



Workshop on the design and use of clinical trials with multiple endpoints, with a focus on prevention of RSV

ABSTRACT

A meeting held in Lisbon, Portugal, in February 2023 focused on critical aspects of clinical trial design for respiratory syncytial virus (RSV) preventative therapies. The meeting addressed two primary areas: enhancing the efficiency and success of randomized controlled trials (RCTs) for RSV preventative therapies and designing RCTs to better inform post-licensure decision-making. Topics included the selection of primary endpoints, innovative approaches to incorporating multiple endpoints and historical data, and the challenges and benefits of sequential trial designs. The discussion also touched on *meta*-regression models for obtaining more robust, context-specific estimates of vaccine efficacy. Overall, the meeting underscored the importance of balancing efficiency and robustness in RSV vaccine trial design, while recognizing the need for further discussions involving regulatory and advisory bodies.

Background

Randomised, controlled clinical trials are considered the gold standard for evaluating the safety and efficacy of new medical products, including preventive products such as vaccines. However, licensure trials are resource intensive. Bringing a new drug or vaccine to market can be extremely expensive, with estimates ranging from \$800 million to \$2 billion [1,2]. Late-stage failures and the rising costs of Phase III trials are major factors contributing to these development costs [3]. Consequently, improving the power and cost-effectiveness of a trial are valuable objectives to pursue, including inclusion of additional experts in design considerations, such as health economists.

When designing a randomized controlled trial (RCT) for regulatory approval, several decisions must be made that can affect its ultimate success and efficiency. These include the choice of the primary clinical endpoint(s), where to enroll subjects, which subjects to exclude, how many subjects to enroll and follow-up, and how to analyze the data. Decisions made when designing a trial are typically meant to maximize the chances of licensure if the intervention is efficacious. However, decision-making can be difficult prior to the start of a trial, especially when knowledge of the incidence of the primary endpoint(s) is uncertain. Also, the selection of primary outcomes for a trial might not be those most relevant for deciding on the public health deployment of the intervention post-licensure, including in low- and middle-income countries (LMICs). Furthermore, trials might not have sufficient evidence within key subgroups or geographic locations, as trials are often not designed to provide the information needed for country-level decision-makers during the post-licensure phase. Many countries have to rely on randomised clinical trial data from other countries, where the outcomes and subgroups studies may have differed from their priorities.

To accelerate clinical development and increase the chances that an efficacious vaccine is approved in a timely fashion, innovative trial designs can be beneficial. Such designs could include incorporating multiple endpoints in the analysis, incorporating data from previous trials into the analysis, and using sequential trial designs with frequent

evaluation points [4].

A meeting was held February 21–22, 2023 in Lisbon, Portugal to discuss technical, policy, and implementation issues related to the design of clinical trials, with a focus on preventative therapies against RSV. The meeting covered two general topics: 1) how to decrease the required sample size and increase chances of success of RCTs for safe and efficacious vaccines (by incorporating multiple endpoints in clinical trials, and incorporating historical data from previous trials) and 2) how to design and analyze RCTs to better inform post-licensure decision-making (Fig. 1). Attendees included representatives from the World Health Organization (WHO), the European Medicines Agency (EMA), the United States Center for Disease Control and Prevention (CDC), several vaccine manufacturers, the Bill & Melinda Gates Foundation (BMGF), and academic trialists, statisticians, and epidemiologists. (see Box 1)

Objectives of the workshop

The workshop was organized to address three questions with a focus on RSV prevention:

- 1) How can multiple clinical endpoints be incorporated into an analysis plan?
- 2) How can data from previous trials (e.g., Phase IIb) be integrated with Phase III results to design more efficient trials?
- 3) How do we optimally use data from clinical trials with multiple sites to inform decision-making by National Immunization Technical Advisory Groups (NITAGs)?

