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From setbacks to success: lessons from the journey of RSV vaccine development

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***Abstract*:** Respiratory syncytial virus (RSV) causes high worldwide infant mortality, as well as a high disease burden in the elderly. Efforts in vaccine development over the past 60 years have recently delivered three approved vaccines and two monoclonal antibodies (mAbs). Looking back at the eventful history of RSV vaccine development, several factors can be identified that have hampered the developmental pathway, including the occurrence of enhanced RSV disease (ERD) in the first vaccine attempt and the difficulty in characterizing and stabilizing the pre-fusion F protein as a vaccine target. Moreover, the need for large trials to test vaccine efficacy, usually done late in development, and the lack of a correlate of protection (CoP) result in significant uncertainties in RSV vaccine development. The use of controlled human infection models (CHIMs) may provide a solution for some of these problems: through swift, cost-efficient and closely monitored assessment of vaccine safety and efficacy in early clinical phases, vaccines can either 'fail fast' or show results supporting further investments. Moreover, CHIMs facilitate the assessment of disease and could assist in the identification of a CoP supporting late-stage development. Although some factors may affect translatability to real-world vaccine efficacy, CHIMs can support the clinical development pathway in various ways. We advocate for, and demonstrate, a conceptual and rational design of RSV vaccine development. Assessing protective efficacy early on would result in the most cost-efficient pathway and identification of target populations should be done as early as possible. For RSV, elderly individuals and people in low- and middle-income countries are high-impact populations for RSV prevention. While RSV immunization is now available in certain regions, global access is not accomplished yet, and worldwide prevention does not seem within reach. Quick and cost-effective assessments of candidates currently in the pipeline could contribute to future successes in the battle against RSV.

Plain language summary

From setbacks to success: lessons from the journey of RSV vaccine development

Respiratory syncytial virus (RSV) leads to the deaths of many young children worldwide, as well as severe infections and deaths in the elderly. The search for an effective vaccine has lasted over 60 years, in which many vaccine candidates were developed and tested. Only recently, three vaccines and two monoclonal antibodies were approved for medical use, to prevent disease in newborns, pregnant individuals and the elderly. Several lessons can be learned from the long and difficult journey of RSV vaccine development. The efficacy of a vaccine is often only studied in large trials, sometimes with over 10 000 participants; this could also be done, however, in smaller studies in which participants

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receive the vaccine candidate and are given the virus under controlled conditions. Though these smaller studies may not substitute the larger one, they can still save time and money, and provide more information about RSV disease and how the immune system battles the virus. Many RSV vaccine candidates are still being developed; we advocate for and demonstrate a thoughtful design of the steps to test these vaccines, using the controlled infection studies to test in a time- and cost-efficient manner.

Keywords: clinical development, controlled human infection model, RSV, therapeutic, vaccine

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Introduction

Respiratory syncytial virus (RSV) is a major cause of upper respiratory tract infections (URTIs) in adults, and bronchiolitis and viral pneumonia in children, affecting 64 million people globally each year and posing the second highest disease burden in infants.[1–3] In addition to high infant mortality and a significant number of children facing long-term health consequences, attention has been focused more recently on its prevalence in adults, highlighting the considerable burden RSV places on society and health care systems.[4]

After over 60 years of strenuous efforts by the scientific community, finally three RSV vaccines have become available: in 2023, Arexvy® (GSK) was registered for use in older adults and Abrysvo® (Pfizer) for use in older adults and pregnant individuals in Europe and the United States; in 2024, mRESVIA® (Moderna) was approved for use in older adults in the US.[5–7] Passive immunization through monoclonal antibodies (mAbs) was available already with Synagis®, approved in 1998 for use in children at high-risk for RSV disease; in 2022 Beyfortus® received market approval by the Food and Drug Administration (FDA) and European Medicines Agency (EMA), to protect neonates and infants.[8] The development of effective vaccines inducing active immunity against RSV has been hampered by the young age of the major target population, the occurrence of vaccine-induced enhanced RSV disease (ERD), candidates failing in late clinical testing stages, and the late characterization of the pre-fusion F protein (preF) as an effective vaccine target.[9,10] Often, our understanding of the virus and immunity has come at the expense of failures of vaccine candidates in clinical testing phases.

Valuable lessons can be learned from the decades of RSV vaccine research and development. Notwithstanding the three approved vaccines, the current pipeline still contains numerous candidates under development; evaluating the advancements made in the research field can improve the efficiency of ongoing vaccine development. Moreover, the availability of the current safe and effective vaccines may not be sufficient for effective global prevention of RSV disease; improvement in worldwide vaccine access and healthcare availability is necessary too.

In this paper, through the analysis of the RSV vaccine pipeline, we aim to exhibit the lessons learned from prior failures and advancements and reflect on how these lessons can be leveraged for ongoing and future vaccine developments. An important tool to ameliorate current and future endeavours is controlled human infection models (CHIMs). In CHIMs, a well-characterized pathogen is administered to healthy volunteers (or, in some cases, patients) in a controlled setting to study disease and pathogen characteristics, as well as the protective effect of a vaccine, under carefully monitored, safe circumstances. We summarize the benefits and limitations of CHIMs early in clinical vaccine testing to enable its rational use; in addition, we illustrate the failure-prone development pathway of RSV vaccines and the potential added value of CHIMs, using a methodology based on critical questions in vaccine development and the risks and costs involved.

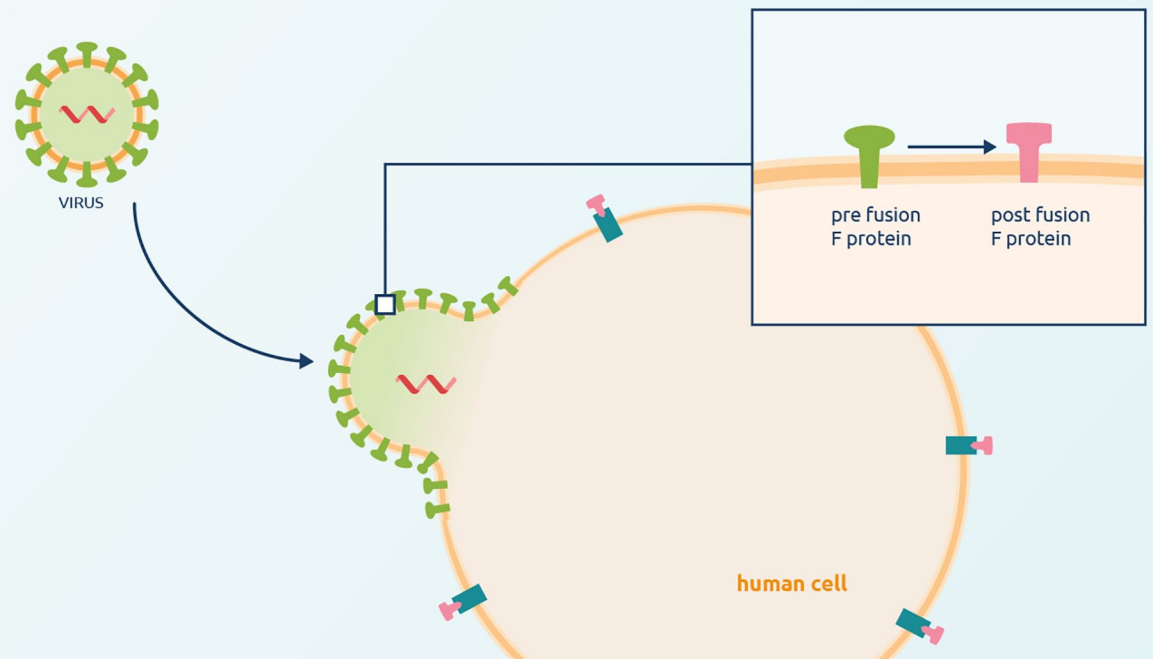

Figure 1. The F protein undergoes conformational changes after fusion with the human cell.
Source: Illustration by F. van Meurs.

