higher levels of inflammatory cytokine expression, despite decreased viral replication.

3.2. Type 1 and Type 2 responses

In murine and bovine RSV infection, Th1-type 1 (Type 1) responses are generally protective, while Th2-type (Type 2) responses have a more uncertain role [42]. Type 1 cytokines promote cell-mediated resistance to viral infection and other pathogens through pro-inflammatory mechanisms. They are generally considered to be protective in RSV

infection and are required for complete viral clearance. Type 2 cytokines counteract and limit this response, facilitating eosinophil responses and mucus production. Type 2 cytokines have been linked to enhanced RSV disease in mice but may prevent tissue damage resulting from an uncontrolled Type 1 response [43]. Thus, there needs to be a balance between Type 1 and 2 responses.

The relationship between cytokines involved in the Type 1 response and disease severity is evident. Deficiencies of Th1 cells or pathways linked to Type 1 responses can enhance RSV disease severity. This relationship is recapitulated in humans, with Type 1 responses broadly being seen as strongly protective against more severe infection in humans [16]. However, our recent studies of infants show that both interferon levels and viral load are paradoxically reduced in anterior nasal samples from infants with severe bronchiolitis and respiratory failure [44]. In the design of biomarker panels, inclusion of Type 1 response markers is clearly important.

Type 2 cytokines also have a role in the immune response to RSV. Mice vaccinated with formalin-inactivated (FI) RSV that are subsequently inoculated with RSV demonstrate an IL-4 dominant immune response and delayed viral clearance and more severe immunopathology [45]. This effect has been attributed to alterations in antigen processing that result from formalin treatment [46].

IL-6 is up-regulated after infection in mice and mediates resolution by inducing production of IL-27. This suppresses pathogenic immune responses in RSV infection, and accordingly, IL-6 may be associated with reduced disease severity [47]. Similarly, deletion or depletion of IL-10 in several studies of murine models resulted in enhanced T-cell mediated immunopathology and more severe disease [48–51].

IL-13 is a critical cytokine in the allergic response, associated with reduced RSV disease severity in the murine model. One study demonstrated that overexpression of IL-13 resulted in decreased viral titres, protection against RSV-induced weight loss and diminished lung IFN-γ production [52]. However, RSV infection can induce an IL-13 dependent change in airway function, contributing to the development of severe allergic asthmatic responses [53], while a further study implicated IL-13 in AHR during RSV infection [54]. It has been suggested that experimental use of different viral strains may account for this discrepancy [52].

A high IL-4/IFN-γ ratio is a marker of Th2 bias and has been linked to more severe RSV infection in humans [16], particularly in children. Th2 cytokines are promising potential biomarkers for severe RSV disease, due to inhibitory effects on the protective Th1 response and role in the development of AHR.

3.3. Chemokines

Chemokines are a diverse group of molecules with varied effects, some of which have a clear role in RSV disease severity.

CCR1 knock-out has no impact on RSV clearance in mice, but leads to decreased AHR and mucus production, and a significant increase in IFN-γ and CXCL10 [55]. CCR1 blockade promotes inhibition of inflammatory mediators with minimal impact on RSV replication, indicating a possible use for CCR1 levels in predicting disease severity.

CCL3 is significantly upregulated during primary RSV infection in the murine model [14]. While CCL3 inhibition increases the proportion of pro-inflammatory cells [56], two further murine studies demonstrated that this chemokine is associated with increased disease severity [57,58], and is also associated with disease severity in human adults [16].

CCL5 is involved in the recruitment of monocytes, memory T-cells and eosinophils to sites of inflammation [59], and levels of this chemokine have been shown to correlate with RSV disease severity in mice [60]. Tekkanat et al. [61] treated mice with anti-CCL5 antibody, resulting in decreased AHR and increased IL-12 production. This suggests that CCL5 influences the Th1:Th2 balance, and inhibiting this chemokine may be protective against RSV disease [61]. CCL5 has also been shown to be upregulated in human disease [16] and deserves further study as a disease marker.

One study, conducted using CXCR2(-/-) mice, concluded that CXCR2 significantly increased AHR [62]. In contrast, neonatal mice deficient in CX3CR1 develop significantly greater neutrophilic inflammation in the lungs when compared with wild-type mice infected with RSV [63]. Similarly, antibody-mediated neutralisation of CXCR3 results in a significant increase in AHR and impaired viral clearance [64].