Incorporating multiple endpoints in clinical trials

In clinical trials designed for obtaining licensure, regulatory agencies require the selection of a primary clinical endpoint, or sometimes two co-primary endpoints depending on the questions to be answered on efficacy or safety. This selection is usually made following scientific advice from the regulatory bodies before the study begins to assess the

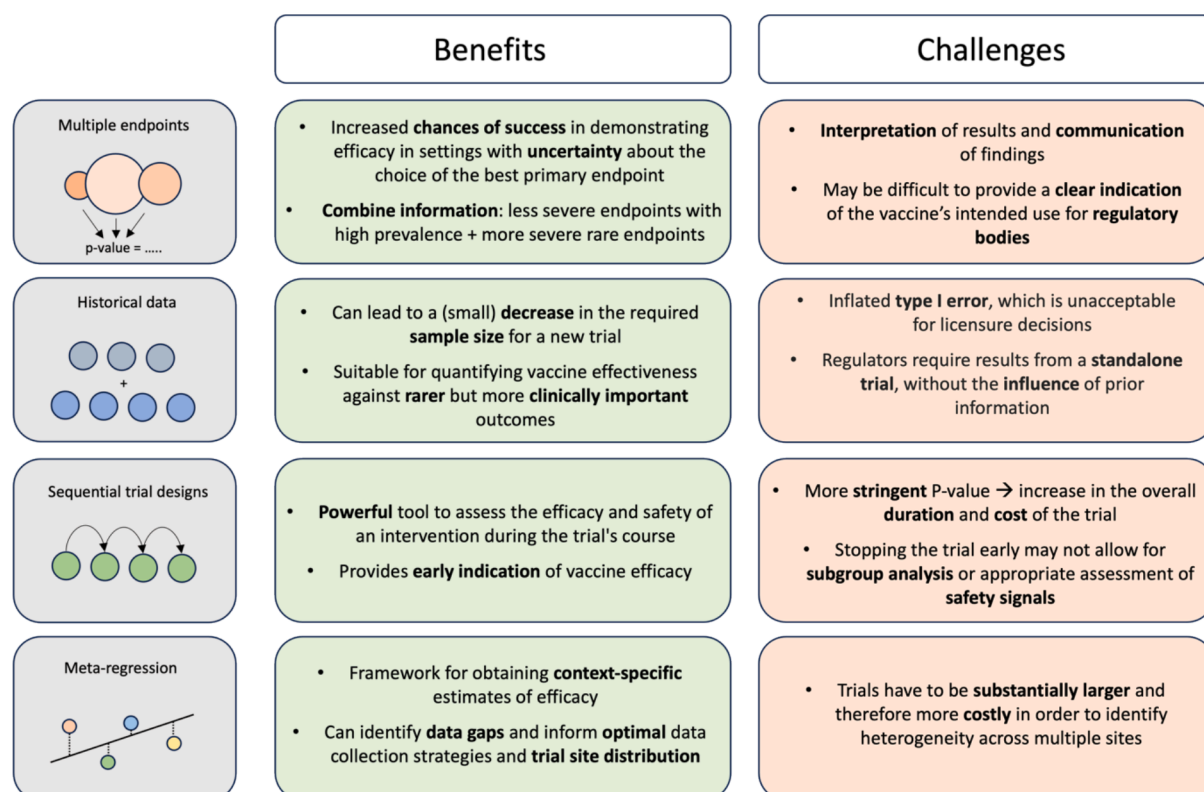


Fig. 1. Summary of the benefits and challenges of different approaches to attempt making clinical trials more efficient as discussed during the meeting.