A long, eventful history of RSV vaccine development

Efforts to develop RSV vaccines go back to 1966 when a clinical trial using two formalin-inactivated RS-virus (FI-RSV) vaccine candidates was conducted.[11] Immunization of infants with these vaccines resulted in ERD upon subsequent natural RSV exposure: 80% of vaccinated children were hospitalized, compared to 5% in the control group, and two infants died due to ERD.[11–13] After these events, investments in RSV vaccine development were limited for decades; research focused on ERD pathophysiology and revealed several possible reasons for the vaccine failure.[12] Formalin inactivation of the virus presumably resulted in the induction of a Th2-type immune response, loss of regulatory T cells and in hypothesized alterations to epitopes of the F and G proteins, resulting in a poor neutralizing capacity of antibodies that possibly enhanced host cell entry and viral replication.[13–15]

The major target population of RSV vaccine development has been infants since the peak of severe RSV cases lies before the age of 6 months.[16] In this population, vaccine responses are generally limited, as the adaptive immune system is still in development, and protection is based on transplacentally acquired maternal antibodies. This limitation in vaccine response has proven to be an additional challenge to RSV vaccine development.[17,18] From the 1970s onwards, efforts focused on the development of live attenuated vaccines (LAVs), as they are not associated with ERD.[19]

The identification of the RSV F-protein in the 1990s was a significant step in developing RSV vaccines, shifting the focus towards an F-protein-elicited antibody response.[20,21] Together with the G protein and SH protein, the F protein is located in the viral envelope surrounding the viral nucleocapsid. The F protein facilitates fusion and host cell entry; in the 2000s, it was discovered that the F protein undergoes significant conformational changes during the fusion process (see Figure 1).[22] Many antibodies directed at the F protein can bind both to its pre-fusion (preF) and postfusion (postF) conformation; however, antibodies binding to sites specific to preF have a significantly higher capacity to neutralize the virus.[23–25] After managing to stabilize the F protein in its preF conformation in 2013,[23,26] the pursuit of an RSV vaccine was boosted and a plethora of

candidates was developed, encompassing various types such as including LAVs, recombinant proteins, viral vectors, messenger RNA (mRNA) and peptide vaccines, but also mAbs, with a rational design focused on the preF protein.[10,27] This history highlights that insufficient understanding of the virus and antibodies targeting it has substantially delayed RSV vaccine development.

In 2023, two subunit vaccines containing preF – Arexvy® and Abrysvo®– received market approval in Europe and the United States.[5,6] Most recently, in 2024, the first mRNA RSV vaccine for older adults – mRESVIA® – was approved by the FDA and EMA.[7,28] Behind this success of RSV vaccines, there is a full graveyard of candidates having failed at various testing stages. To date, the pipeline still contains many candidates aiming to reach the market successfully. While various immunization solutions are now available for different populations, gaps remain and sustained efforts are required to ensure vulnerable populations can be protected against RSV disease. To obtain a comprehensive overview of the RSV vaccine landscape, we conducted a literature search combining multiple search strings in Medline, supplemented by a grey literature search (no predefined search string) and a semi-systematic search in Globaldata.com (see Supplemental Materials). Over the last 15 years, more than 35 RSV vaccines have been developed and clinically tested; development was halted for at least 10 candidates, of which 8 due to lack of protective efficacy. The current pipeline contains over 20 possible candidates in clinical testing phases (see Supplemental Materials).

Lessons learned on clinical development

Taking into account the decades-long efforts of the scientific community, several factors can be identified that have hindered the progress towards more safe and effective RSV vaccines. Vaccine development, in general, has a high-cost, high-risk profile when compared to conventional drug development.[29] Following the traditional roadmap for conventional drug development, drug safety is assessed in healthy volunteers in phase I trials, before it is administered to patients to study efficacy. As pharmaceutics progress through these early testing phases, costs increase while uncertainty remains concerning the efficacy and real-world translatability of acquired data.[30]

Vaccine development does not seem to fit this roadmap very well, for various reasons. First, as the 1966 ERD cases demonstrate, their safety profiles cannot be fully assessed in the absence of the pathogen they aim to protect against. Secondly, as most vaccines are prophylactic – aimed at preventing rather than treating disease – large field studies are required to study their efficacy, with larger populations than for other therapeutics, where a selected patient population can be used for drug testing. Traditional drug phase II/III clinical trials comprise study populations of 100 to several thousands of patients, generally recruited through physicians, outpatient clinics or patient associations. Studying the preventive capacity of vaccines, however, may require study populations of up to tens of thousands of subjects at risk of contracting a naturally encountered infection followed over a substantial period, depending on disease incidence. Consequently, relieving the uncertainty of vaccine effectiveness comes with significant financial costs and time, making investments in this area less attractive when compared to traditional drug development.

An example of this extensive financial risk is the RSV F nanoparticle candidate, which failed to meet its clinical endpoints in a phase III trial in 2016.[31] In total, 11,850 older adults were enrolled and followed for a single RSV season; the vaccine showed no significant effect on attack rates, which could be explained by a mild RSV season that year, and pre-existing immunity in the study population. Consequently, while the vaccine did not meet its clinical endpoints, it cannot be ruled out that under more advantageous circumstances it could have demonstrated efficacy.[31] The failure of the RSV F nanoparticle vaccine shows that, while requiring enormous financial investments, outcomes of late-phase vaccine trials are highly uncertain and depend heavily on disease incidence and target population.

Another factor amounting to the uncertainty early in vaccine development is the discrepancy between promising early clinical studies and a poor protective capacity in later testing phases. Janse et al. identified this discrepancy as the most common hurdle in vaccine development.[32] A method to reduce this disparity is to assess early predictors of protective capacity, called correlates of protection (CoP). CoPs are available for other pathogens: for SARS-CoV-2, the ability of a

vaccine to induce virus-neutralizing antibodies provides up to 95% predictive value of efficacy in late-stage trials.[33,34] A CoP for influenza was identified as early as 1949 when the protective effect of antibodies measured by the hemagglutination inhibition (HAI) assay was established. An HAI titre of 1:40 is associated with a 50% reduction in contracting the virus, with protective efficacy increasing as titres rise.[35] The establishment of a strong correlate of protection is a complex process as CoPs are defined for a specific endpoint (e.g. infection, disease, severe disease and hospitalization), may differ between natural infection and vaccination, and may vary across target populations. In addition, it is important to differentiate between early putative CoP and those recognized by regulatory authorities as supportive of licensure, as the level of supportive evidence to get from one to the other is substantial.

RSV lacks a strong CoP measurement: some vaccines inducing neutralizing antibodies have failed to show protective efficacy against RSV. An example is MEDI7510, a subunit RSV candidate which showed promising ability to induce neutralizing antibodies in two phase I trials, both conducted in adults above 60 years of age, yet failed to show efficacy in protecting older adults against RSV.[36–38]

The lack of a CoP has hampered the progress of RSV vaccines through the developmental pipeline with many vaccines failing in late-stage clinical testing at substantial financial costs. In this light, it becomes clear that the rapid success of mRNA vaccines against SARS-CoV-2 is by no means common for all infectious diseases; RSV cannot be considered a 'low-hanging fruit' in this respect. For infections such as RSV, alternative approaches may be necessary in designing and testing a vaccine candidate.