3.4. Metabolomics

Measurements of various metabolites have recently been investigated as potential biomarkers of RSV disease. One study in a mouse model found 15 metabolites including glutaric acid, hydroxyglutaric acid and spermine were upregulated in mice infected with RSV compared with controls [28].

4. Adaptive immune response

The adaptive immune response allows the host to precisely target pathogens including RSV, while minimising tissue damage. However, while cytotoxic T-lymphocytes mediate resolution of RSV infection, long-term immunity is not effectively established.

4.1. T-Cell response

Eradication of RSV infection relies upon an effective T-cell response, and defective T-cell responses in children or in animal models are associated with increased RSV disease severity and delayed viral clearance[42]. T-cell defects result in progressive but atypical viral replication and airway inflammation [65]. In mice, T-cell transfer can augment acute disease [43] and it has been suggested that T-cell function may be actively dysregulated by RSV infection [66].

$CD4^+$ cells have antiviral effects, promote B-cell activation but can augment disease as shown in one study of mice infected with RSV [67]. Neonatal infection with RSV primes mice for augmented eosinophilic disease in adulthood [68] and selective deletion of IL-4Rα, expressed on $CD4^+$ cells, prevents immunopathology on reinfection in mice which had been originally infected as neonates [69].

In neonatal cattle, the immune response in the lungs is characterised by $CD8^+$ *T*-cell infiltration, with these T-cells outnumbering $CD4^+$ cells by a ratio of 3:1 by day 10 of infection [70]. Gnotobiotic calves can be selectively depleted of T-lymphocyte subsets using monoclonal antibodies. $CD4^+$-depleted calves exhibit poor neutralising antibody production without impairment of viral clearance [71], while $CD8^+$ *T*-cell depletion (which does not affect antibody production) delays viral clearance. However, combined $CD4^+$ and $CD8^+$ depletion in vivo results in reduced weight loss during RSV challenge [72].

One study found that control mice developed airway eosinophilia and AHR in response to RSV infection, while $CD8^+$-depleted mice did not [38]. It was also found that $CD8^+$ *T*-cells enhanced disease during RSV re-infection in a study of BALB/c mice [73]. Several animal studies have reported RSV disease severity to be associated with Th17 levels [74–76]. Pre-exposure of mice to *B. pertussis* protects from RSV infection in mice, an effect which is blocked by IL-17 depletion [77].

Regulatory T-cells (T_{REG}) have an important role in regulating adaptive immunity [78,79]. T_{REG} depletion increases disease severity and inflammation [80–83], but with no impact on viral clearance [84], a relationship which is similar to that observed in humans [16]. “Bystander” recruitment of heterlogous systemic memory T-cells impaired viral immunity and slightly increased weight loss in a study of TCR-transgenic mice [85]. Similarly, it has been noted that depletion of T-cell derived IL-10 is associated with increased inflammatory cells and production of inflammatory mediators [48].

Overall, levels of $CD4^+$ and $CD8^+$ *T*-cells provide promising potential as biomarker targets. The inverse correlation between levels of

circulating CD4$^+$ *T*-cells and disease severity remains in humans [16]. The patterns identified in the murine model may not be directly comparable to those in humans due to the variation in disease pathogenesis and the direct inoculation of RSV into the lower respiratory tract in murine studies. It may be more beneficial to consider T-cell differentiation as a marker of severity, rather than cell numbers.

4.2. B-Cell and antibody response

We have previously reviewed this topic in animal models in detail [86].

Following neonatal infection, wild-type mice exhibit an RSV-specific IgE response at reinfection. Increased AHR, airway eosinophilia and mucus hyperproduction occur. In two studies, administration of anti-IgE prevented AHR. As a result, it was concluded that specific IgE may be associated with severity of disease [87,88]. The magnitude and diversity of IgE response was correlated with severity of clinical signs of infection, in a study of bRSV in calves [89]. Similarly, virus-specific IgE contributed to the development of lung pathology and enhanced clinical disease in calves infected with bRSV [90,91].