The development of RSV preventative therapies has been remarkably challenging [5]. A formalin-inactivated vaccine for infants tested in the 1960s increased the severity of RSV disease and caused some deaths, stalling progress for decades. In 1996, RSV-IGIV, an intravenous immunoglobulin preparation, became the first FDA-approved agent for preventing RSV in preterm infants. However, despite initial success, there were safety concerns and logistical issues related to the intravenous administration of a large volume of product and questions about its effectiveness in certain patient groups [6]. A breakthrough occurred in 1998, with the licensure of palivizumab, an anti-RSV monoclonal antibody delivered intramuscularly. Another pivotal moment was the resolution of the RSV fusion (F) protein in its two conformations: the metastable pre-fusion (preF) and the post-fusion (postF) forms. PreF-binding antibodies proved more effective at neutralizing RSV than those targeting postF. This discovery enabled mapping of potent neutralizing epitopes exclusive to the preF form, driving structure-based vaccine design through stabilization of the RSV F protein in the preF conformation [5]. Recently, there have been a string of successes. A Phase III clinical trial of a maternal vaccine targeting preF of RSV showed efficacy in preventing RSV lower respiratory tract infection in infants born to vaccinated mothers, providing protection via passive antibody transfer to the infant [7]; and an extended half-life monoclonal antibody against the preF site was shown to be efficacious in infants [8]; FDA and EMA approval swiftly followed for both products [9–12]. In addition, two vaccines have been shown to be effective and licensed in older adults [13–15], while marketing authorization applications have been submitted for a third investigational vaccine [16].

Box 1. History of RSV immunization development:

vaccine's efficacy. Determining which endpoint should be designated as the 'primary' one can be a challenging decision. All potential outcomes under consideration should have clinical relevance, but the definition of clinical relevance may vary among different committees and countries. One potential solution would be to simultaneously consider multiple clinical endpoints.

In the first session of the meeting, we focused on methods for analyzing data on multiple endpoints, comparing the widely applied and most conservative approach, the Bonferroni test, which evaluates each endpoint individually and tests whether any of them are significant, to permutation tests, which account for the correlation between overlapping or nested outcomes [17–20]. We also discussed alternative approaches for integrating multiple endpoints, such as constructing a single composite endpoint (i.e., defined as having outcome A OR outcome B). Throughout the discussions, we examined the limitations, advantages, and extensions of these methods, as well as their possible future applications. Additionally, we discussed the different perspectives and focus of different bodies, e.g. those who license the vaccine and those responsible for decisions about post-licensure deployment of the vaccine, given the criteria for their decisions may be different.

Considerations in the choice of a primary endpoint for clinical trials

A cautionary tale about the influence of which primary endpoint to choose comes from a Phase III clinical trial of a maternal vaccine candidate targeting the prevention of respiratory syncytial virus (RSV) in infants (the Prepare trial) [21]. The vaccine did not demonstrate statistically significant efficacy against the pre-specified primary endpoint of medically significant RSV lower respiratory tract infection (LRTI). This may have been due to an unexpectedly lower incidence of primary endpoint events among the enrolled infants and lack of inclusion of all episodes [21]. As a result, the vaccine fell short of the regulatory threshold for licensure. The efficacy estimate for the primary endpoint was 39.4 % with 97.52 % confidence interval [CI], −1.0 to 63.7. However, the vaccine demonstrated statistically significant effects against secondary endpoints including hospitalization due to RSV LRTI. During the meeting, it was postulated that the vaccine might have met criteria for licensure had the trial specified composite endpoints (such as medically significant RSV LRTI and/or hospitalization due to RSV LRTI) in its analysis plan or adopted an alternative trial design or analysis strategy.

The selection of trial endpoints must also take into account the need for objective and consistent definitions and measurements of endpoints. This is required by regulators with whom there is pre-trial agreement on the choice of the endpoints. Without standardized definitions, the comparability and reliability of study results can be compromised. This issue becomes particularly challenging when multiple products are under evaluation, recommended, or marketed for the same disease. For instance, the definition of severe lower respiratory tract infection (LRTI) in one study may differ significantly from another study's definition. These discrepancies in definitions can lead to confusions when comparing the efficacy endpoints across studies. Therefore, it is imperative to strive for harmonization and standardization of endpoint definitions across trials and studies. This ensures that the evaluation of different products or interventions is based on consistent criteria, promoting more accurate and meaningful comparisons and assessments within the context of the same disease [22].