CHIMs for RSV

CHIMs are innovative clinical trials that can be used for early evaluation of the efficacy of new interventions, investigating their mode of action *in vivo*, as well as understanding disease characteristics.[39] The concept of CHIMs has been widely established within the scientific community; however, they have only been used sporadically for studying RSV vaccines. The EMA and World Health Organization (WHO) support the use of CHIMs for the evaluation of vaccines, provided they are performed according to ethical and scientific guidelines.[40,41] Out of all vaccine candidates mentioned in the Supplemental Materials, only a few were tested for efficacy with a CHIM: RSVpreF (Abrysvo®), MVA-BN-RSV, AD26.RSV.PreF and MK1654; for IVX-A12, a CHIM is planned in the next research phase, and for MV-012-968 a CHIM was conducted but no results were published.[42,43] For RSV specifically, CHIMs may solve to a considerable extent the problems faced during vaccine development, due to various reasons.

Firstly, CHIMs allow for extensive safety control and close monitoring of the disease. This is also particularly important given the possibility of the development of vaccine-induced ERD. Thus, assessing safety may preferably be done not only regarding vaccine administration but also by exposing vaccinated individuals to the virus.

Secondly, CHIMs allow for a comprehensive assessment of the immunological response to the induced disease. This leads to a better understanding of disease and possibly to the identification of a CoP associated with vaccine efficacy. Indeed, standardization of study timelines for sampling of blood, bodily fluids or tissue(s) can be pre-defined and performed at timepoints most suitable to assess disease and immune characteristics. In some cases, the use of these immune assays may help to gain novel knowledge of interactions between vaccines and the immune system.[44]

Thirdly, CHIMs are less costly and less time-consuming compared to large field trials studying vaccine efficacy. Smaller study populations can be used in which all participants are exposed to the virus; incidence of infection is therefore independent of RSV seasonality, circulation, or virulence of circulating strains. For healthy elderly, the annual risk of contracting a wild-type RSV infection generally varies between 3% and 7%[45]; infection rates of up to 77% can be achieved in RSV CHIMs.[46–48] In addition, intervals between vaccination and inoculation are identical for all CHIM participants, leading to a high homogeneity of data. To further lower costs, Mazur et al. recently demonstrated that conducting RSV CHIMs in an outpatient setting is safe and feasible; ongoing conversations with ethical and

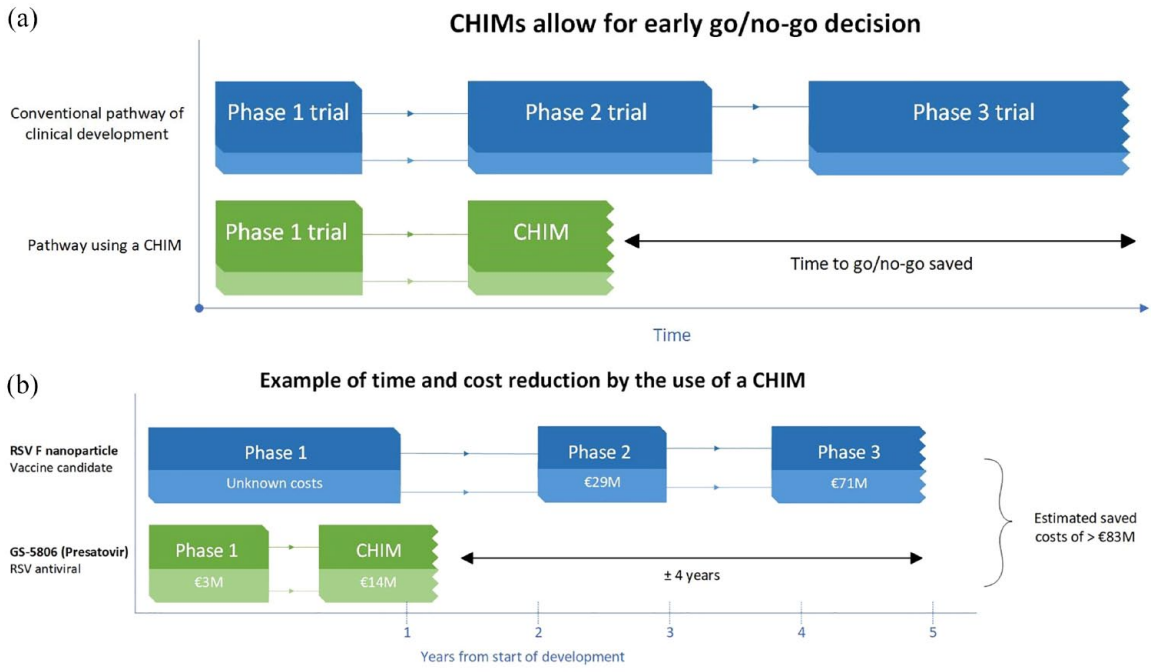

Figure 2. (a) A conceptual illustration of the time saved to a go/no-go decision for further development of a compound, by using a CHIM instead of following the conventional pathway of clinical development. (b) Comparison of the time and costs spent in clinical testing of the RSV F nanoparticle vaccine with GS-5806, both having failed to meet clinical endpoints. The use of a CHIM has facilitated GS-5806 to 'fail fast', saving up to 4 years and over €83M in estimated costs.

regulatory authorities have paved the way for future outpatient RSV CHIMs (publication pending).

With a pipeline full of candidates, a swift assessment of efficacy in a standardized setting is essential for selecting the most attractive vaccine to progress to the next testing phase. A go/no-go decision to move to a phase III trial to better estimate real-world efficacy should be made in an early phase and based on preliminary data on efficacy; CHIMs can play a crucial role in this decision-making.

The value of CHIMs for rapid vaccine testing is further illustrated in Figure 2(a); a go/no-go decision can be made early on when compared to the conventional developmental pathway. In Figure 2(b), the RSV F nanoparticle candidate is taken as an example, compared to GS-5806, an antiviral aimed against RSV which was tested in a CHIM in 2012.[49] While no estimated trial costs are available on globaldata.com for the phase I RSV F nanoparticle vaccine, the estimated costs of phase II and phase III trials amount up to €100M (for search terms, see Supplemental Materials).[50] The RSV F nanoparticle candidate failed to meet its clinical endpoints in the phase III trial, conducted more than 4 years after the start of the phase I trial. GS-5806 showed no antiviral efficacy in the CHIM, which was executed approximately 1 year after the start of the phase I trial. The clinical trials for GS-5806 have a combined estimated cost of €17M, resulting in a cost reduction of at least €83M when compared to the RSV F nanoparticle vaccine. The use of a CHIM has facilitated GS-5806 to 'fail fast', and saved substantial (financial) resources compared to the RSV F nanoparticle candidate.