However, in another study, investigators depleted mice of B-cells and reported that depletion was associated with more severe RSV disease at both primary challenge and reinfection compared to controls. The authors concluded that the presence of RSV-specific antibody reduced illness severity [92]. Similarly, impairment of B-cells induced lung inflammation in mice challenged with RSV [82]. In humans there is some ambiguity in the contribution of B-cell responses to more severe disease, with some markers of plasma cell activity, such as APRIL and BAFF being found at higher levels in children being ventilated for severe RSV disease, while other studies have found these to correlate with decreased hypoxia, and increased neutralising antibody (and thus decreased disease severity) [16].

Calves with a wide range of antibody titres seem susceptible to RSV infection, suggesting that serum antibody protection is limited [93], and no clinical differences were observed between calves stratified into high and low bRSV-specific antibody groups [94]. It should be noted that there is not significant placental transfer of RSV antibodies in calves, so most antibody is derived from colostrum and these are at very low levels when compared with humans. In a bovine model, the level of specific maternally-derived antibodies inversely correlated with severity of disease, although did not prevent development of disease [95]. However, another study [96] observed that a high level of maternal antibody in early infection hindered the development of appropriate T- and B-lymphocyte responses during more severe infection, suggesting that a high level of maternal antibody may be harmful in this animal model. There is conflicting evidence for the effect of the adaptive immune response on RSV disease severity. There is good evidence that T_{REGS} act effectively to modulate disease, but evidence of the long-term effects of RSV-specific antibody on subsequent lung health is contradictory. The impact of RSV-specific antibody on disease severity varies between studies. However, it is clear that passive transfer of neutralising antibody (e.g., palivizumab or nirsevimab) offers a significant protective effect in human infants [97].

Many of the relationships outlined in this section between factors involved in adaptive immunity and disease severity are similar to those noted in humans, making markers of these responses potentially useful in biomarker development [16]. Neutralising antibodies and genes effecting their generation may be useful as correlates of protection for RSV vaccines, however they may not be useful as biomarkers of severity, due to the relative lateness in the immune response where antibodies play a role.

5. Genetics and transcriptomics

Genetic factors play a role in the severity of murine RSV disease, [3] but are not well-characterised in other animal models. However, murine study findings are often not applicable to human populations, due to the genetic homogeneity of laboratory mouse populations and important differences in the innate immune systems.

One study [98] used microarrays to analyse the response to RSV infection, with weight loss, breathing difficulty and mortality as markers of disease severity. Many age-associated transcriptomic differences were correlated with disease severity, including deficiencies in the CD8$^+$ cytotoxic T-cell response and decreased IFN-γ expression The confounding effect of age precluded identification of individual transcriptomic differences associated with severity. A similar study which characterised the role of ageing in disease severity in mice [99] reported that older mice exhibited higher IFN-γ production and more severe disease. Another murine study [100] showed that interferon-induced protein 44 (*IFI44*) and interferon-induced protein 44-like (*IFI44L*) are upregulated after RSV infection and that overexpression of these markers was sufficient to restrict RSV infection at an early time post-infection.

There are very few data on the effect of bRSV on the bovine transcriptome. One study using microarrays from lung tissue to investigate the immune response to bRSV in calves [49] reported increased expression of IL-6 and IL-8, which have been implicated in disease pathogenesis in other models. Another study using RNA-seq [101] found several genes (*CCL8, SLCO2B1, ADM, IFI27*) were significantly up-regulated, and two genes (*COL1A2, COL1A1*) were significantly down-regulated, in bRSV challenged relative to control healthy calves. IFI27 has previously been implicated in severe RSV infection in humans [102,103]. Other targeted methods such as polymerase chain reaction (PCR) have been used to analyse gene expression in response to RSV. One study [104] used real-time PCR to measure the levels of inflammatory cytokines in the lungs of neonatal cattle in response to RSV infection, identifying genes related to IFN-γ, IL-8 and IL-12p40 upregulation [98]. These findings indicate an immune response characterised by neutrophil infiltration and Th1-type cytokines, as is generally expected in human infection.

Transcriptomics studies in murine and bovine models thus far reflect findings established by other methods – including correlations between disease severity and antigen presentation, CD8$^+$ *T*-cells and IFN-γ expression. Transcriptomic analyses of other models may improve our understanding of RSV pathogenesis and improve the applicability of findings to human disease.

6. Conclusions

Despite the recent introduction of highly effective vaccines and long-half-life monoclonal antibody prophylaxis, RSV infection remains a major cause of morbidity and mortality worldwide in humans. Animal models have been used extensively to investigate the components of the immune response associated with the severity of disease, and identifying biomarkers of severity could improve care and outcomes in humans with RSV infection.