From a public health and policymaker standpoint, the choice of endpoints should align with their contribution to the disease burden to enhance the post-licensure deployment of the vaccine. This would mean prioritizing the most severe outcomes, such as hospitalization and death. While higher efficacy is typically expected against more severe disease, these outcomes generally have lower incidence rates compared to less severe endpoints and therefore may provide insufficient statistical power to drive a successful trial, unless the number of participants to be enrolled is increased considerably as well as the cost and potential duration of the trial.

For vaccine manufacturers, the primary goal before licensure is to conduct a successful clinical trial that maximizes the chances of approval. Consequently, trials often focus on less severe endpoints with higher incidence rates to ensure sufficient statistical power within a manageable trial size [8]. For example, the evidence from the GSK RSVPreF3 vaccine trial in older adults was graded stronger for less severe outcomes, like RSV LRTI and medically attended RSV LRTI, than for more severe outcomes, like hospitalization and death due to RSV, according to the Grading of Recommendations, Assessment, Development and Evaluation Summary as presented in an ACIP meeting [23]. The choice of endpoints is often based on the assumption that if efficacy is demonstrated against the more common but milder endpoints, the vaccine is likely to be efficacious against the more severe endpoints which are of greater public health importance, though demonstration of this may await post-licensure effectiveness studies. Several approaches have been developed to design and analyze trials with multiple outcomes [17,24]. Certain types of multiple endpoint analysis allows the use of both more severe and more common endpoints in the analysis, to decrease the required sample size [25].

Strengths and limitations of adopting a multiple endpoint approach: Considerations from different perspectives

A common way to incorporate data on multiple endpoints is to create a composite endpoint. For instance, if a subject has outcome A OR outcome B, they are categorized as having the composite outcome. An example is the MAKI trial of the effectiveness of palivizumab for the prevention of asthma, where the composite endpoint was defined as current asthma consisting of both parent-reported wheeze in the past 12 months and/or asthma medication in the past 12 months [26]. An advantage of this approach is that it provides a straightforward way to incorporate data from multiple endpoints of interest, increasing the power of a study, and it is fairly simple to interpret [7]. The reduction in the required sample size is greatest when there is little overlap in disease definitions. However, the conclusions based on composite endpoints can be misleading when there is a difference in frequency of events, clinical importance, or the effectiveness of the intervention on each component of the composite endpoint. Additionally, it does not offer the flexibility to incorporate weighted values that reflect the statistical importance of different outcomes.

Approaches that consider the correlation and overlap between the outcomes can be more powerful than methods that analyze each outcome individually. Typically, permutation-based approaches [20] would provide more weight to outcomes based on their frequency (e.g., inverse-variance weights). However, it was proposed at the meeting that alternative weights could be considered that incorporate viewpoints from different stakeholders about the importance of the endpoints (e.g., based on severity, or based on qualitative priorities of vaccine recipients). Those weights should be pre-specified in the protocol. During the meeting, there was a general agreement that this approach may be more suitable for a Phase IV trial after the vaccine has already been authorised. For example, it might be useful to evaluate the effectiveness of the extended half-life RSV prophylaxis, nirsevimab, or of the maternal RSVpreF vaccine, and to compare performances across countries; both therapeutic preventive strategies showed positive results from the Phase III Melody and Matisse trials, respectively [7,8].

A challenge related to the use of these methods comes in the interpretation of results and communication of findings to various stakeholders. For example, the permutation-based approach that uses a weighted average to combine different outcomes [25], which was presented during the meeting, might show an overall significant effect of the intervention, even when the effects against individual outcomes are not significant when tested individually in a post-hoc analysis. Although this would benefit the power of the trial, manufacturers and regulatory bodies require primary endpoints to be clinically meaningful and interpretable so that they can develop label indications and appropriately weigh the benefits against risks. The relevance of a measure that integrates multiple outcomes may not be clear, some of which individually might not reach statistical significance in a post-hoc analysis.