The translatability of a CHIM

A major discussion regards the validity of CHIMs for their translatability to real-world disease and intervention. CHIM translatability depends on several factors, including the challenge agent used for inoculation. The isolation of a wild-type pathogen (from a clinical sample, possibly requiring

informed consent from the source patient), the selection of a virus strain suitable to infect a study population with pre-existing immunity to RSV, as well as its production under Good Manufacturing Practice (GMP), are all time-consuming and expensive processes. When designing a novel CHIM, this may amount to substantial costs and can possibly delay the execution of the trial. Furthermore, the production process and the time it takes may increase the gap between circulating pathogens and challenge agents used to induce the target disease.[30] This is a major problem for rapidly mutating viruses, such as influenza; a single influenza season may render a GMP strain obsolete. For RSV, only a single GMP challenge strain is currently available: the RSV-A Memphis-37b strain. It was selected as the only stable, reproducible and effective challenge agent from 10 possible strains including 6 RSV-A and 4 RSV-B viruses.[51] Although its mutation rate is much lower than for influenza, this strain could become outdated with time.[39,48] Recent efforts to select a new RSV-A challenge strain have shown encouraging results.[52] However, in the recent past the RSV-NICA strain was shown to decrease in infectivity after long-term cryo-storage, demonstrating another challenge in challenge strain development.[52] While there are currently none available, work is ongoing in the Inno4vac subtopic CHIMICHURRI to identify and produce an RSV-B strain for use in CHIMs.[53]

Second, there is a possible downside to the advantage of timeline standardization that can make CHIMs preferable: a standardized, short interval between immunization and inoculation may result in an overestimation of the clinical vaccine efficacy. This is particularly the case when disease incidence or occurrence of outbreaks are unpredictable, and the time between vaccination and infection is highly heterogeneous. While in temperate climates RSV seasonality is generally stable, incidence is more variable in (sub)tropical countries, possibly complicating the timing of (large scale) immunization.[54] For RSV, it has even been suggested that periodic immunoprophylaxis with monoclonal antibodies would better suit (sub)tropical populations than immunization by vaccines, as these are more fit to induce the necessary year-round high levels of antibodies.[55]

Finally, CHIM study populations may conceivably differ from the real-world population vaccines are developed for. Firstly, the selection of a population suitable for controlled infection with an RSV challenge virus may be challenging, as many adults have a high background immunity against the virus and will develop no or minimal URTI symptoms.[39] Screening for existing immunity may increase study costs and delay timelines. In addition, the selection of such a 'serosuitable' CHIM population may lead to sampling error when compared to conventional phase III trials, having larger study populations that are more representative of the general population. Moreover, RSV mainly affects infants and the elderly, leading to bronchiolitis and viral pneumonia, while RSV CHIMs conducted in healthy adult populations mostly lead to mild URTIs. Including children or vulnerable elderly in CHIMs is generally considered unethical and translation of results in adults to these populations is generally unwarranted.[56,57] Further, although for many diseases prevalence and health burden is highest in low-and-middle-income countries (LMICs), the majority of clinical trials are conducted in high-income countries (HICs).[58] This is also the case for RSV: 99% of infant deaths occur in LMICs, and this global inequality calls for a focus on LMICs in RSV vaccine development.[10,59]

It is not uncommon that vaccines demonstrate high efficacy and effectiveness in HIC populations, while subsequently showing disappointing results in LMICs. Variability of vaccine responses in LMICs is determined by socio-economic, genetic and immunological factors such as exposure to other microorganisms and parasites, and a different diet and microbiome.[60] Consequently, reliable testing of vaccine efficacy requires a considerate selection of study population for clinical trials, and CHIMs specifically, to increase the validity of study results for those most in need of disease prevention. Using CHIMs may, in fact, contribute to the required focus shift towards LMIC populations: firstly, because an affordable development pathway will result in affordable vaccines; secondly, because conducting a CHIM in LMICs requires lower financial investments and operational efforts than large field trials. Furthermore, as phase III trials are often set up in multiple countries, efficacy data may be too heterogeneous to warrant translatability of data to the vaccine target populations in LMICs, while CHIMs can focus on small, immunologically more homogenous populations.

As a result of the limitations in CHIM translatability, the question remains whether CHIMs can replace the traditional large efficacy trials. CHIMs can provide valuable information that cannot be generated otherwise. An example is the approval of the cholera vaccine Vaxchora® in 2017 after its safety and efficacy were demonstrated in a cholera CHIM, without large efficacy trials being conducted in a real-world population.[61,62] For RSV, however, the predictive value of a CHIM for protective efficacy in a phase III trial remains unclear, and promising data from an RSV CHIM does by no means warrant market approval. It is imperative to keep discussions with regulatory authorities ongoing regarding the role of CHIM data in vaccine approval; ideally, conclusive CHIMs should be considered an important part of the submission dossier, answering questions beyond phase III trials. In Europe, public-private partnerships such as the Innovative Medicines Initiative have provided a neutral forum for cross-stakeholder alignment on these regulatory considerations. A recent example is the 2022 Inno4vac Regulatory Workshop, in which challenge strain development and GMP production were discussed by scientific and regulatory experts.[63] This interaction also furthered the methodological development of CHIMs and delineated the valuable role of CHIMs in vaccine approval.

CHIMs can provide an early indication of vaccine efficacy and promote further development, or in case of failure support early termination or inform candidate redesign. Indeed, in hindsight, the history of RSV vaccines shows the importance of allowing ineffective candidates to "fail fast", preventing large and costly trials.[64] An additional benefit is that substantially fewer people participate in potentially risky trials, which is desirable from an ethical perspective.

A conceptual, rational pathway

To further illustrate the failure-prone development of RSV vaccines, we use a method that describes the development pathway through different questions that are essential to answer on the road towards market approval. A question-based decision tree, containing the essential development questions and the order in which they are assessed, can be generated by the use of a tool available on https://www.pauljanssenfuturelab.eu/our-resources/.[64] The methodology of incorporating risks in project valuation and finding optimal, case-based development paths has been described by de Visser et al., and the tool was previously applied to vaccine development by Roestenberg et al.[30,64] To illustrate the added value of RSV CHIMs, we have identified four questions essential for RSV development, each with assigned generalized costs and probability of success (PoS) involved to answer them (Figure 3).

Making an accurate estimation of drug development costs and revenue after market approval is demanding and notoriously obscure; this method aims to investigate the effect of different distributions of these costs, rather than the absolute values. The same holds true for the PoS of a question: while the exact number cannot be reliably estimated, some questions can be more straightforwardly assessed than others. The PoS reflects the probability of finding reliable and favourable results that answer the individual questions; the combination of PoS and associated cost distribution defines the optimal order in which questions are to be addressed. The overall PoS of RSV vaccine development can be estimated based on the data available in the Supplemental Materials, which shows that three out of the 40 (7.5%) clinically tested RSV vaccines have received market approval. The probability for therapeutics against infections to reach approval is estimated at 8% by Gupta Strategists as well.[65]

If we distribute the costs and risks equally over the different questions, all pathways are equally cost-effective, as is reflected by the equal, positive project values in Figure 4, for both the optimal and a random other, user-defined route. The absolute project values do not necessarily refer to real-world numbers but can be used to compare the cost-effectiveness of different pathways.

In reality, however, the risks are not evenly distributed: for example, while many RSV vaccines induce an immune response, only a few show protective efficacy. Assessment of the therapeutic window concerns an interplay between a vaccine's safety and its efficacy and is to be evaluated during all phases of clinical testing. Factors affecting vaccine safety and efficacy in the target population, such as immunological differences, comorbidities, or age, may result in the need for additional clinical studies; assessing this question therefore has a relatively low PoS.