While contemporary studies of the human and animal models of RSV infection typically highlight similarities, most RSV studies have been conducted in murine models which have limitations with respect to understanding the disease in humans. However, knowledge of the factors affecting disease severity will be necessary for any advances in risk stratification, and animal models continue to provide a practical route to deeper understanding of potential mechanisms.

Promising candidates for further study (Table 1) include markers of NK cell activity, molecules such as IFN-γ and chemokines influencing the Th1:Th2 balance. Measures that reflect virus-specific CD4$^+$ and CD8$^+$ *T*-cells, and neutralising antibodies in local mucosal sites may also contribute significantly to predicting the outcome of RSV infection.

CRediT authorship contribution statement

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Table 1
Summary of possible biomarkers of RSV disease severity in animal models, and their contribution to severity in each model, in comparison with data from human infant studies.

	Severity	Murine models	Bovine models	Other models	Human infants (mild vs. severe RSV disease) from [6]
Innate immune response	↑	NK cells [21], monocytes [23]			Neutrophils
	No effect	Alveolar macrophage [13]			
	↓	SP-A [105], SP-C [106] SP-D [107], alveolar macrophages [13,15], DCs [17,18], TLR3 [108], TLR7 [75], NOD2 [109], perforin [20], eosinophils [22]			
Chemokines and cytokines					Respiratory tract: IL-1β, IL-6, IL-8, IL-4:IFN-γ, MIP-1β
	↑	IFN-γ [32], IL-5 [110], TNF [56], TNF-α [40], IL-4 [45], IL-13 [53,54], CCL3 [57,58], CCL5 [61], CXCR2 [62]			Peripheral blood: IL-6, IL-10, IL-8, IL-4:IFN-γ
	No effect				
	↓	IFN-γ [31,40], IFN-γR [29], IL-12 [36], IL-2 [37], IL-6 [47], IL-10 [48–51], IL-13 [52], CX3CR1 [63], CXCR3 [64]			Respiratory tract: IFN-γ Peripheral blood: IL-4, IL-12, IFN-γ,
Adaptive immune response	↑	$CD4^+$ [67,72], $CD8^+$ [38,72,73], memory T-cells [85], IL-4Rα [69], Th17 [74–76], RSV-specific IgE [88]	RSV-specific IgE [89,90,111]		nBreg cell. RSV-specific IgG, IgA, IgM, pre-F and G antibodies
	No effect		bRSV-specific antibodies [93] IgG1 [94]	bRSV-specific antibodies in an ovine model [112]	
	↓	T-cells [65], T_{REG} [2-6] [79–83], B-cells[82,92]	$CD8^+$ [71]		T-cells, B-cells, cytotoxic NK cells, plasma cells, RSV-specific IgE

Abbreviations: IFN-γ, interferon-gamma; IFN-γR, interferon-gamma receptor; IFN-R, interferon receptor; IL, interleukin; NK, natural killer; NOD, NOD-like receptor; Th, T-helper; TLR, Toll-like receptor, IFN-γ, interferon-γ; IL, interleukin; MIP-1β, macrophage inflammatory protein-1β; nBreg, neonatal-specific regulatory B cell; NK, natural killer;.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Jeroen Aerssens reports a relationship with Janssen Pharmaceutica NV that includes: employment.

Jeroen Aerssens reports a relationship with Johnson and Johnson Ltd that includes: equity or stocks.

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SBD has previously received honoraria from Sanofi for taking part in RSV advisory boards and has provided consultancy and/or investigator roles in relation to product development for Janssen, AstraZeneca, Pfizer, Moderna, Valneva, MSD, iLiAD, MundiPharma and Sanofi with fees paid to my institution. SBD is a member of the UK Department of Health and Social Care's (DHSC) Joint Committee on Vaccination and Immunisation (JCVI) RSV subcommittee and Medicines and Healthcare products Regulatory Agency's (MHRA) Paediatric Medicine Expert Advisory Group (PMEAG), but the reviews expressed herein do not necessarily represent those of DHSC, JCVI, MHRA or PMEAG.

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DO was an employee of Janssen Pharmaceutica NV

JA was an employee of Janssen Pharmaceutica NV and is a shareholder of Johnson & Johnson.

DT, JP, CM, JM have no conflicts to declare.

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

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