In conclusion, the various needs and perspectives of different stakeholders drive the design of clinical trials. The meeting participants agreed that while a single-endpoint approach may be more straightforward for regulatory approval, a multiple-endpoint approach can increase the likelihood of detecting an effect and obtaining approval, if multiplicity issues are also taken into account. By combining multiple endpoints in the analysis, different stakeholders can make informed decisions based on the clinical trial data; a trial can gain power by evaluating non-severe endpoints with higher incidence rates, as well as incorporating information of more severe endpoints while enabling decisions about the intervention's efficacy in public health practice to be made later. However, questions about how the results of analyses that use multiple endpoints would be incorporated into licensure and labeling decisions need to be resolved.

Making trial designs more efficient

During the second session of the meeting, we focused on two complementary topics: incorporating estimates of vaccine efficacy from previous trials and sequential trial designs.

In general, when conducting a new evaluation of preventative therapies (i.e., active and passive immunization), data from previous trials are ignored beyond support for sample size calculations, despite the potential to provide valuable information. For example, Phase IIb trials may provide evidence of a beneficial but not statistically significant effect of vaccination against clinical endpoints; incorporating data from the Phase IIb trial into the analysis of a Phase III trial could allow for a smaller trial and accelerate the licensure of the vaccine. The Phase III trial could be conducted as a traditional trial with a fixed sample size, or as a group sequential Bayesian trial where vaccine efficacy is evaluated on an ongoing basis and the trial is stopped when sufficient evidence of efficacy has been collected. We discussed limitations and extensions of these approaches. We also considered situations in sequential trials where the decision of whether to continue or stop the trial is unclear.

Incorporating historical data from previous trials

A Bayesian method for incorporating data from previous trials was discussed, in which estimates of vaccine efficacy from a previous trial are used to inform the prior distribution estimate for a new trial using the dynamic borrowing prior distributions methods [27]. Including prior information from previous and historical trials into new trials would potentially decrease the required sample size of the new trial and allow for more efficient use of resources. The downside of incorporating historical data from previous trials in new trials is that the use of historical data can inflate the type I error, which is unacceptable for licensure decisions. To correct for this, the threshold on the type I error should be more stringent, and, consequently, the benefit of incorporating previous evidence is reduced, yielding only a modest reduction in sample size needed for the new trial.

There were a number of important concerns raised about this approach. Regulators may remain unconvinced that a Bayesian trial design offers power advantages over a frequentist design whilst also having appropriate frequentist properties in this setting [28,29]. This is largely due to challenges in accepting approaches that can raise the type I error such as informative Bayesian priors when estimating vaccine efficacy. Regulators often would also expect to see results from a standalone trial, without the influence of prior information.

Additionally, other concerns were raised about Bayesian trial designs. Defining type I error in the Bayesian setting relies on simulations, for which the same standards should apply; however, what remains unclear are the situations in which compliance to these standards can be robustly demonstrated. There was also discussion about whether there is any benefit of using a Bayesian approach, given Bayesian approaches often need to be benchmarked against equivalent frequentist concepts (i. e., power) in the context of trial design. Finally, there may be issues with combining data from Phase II and Phase III trials given potential differences in manufacturing methods for the vaccine and/or definitions of endpoints considered in the trials.

While there was limited support for applying these approaches to RCTs used for licensure, there was discussion about whether statistical methods that integrate data from multiple sources could be applied to post-licensure studies or to support decision-making. When the focus is on estimating real-world effectiveness, these methods could provide a more timely and reliable assessment. This may be particularly valuable for quantifying real-world vaccine effectiveness against rarer but more clinically important outcomes, e.g., severe disease or death. For example, such methods could be used to evaluate the effectiveness of nirsevimab against hospitalization or intensive care unit admission due to RSV; furthermore, they could be used for safety evaluations of adverse events following receipt of maternal vaccines.