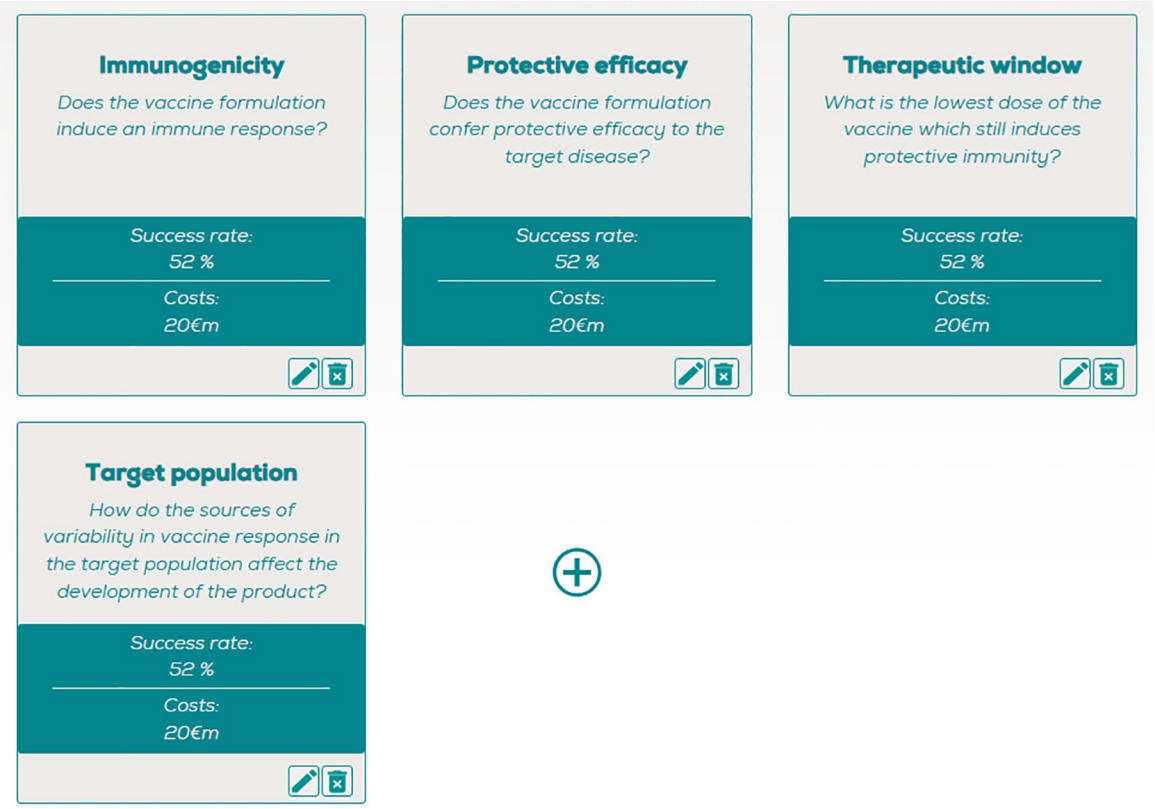

Figure 3. Four essential questions in RSV vaccine development, entered in the question optimizing tool. For every question, estimated costs and PoS are entered. In this example, we've used a total out-of-pocket project cost of €80M and an estimated revenue of €800M, based on the numbers used by Roestenberg et al.[30]
PoS, probabilities of success; RSV, Respiratory syncytial virus.

Shifting the success rates towards a more representative distribution for RSV vaccines, keeping overall PoS fixed at 7.5% (Figure 5), results in the identification of a pathway that is most cost-effective (Optimal route). Early assessment of protective efficacy, as well as identification of variability in vaccine response in the target population, is significantly more cost-effective than the User-defined route in Figure 5, which reflects a more conventional pathway in which efficacy and target population are investigated later.

Next, we illustrate the addition of a CHIM in the development pathway, providing early assessment of protective efficacy. A CHIM can increase the PoS of protective efficacy; uncertainty is reduced in an early stage and candidates can be abandoned at relatively little cost. Moreover, CHIMs are independent of circulating strains, while the validity of field trials may vary between years. CHIMs will, however, lead to an increase in total project costs, as they can seldom replace large field trials. Figure 6 shows that an increase of 4% in PoS outweighs possible additional costs of €2M: assessing protective efficacy early is still the most cost-effective, as is reflected by the highest project value.

Using this method, we demonstrate that a thoughtful and calculated approach, based on the essential questions in vaccine development, results in an optimal order of addressed questions that helps rationalize and guide the clinical development programme. Furthermore, it demonstrates the added value of early CHIMs in RSV vaccine development, even if additional costs are introduced.

Worldwide prevention within reach?

Looking back at the history of RSV vaccine development, valuable lessons can be learned regarding the development and testing of vaccine candidates

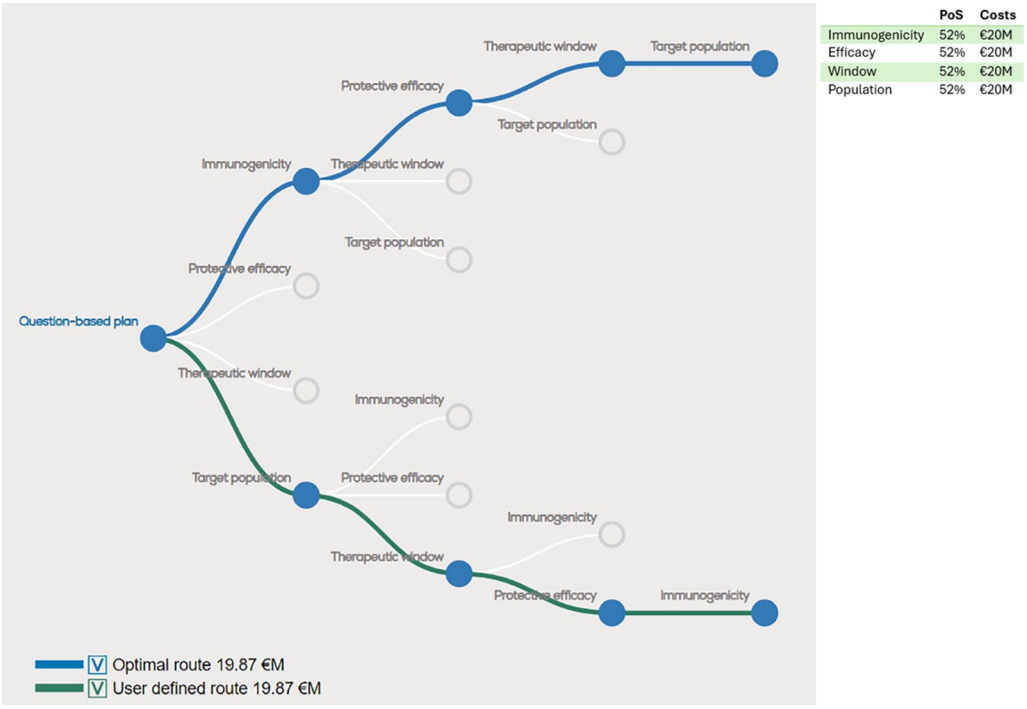

Figure 4. A conceptual, question-based approach visualized by a pathway of key questions in vaccine development. Here, an equal distribution of costs and probability of success is demonstrated, resulting in equal project values of the different routes (see lower left corner).
PoS, probabilities of success; RSV, Respiratory syncytial virus.

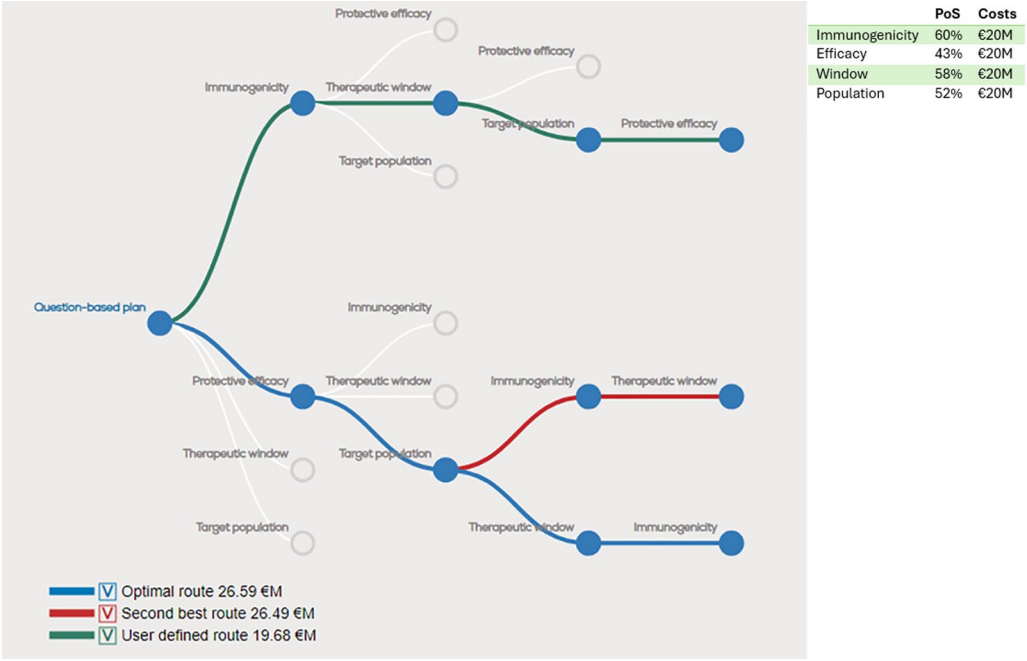

Figure 5. Applying the conceptual pathway to the RSV field results in a shift towards a more realistic distribution of PoS. The most cost-effective route involves early assessment of protective efficacy and the target population (Optimal route and Second best route). The User-defined route, starting with investigation of immunogenicity and therapeutic window, results in a significantly lower project value.
PoS, probabilities of success; RSV, Respiratory syncytial virus.

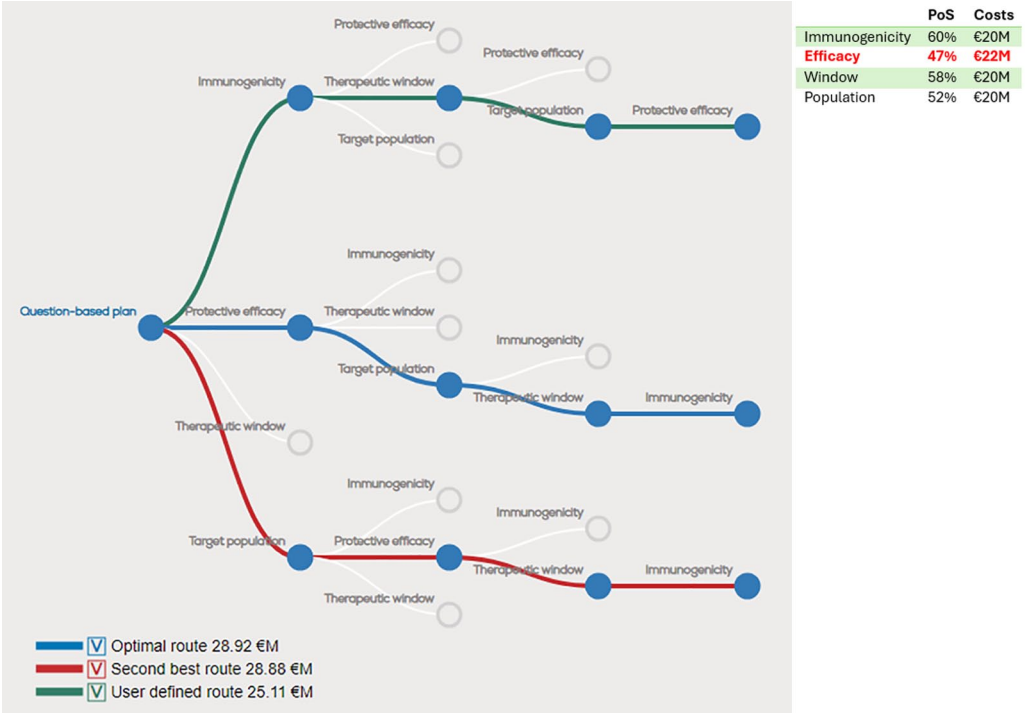

Figure 6. Using a CHIM may result in higher costs (e.g. €2M), but also increases the PoS of assessment of protective efficacy (e.g. by 4%). Early assessment of protective efficacy and target population remains more cost-effective when compared to the User-defined route, in which protective efficacy is investigated in a later stage. The overall project value in this figure is higher than in Figure 5, demonstrating the added value of using a CHIM despite an increase in financial investments.

in general. The use of CHIMs can decrease the costs of clinical trials, shorten development timelines and diminish the uncertainties associated with early phase investments. Furthermore, they can contribute to the characterization of disease and CoPs, and help shift the focus of vaccine research to LMICs. Currently, the development pipeline contains many RSV vaccine and mAb candidates. While it seems inconceivable that these will all be tested in large phase III efficacy trials, the high failure rate of clinically tested RSV vaccine candidates in the past demonstrates the need for a filled pipeline to succeed in developing a successful vaccine. It can be concluded that RSV is no 'low-hanging fruit' in vaccine development. Decades of research and development have resulted in a graveyard filled with failed candidates, while still a CoP is lacking.

Even though currently three safe and effective vaccines and two monoclonal antibodies have received market approval, effective global prevention of RSV disease does not appear to be within reach. Various barriers may limit the implementation of an available therapeutic. While Abrysvo® and Arexvy® show promising cost-effectiveness in the US, this is highly dependent on price-per-dose, and availability of the vaccines in LMICs may significantly be limited due to high production costs.[66,67] Poor healthcare accessibility in LMICs may play a role as well, as demonstrated by the 50%–80% of infant RSV deaths occurring out-of-hospital.[68] Implementation of an otherwise efficacious vaccine could prove to be problematic in countries where access to regular healthcare is insufficient. An intensified interaction between vaccine developers and relevant local authorities and funders (e.g. GAVI) may assist in identifying and possibly overcoming challenges of vaccine introduction and vaccination programme implementation.[69–71]

Conclusion

Examining the lessons learned from the past as well as the challenges faced in the present, we advocate for a rational approach to the clinical testing of RSV vaccine candidates. This rational

approach comprises various considerations: significant uncertainty in early testing phases due to the lack of a CoP; a considerable probability of failure and the advantage of 'failing fast'; the value of CHIMs in reducing costs and shortening timelines; and finally, the need for well-defined target population early in development to define trial endpoints, optimize clinical relevance and estimate vaccine demand. Taking into regard these factors as early as possible allows for an analytic and conceptual view of the development process, as visualized in Figures 3 and 4. Evaluating this conceptual view after every step made in the process facilitates a more dynamic developmental pathway. Undertaking this rational and dynamic design will prevent the arduous and eventful history of RSV vaccines from recurring in present and future efforts, and possibly contribute to worldwide prevention of RSV disease.

Declarations

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Not applicable.