Sequential trial designs

In sequential trial designs, vaccine efficacy is evaluated on an ongoing basis, and the trial is stopped when sufficient evidence to establish efficacy has been collected. Sequential trial designs can be a powerful tool to assess the efficacy and safety of an intervention during the trial's course. Such designs are particularly useful when there is a high degree of uncertainty in key determinants of the sample size, such as the incidence rate of the primary endpoint. However, conducting multiple interim analyses requires using a more stringent P-value, which can increase the overall duration and cost of the trial [27].

In sequential trials, there is a trade-off between the number of interim analyses and the final sample size. By limiting the number of interim analyses, the penalty for additional analyses can be minimized. Increasing the number of interim analyses from two to five may result in a significant increase in the penalty, but beyond a certain threshold, further analyses will not have a substantial impact on the required sample size [27]. Having a high frequency of evaluation of efficacy would be possible with certain analytical strategies. However, the utility

of such an approach was questioned by participants. As noted by participants, trials with sequential designs with a limited number of interim evaluations are already in routine use.

General considerations on the need for more efficient trial designs for RSV

There was a general discussion as to whether having smaller, more efficient trials is desirable. Stopping the trial earlier might make it even harder to evaluate an intervention's efficacy in specific subgroups or geographic regions. This information could be crucial for advisory bodies to make recommendations for use post-licensure. Additionally, studies not powered for critical subgroup analyses or safety outcomes may fail to adequately assess a potential safety issue that could represent a true signal. For instance, the maternal RSVpreF vaccine has shown a higher (though not statistically significant) rate of preterm birth in the vaccine arm, raising concerns about a potential true safety signal. In the context of regulatory interactions and committee meetings for RSV maternal vaccines, it has often been stated that the bare minimum sample size should not be the goal. Rather, larger trials are needed to provide comprehensive data across various settings and populations. Ideally, each country would want to understand whether the intervention works (and is safe) in their specific context.

For RSV in infants, and young children in particular, reducing the required sample size may not be a first priority, since RSV disease is relatively common (although severe outcomes are much less common). RSV is typically a highly seasonal pathogen, with epidemics occurring during the winter months in most locations, though the seasonal patterns can vary between temperate and tropical regions. Although sequential trials with evaluations occurring after each season could be valuable, correctly anticipating the RSV season at each site and enrolling participants prior to the start of the season is much more critical.

Extrapolating clinical trial results across settings

The third session focused on using *meta*-regression models to extrapolate clinical trial results across settings, including both high-income countries (HICs) and low- and middle-income countries (LMICs). Vaccine trials, including those for RSV vaccines, are often conducted across multiple sites, representing diverse settings. In deciding on study sites, researchers must balance the need for geographic representation with practical considerations of study logistics, cost, and participant recruitment. Since trials are typically not powered to provide subgroup- or country-specific results, *meta*-regression models could offer a framework for comparing results between sites and obtaining more robust, context-specific estimates of efficacy.

During the meeting, we discussed results from *meta*-regression models applied to data from real-world clinical trials and case-control studies that evaluated rotavirus vaccines, and we discussed extensions and future directions in the context of RSV.

Detecting heterogeneity in vaccine efficacy across settings

Clinical trials are usually not designed to detect heterogeneity in vaccine efficacy estimates across different settings. When heterogeneity is observed, it may be due to chance or differences in the interpretation of case definitions and criteria for hospitalization (when using hospitalized disease as an outcome) among study participants and clinicians in different settings.

Heterogeneity in vaccine efficacy estimates may also reflect true differences in vaccine performance across countries or settings. The efficacy of a vaccine might differ between HIC and LMIC settings due to variations in natural exposure and other factors such as malnutrition and the presence of co-infections. For example, the efficacy of rotavirus vaccines has generally been found to be substantially higher in HICs than in LMICs [30]. Conversely, in a post-hoc analysis of the Prepare trial of a maternal RSV vaccine candidate [21], vaccine efficacy was

higher in LMIC sites than in HIC sites, although the difference in efficacy was not statistically significant.