Consent for publication
Not applicable.

Author contributions
Victor M. Cnossen: Conceptualization; Investigation; Resources; Supervision; Visualization; Writing – original draft; Writing – review & editing.

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CV is a current employee of Vaccines Europe (EFPIA), a former employee of Sanofi, and holds Sanofi shares. No further competing interests are declared.

Availability of data and materials
An overview of RSV vaccine candidates and the search strategies used for the collection of data for this review article can be found in the supplementary materials.

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References
1. Cohen C and Zar HJ. Deaths from RSV in young infants—the hidden community burden. *The Lancet Global Health* 2022; 10(2): e169–e170.
2. Li Y, Wang X, Blau DM, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. *Lancet* 2022; 399(10340): 2047–2064.
3. Chen S, Gu W, Wu M, et al. Risk factors for recurrent wheezing after bronchiolitis in infants: 2-year follow up in China. *BMC Infect Dis* 2021; 21(1): 250.
4. Fleming DM, Taylor RJ, Lustig RL, et al. Modelling estimates of the burden of Respiratory Syncytial virus infection in adults and the elderly in the United Kingdom. *BMC Infect Dis* 2015; 15(1): 443.
5. Papi A, Ison MG, Langley JM, et al. Respiratory syncytial virus prefusion F protein vaccine in older adults. *N Engl J Med* 2023; 388(7): 595–608.
6. Kampmann B, Madhi SA, Munjal I, et al. Bivalent prefusion F vaccine in pregnancy to

prevent RSV illness in infants. *N Engl J Med* 2023; 388(16): 1451–1464.

7. Mullard A. FDA approves mRNA-based RSV vaccine. *Nat Rev Drug Discov*. Epub ahead of print 7 June 2024.
8. Fleming-Dutra KE, Jones JM, Roper LE, et al. Use of the pfizer respiratory syncytial virus vaccine during pregnancy for the prevention of respiratory syncytial virus–associated lower respiratory tract disease in infants: recommendations of the Advisory Committee on immunization practices —United States, 2023. *MMWR Morb Mortal Wkly Rep* 2023; 72(41): 1115–1122.
9. Borchers AT, Chang C, Gershwin ME, et al. Respiratory syncytial virus: a comprehensive review. *Clin Rev Allergy Immunol* 2013; 45(3): 331–379.
10. Mazur NI, Higgins D, Nunes MC, et al. The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates. *Lancet Infect Dis* 2018; 18(10): e295–e311.
11. Kim HW, Canchola JG, Brandt CD, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine12. *Am J Epidemiol* 1969; 89(4): 422–434.
12. Acosta PL, Caballero MT and Polack FP. Brief history and characterization of enhanced respiratory syncytial virus disease. *Clin Vaccine Immunol* 2016; 23(3): 189–195.
13. Kaaijk P, Luytjes W and Rots NY. Vaccination against RSV: is maternal vaccination a good alternative to other approaches? *Human Vaccines Immunother* 2013; 9(6): 1263–1267.
14. Gerretsen HE and Sande CJ. Development of respiratory syncytial virus (RSV) vaccines for infants. *J Infect* 2017; 74: S143–S146.
15. Murphy BR and Walsh EE. Formalin-inactivated respiratory syncytial virus vaccine induces antibodies to the fusion glycoprotein that are deficient in fusion-inhibiting activity. *J Clin Microbiol* 1988; 26(8): 1595–1597.
16. Shay DK, Holman RC, Roosevelt GE, et al. Bronchiolitis-associated mortality and estimates of respiratory syncytial virus—associated deaths among US Children, 1979–1997. *J Infect Dis* 2001; 183(1): 16–22.
17. PrabhuDas M, Adkins B, Gans H, et al. Challenges in infant immunity: implications for responses to infection and vaccines. *Nat Immunol* 2011;12(3):189-194.
18. Eichinger KM, Kosanovich JL, Lipp M, et al. Strategies for active and passive pediatric RSV immunization. *Ther Adv Vacc Immunother* 2021; 9: 2515135520981516.
19. Karron RA, Atwell JE, McFarland EJ, et al. Live-attenuated vaccines prevent respiratory syncytial virus–associated illness in young children. *Am J Respir Crit Care Med* 2021; 203(5): 594–603.
20. Kuo-Hom Lee Hsu, Lubeck MD, Bhat BM, et al. Efficacy of adenovirus-vectored respiratory syncytial virus vaccines in a new ferret model. *Vaccine*. 1994;12(7):607-612.
21. Beeler JA and van Wyke Coelingh K. Neutralization epitopes of the F glycoprotein of respiratory syncytial virus: effect of mutation upon fusion function. *J Virol* 1989; 63(7): 2941–2950.
22. Lamb RA and Jardetzky TS. Structural basis of viral invasion: lessons from paramyxovirus F. *Curr Opin Struct Biol* 2007; 17(4): 427–436.
23. McLellan JS, Chen M, Leung S, et al. Structure of RSV fusion glycoprotein trimer bound to a prefusion-specific neutralizing antibody. *Science* 2013; 340(6136): 1113–1117.
24. Andreano E, Paciello I, Bardelli M, et al. The respiratory syncytial virus (RSV) prefusion F-protein functional antibody repertoire in adult healthy donors. *EMBO Mol Med* 2021; 13(6): e14035.
25. Collins PL and Graham BS. Viral and host factors in human respiratory syncytial virus pathogenesis. *J Virol* 2008; 82(5): 2040–2055.
26. Krarup A, Truan D, Furmanova-Hollenstein P, et al. A highly stable prefusion RSV F vaccine derived from structural analysis of the fusion mechanism. *Nat Commun* 2015; 6(1): 8143.
27. Verwey C and Madhi SA. Review and update of active and passive immunization against respiratory syncytial virus. *BioDrugs* 2023; 37(3): 295–309.
28. European Medicines Agency. mResvia. https://www.ema.europa.eu/en/medicines/human/EPAR/mresvia
29. Pronker ES, Weenen TC, Commandeur H, et al. Risk in vaccine research and development quantified. *PLoS One* 2013; 8(3): e57755.
30. Roestenberg M, Kamerling IMC and De Visser SJ. Controlled human infections as a tool to reduce uncertainty in clinical vaccine development. *Front Med* 2018; 5: 297.

31. Novavax Press Release. *Novavax Announces Topline RSV F Vaccine Data from Two Clinical Trials in Older Adults*, https://ir.novavax.com/press-releases/2016-09-25-Novavax-Announces-Topline-RSV-F-Vaccine-Data-from-Two-Clinical-Trials-in-Older-Adults (2016, accessed 8 February 2024).

32. Janse M, Brouwers T, Claassen E, et al. Barriers influencing vaccine development timelines, identification, causal analysis, and prioritization of key barriers by KOLs in general and Covid-19 vaccine R&D. *Front Public Health* 2021; 9: 612541.

33. Abu-Raddad LJ, Chemaitelly H, Coyle P, et al. SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy. *EClinicalMedicine* 2021; 35: 100861.

34. Goldblatt D, Alter G, Crotty S, et al. Correlates of protection against SARS-CoV-2 infection and COVID-19 disease. *Immunol Rev* 2022; 310(1): 6–26.

35. Black S, Nicolay U, Vesikari T, et al. Hemagglutination inhibition antibody titers as a correlate of protection for inactivated influenza vaccines in children. *Pediatr Infect Dis J* 2011; 30(12): 1081–1085.

36. Falloon J, Yu J, Esser MT, et al. An Adjuvanted, postfusion F protein–based vaccine did not prevent respiratory syncytial virus illness in older adults. *J Infect Dis* 2017; 216(11): 1362–1370.

37. Falloon J, Talbot HK, Curtis C, et al. Dose selection for an adjuvanted respiratory syncytial virus F protein vaccine for older adults based on humoral and cellular immune responses. *Clin Vaccine Immunol* 2017; 24(9): e00157-17.

38. Falloon J, Ji F, Curtis C, et al. A phase 1a, first-in-human, randomized study of a respiratory syncytial virus F protein vaccine with and without a toll-like receptor-4 agonist and stable emulsion adjuvant. *Vaccine* 2016; 34(25): 2847–2854.

39. Habibi MS and Chiu C. Controlled human infection with RSV: The opportunities of experimental challenge. *Vaccine* 2017; 35(3): 489–495.

40. World Health Organization. WHO guidance on the ethical conduct of controlled human infection studies, https://www.who.int/publications/i/item/9789240037816 (14 January 2022).

41. European Medicines Agency. Guideline on clinical evaluation of vaccines, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-evaluation-vaccines-revision-1_en.pdf (16 January 2023).

42. Icosavax. Pursuing major unmet needs with our VLP technology. https://icosavax.com/pipeline/ (2024, accessed 13 June 2024).

43. ClinicalTrials.gov. Human challenge study to evaluate the efficacy of MV-012-968 vaccine. https://clinicaltrials.gov/study/NCT04690335 (2022, accessed 13 June 2024).

44. Lindeboom RGH, Worlock KB, Dratva LM, et al. Human SARS-CoV-2 challenge uncovers local and systemic response dynamics. *Nature*. Epub ahead of print 19 June 2024. DOI: 10.1038/s41586-024-07575-x.

45. Falsey Ann R, Hennessey Patricia A, Formica Maria A, et al. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med* 352:1749–1759.

46. Schmoele-Thoma B, Zareba AM, Jiang Q, et al. Vaccine efficacy in adults in a respiratory syncytial virus challenge study. *N Engl J Med* 2022; 386(25): 2377–2386. doi:10.1056/NEJMoa2116154

47. Sadoff J, De Paepe E, DeVincenzo J, et al. Prevention of respiratory syncytial virus infection in healthy adults by a single immunization of Ad26.RSV.preF in a human challenge study. *J Infect Dis* 2022; 226(3): 396–406.

48. DeVincenzo JP, Wilkinson T, Vaishnaw A, et al. Viral load drives disease in humans experimentally infected with respiratory syncytial virus. *Am J Respir Crit Care Med* 2010; 182(10): 1305–1314.

49. ClinicalTrials.gov. *Safety and Efficacy Study of GS-5806 in Healthy Volunteers Infected With Respiratory Syncytial Virus (RSV) (Challenge)*, https://clinicaltrials.gov/study/NCT01756482?intr=GS-5806&rank=1 (accessed 21 August 2015).

50. Globaldata.com. https://www.globaldata.com/ (2024, accessed 24 June 2024).

51. Kim YI, DeVincenzo JP, Jones BG, et al. Respiratory syncytial virus human experimental infection model: provenance, production, and sequence of low-passaged Memphis-37 challenge virus. *PLoS One* 2014; 9(11): e113100.

52. Verstraelen S, Roymans D, Jacobs A, et al. Proof of stability of an RSV Controlled Human Infection Model challenge agent. *Virol J* 2024; 21(1): 112.

53. Inno4vac. CHIMICHURRI – ST2 Controlled Human Infection Models (CHIMs). https://www.inno4vac.eu/st2chimichurri (2021).

54. Staadegaard L, Caini S, Wangchuk S, et al. Defining the seasonality of respiratory syncytial virus around the world: National and subnational surveillance data from 12 countries. *Influenza Other Respir Viruses* 2021; 15(6): 732–741.

55. Mazur NI, Terstappen J, Baral R, et al. Respiratory syncytial virus prevention within reach: the vaccine and monoclonal antibody landscape. *Lancet Infect Dis* 2023; 23(1): e2–e21.

56. Binik A. Should children be included in human challenge studies? *Ethics Human Res* 2024; 46(3): 2–15.

57. Bambery B, Selgelid M, Weijer C, et al. Ethical criteria for human challenge studies in infectious diseases. *Public Health Ethics* 2016; 9(1): 92–103.

58. World Health Organization. Number of clinical trials by year, country, WHO region and income group (1999-2022), https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/number-of-clinical-trials-by-year-country-who-region-and-income-group (2023, accessed 27 May 2024).

59. Wang X, Li Y, Shi T, et al. Global disease burden of and risk factors for acute lower respiratory infections caused by respiratory syncytial virus in preterm infants and young children in 2019: a systematic review and meta-analysis of aggregated and individual participant data. *Lancet* 2024; 403(10433): 1241–1253.

60. van Dorst MMAR, Pyuza JJ, Nkurunungi G, et al. Immunological factors linked to geographical variation in vaccine responses. *Nat Rev Immunol*. Epub ahead of print 28 September 2023. DOI: 10.1038/s41577-023-00941-2.

61. Ii JFM, Smith LL, Brantley P, et al. Vaxchora: The First FDA-Approved cholera vaccination in the United States. P&T 2017; 42(10): 638–640.

62. Chen WH, Cohen MB, Kirkpatrick BD, et al. Single-dose Live Oral Cholera Vaccine CVD 103-HgR Protects Against Human Experimental Infection With *Vibrio cholerae* O1 El Tor. *Clin Infect Dis* 2016; 62(11): 1329–1335.

63. Corti N, Chiu C, Cox RJ, et al. Regulatory workshop on challenge strain development and GMP manufacture – A stakeholder meeting report. *Biologicals* 2024; 85: 101746.

64. de Visser SJ, Cohen AF and Kenter MJH. Integrating scientific considerations into R&D project valuation. *Nat Biotechnol* 2020; 38(1): 14–18.

65. Gupta Strategists. *The cost of opportunity – A study on pharmaceutical R&D costs*. Gupta Strategists, p. 42. https://gupta-strategists.nl/en/research/the-cost-of-opportunity (2019, accessed 13 June 2024).

66. Moghadas SM, Shoukat A, Bawden CE, et al. Cost-effectiveness of Prefusion F protein-based vaccines against respiratory syncytial virus disease for older adults in the United States. *Clin Infect Dis*. Epub ahead of print 30 November 2023. DOI: 10.1093/cid/ciad658

67. Koltai M, Moyes J, Nyawanda B, et al. Estimating the cost-effectiveness of maternal vaccination and monoclonal antibodies for respiratory syncytial virus in Kenya and South Africa. *BMC Med* 2023; 21(1): 120.

68. Srikantiah P, Vora P and Klugman KP. Assessing the full burden of respiratory syncytial virus in young infants in low- and middle-income countries: the importance of community mortality studies. *Clin Infect Dis* 2021; 73(Suppl. 3): S177–S179.

69. Furlow B. US nirsevimab shortage forces drug rationing as RSV rates increase. *Lancet Respir Med* 2023; 11(12): e99.

70. Van Roessel IMAA, Mazur NI, Shah SK, et al. Post-trial access in maternal vaccine trials. *Am J Perinatol* 2019; 36(S 02): S41–S47.

71. GAVI. Vaccine Investment Strategy 2024, https://www.gavi.org/our-alliance/strategy/vaccine-investment-strategy-2024#analysis (2024).