During the meeting, a *meta*-regression framework was presented in which data on widely available predictors (e.g. under-5 mortality rate, WHO region, diarrhea prevalence, gross domestic product per capita) were used to explain variation in estimates of rotavirus vaccine efficacy (and effectiveness) across countries. This framework was then used to extrapolate estimates of vaccine performance to countries without efficacy or effectiveness data. Local decision-makers may find this modeling approach useful, as it is similar to burden modeling used to predict country-specific incidence when estimates are unavailable. However, it requires that there are sufficient efficacy or effectiveness data available from a variety of countries and that widely available predictors of heterogeneity in vaccine efficacy can be identified.

Optimal trial site distribution using meta-regression models

Pharmaceutical companies prioritize product licensure and often do not focus on having sufficient enrollment in individual sites or countries, particularly LMICs, to robustly estimate site- or region-specific efficacy. However, such information is critical to informing policy, as national and regional bodies that make recommendations about vaccines often desire clinical trial data for their specific context. From the perspective of advisory groups such as the WHO Strategic Advisory Group of Experts on Immunisation (SAGE), there is often criticism about limited trial data on vaccine efficacy coming from LMICs [30], and they may request additional trials and/or an impact study to assess effectiveness before making wider recommendations for vaccine use [31,32].

Meta-regression models can be utilized to identify data gaps and inform optimal data collection strategies and trial site distribution. They can be helpful in finding the best trade-off between a well-distributed global representation of participants and maintaining sufficient statistical power at each study site to ensure robust local estimates. It is important to understand the amount of data required to determine how and if vaccine efficacy varies across settings and to enable robust extrapolation across settings.

Using a minimum threshold to determine vaccine efficacy

Instead of aiming for precise point estimates of vaccine efficacy for individual countries or regions, it may be more productive to assess whether a minimum threshold of protection is met within that region. In other words, the focus would be on having the lower 95 % confidence bound exceed a certain value of vaccine efficacy, which would depend on the specific product under consideration. Determining the minimum efficacy threshold requires careful consideration of various factors, including cost-effectiveness, and examples of how this approach has been used in practice would be useful. Incorporating uncertainty ranges in vaccine efficacy estimates in value of information analyses can identify whether these uncertainties should drive decision-making.

Overall opinion on heterogeneity in vaccine performance

Overall, the participants agreed that factors such as malnutrition, HIV, or malaria could lead to heterogeneity in the efficacy of vaccines against RSV, particularly for maternal vaccines. However, heterogeneity in vaccine performance will generally be assessed post-licensure rather than in clinical trials, and this type of *meta*-analytic approach can be useful for understanding predictors of heterogeneity and extrapolating vaccine efficacy and effectiveness estimates across countries.

Conclusions

The recent meeting on the design and use of clinical trials for RSV vaccines and other preventive interventions covered crucial topics that require urgent attention given the high number of products in the

clinical development pipeline. The meeting highlighted a lack of alignment between what is necessary for licensure and what is required post-licensure for informing vaccine deployment decisions, particularly in LMICs. One of the key debates was around whether we should prioritize increased efficiency to achieve licensure more quickly and inexpensively, or aim for more robust and larger trials to provide critical information at the country or regional level and to provide accurate information on safety, especially when concerning rare events.

The approaches covered in the workshop could be particularly valuable in the context of post-licensure studies. These methods are especially useful when the objective is to validate the effectiveness of vaccines within new or specific subgroup populations. It is our hope that this workshop will serve as a starting point for further discussions and meetings that will bring together regulatory and advisory bodies, including those in LMICs, to address these critical issues.

Disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the agencies or organizations with which the authors are affiliated.

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Data availability

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