Report of a one-day convening on regulatory science, practices, and innovative approaches to facilitate approval of novel combination vaccines

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1. Abstract

Combination vaccine formulations contain distinct components targeting multiple strains of a single pathogen or multiple pathogens. By minimizing the number of separate vaccine administrations required, they have been critical in allowing the broad expansion of the number and range of diseases that can now be prevented by immunization. Recent advances in vaccine development and our understanding of the immune system now make it possible to envision how new combination vaccines could play a major role in helping immunization programs address a much wider range of emerging or still problematic pathogens. However, few combinations are currently in the pipeline, in part due to their inherently increased complexity and cost of development compared to standalone formulations. This complexity, in turn, is partly driven by the regulatory requirements surrounding the clinical study program for the combination vaccine, especially the primary clinical endpoints and the required degree of precision around those endpoints, as these ultimately determine the sample size, cost, and duration of the study. As part of a larger effort to facilitate combination vaccine development, vaccine experts at the World Health Organization and PATH coordinated a one-day meeting in March 2025 gathering current and former national regulatory agency staff from a dozen countries, together with vaccine developers, representatives from funding and procurement agencies, and public health and policy officials. The convened participants held spirited discussions on how multiple immune markers and controlled human infection models (CHIM) might contribute to the demonstration of vaccine efficacy. In addition, participants considered the possibility of relying on clinical endpoints when the vaccine components are directed against pathogens causing the same disease syndrome but etiological determination of each component's contribution is not feasible. Regulators welcomed scientifically sound, creative proposals for demonstration of efficacy, and agreed that the benefit-risk of the combination vaccine as a whole should be the primary focus.

Keywords: vaccine development and licensure, syndromic endpoints

Highlights

- Combination vaccines are needed but regulatory challenges are a significant hurdle.
- Regulators are open to innovative approaches to assess combination vaccines.

- Approaches include greater focus on the overall efficacy and effectiveness of the combinations
- Controlled human infection model data and clinical syndromic efficacy endpoints can be valuable
- The benefit-risk of the combination vaccine as a whole should be the primary focus.

2. Introduction

Immunization programs provide a high level of protection against a broad range of diseases affecting infants and young children and are increasingly expanding to other age groups. Recent scientific advances in antigen identification and design, in the development of platform technologies (such as viral vectors and mRNA), coupled with increasingly precise immunological insights, have substantially enhanced the technical feasibility of developing vaccines against a wider array of pathogens. However, the appetite of the public health community to introduce new stand-alone vaccines exceeds the logistical and financial capabilities of many immunization programs, particularly in low- and middle-income countries (LMICs), to absorb them.

What might be the path forward? Critical to the success and sustainability of current programs have been efforts to reduce the number of separate vaccine administrations required through the introduction of multi-pathogen combination vaccine formulations. Two sets of combination formulations, diphtheria/tetanus/pertussis (DTP)-based and measles-based respectively, currently serve as the cornerstones of most immunization programs. Looking ahead, the development and adoption of novel combination vaccines represent an essential strategy to sustain the protective impact of existing programs while facilitating the integration of emerging vaccines, many of which, if available only as stand-alone formulations, would face significant barriers to introduction.

Compared with stand-alone formulations, multi-pathogen combination vaccines confer multiple programmatic advantages, including improved timeliness of vaccination, higher and more equitable coverage, and reduced costs related to storage, administration, and delivery. Beyond these operational benefits, the ability to minimize the number of injections while simultaneously broadening disease coverage along the life course has the potential to enhance community acceptance, minimize vaccine hesitancy, and possibly result in a reduction in the high number of unvaccinated children, especially in Africa.[1]

Unfortunately, there is a paucity of new combination vaccines in development, with the notable exception of a few designed to protect adults from viral respiratory diseases[2]. While significant technical and developmental challenges do exist for most hypothetical combinations, and these become more difficult to resolve if no single developer has intellectual property rights to all components of an envisioned combination, the overarching issue is the poorly defined return on investment (ROI) on combination vaccines as perceived by vaccine developers. ROI is heavily dependent on the likelihood that a combination vaccine, if successfully developed, will be widely recommended, procured, and introduced. Such recommendations are in the domain of national immunization technical advisory groups (NITAGs), informed by guidance from expert bodies at global and regional levels. However, few policy recommendations express an intrinsic preference for combination formulations over their standalone equivalents.

Furthermore, policy makers usually do not proactively identify and communicate what would, in their opinion, constitute desirable future vaccine combinations. Taken together, these factors contribute to developer uncertainty regarding the ultimate demand (commercial value) of potential combination formulations. Such uncertainty is then weighed against the inherent technical and clinical complexity associated with developing and assessing combinations, which can be considerable. For example, the research and development programs resulting in DTP-containing penta- and hexavalent combinations entailed major personnel and financial expenditures that extended over a decade.

Some activities are underway to address this situation. First, to help policy makers assess the health and economic benefits of combination vaccines, the World Health Organization (WHO) and PATH, in close collaboration with national and regional immunization policy makers and funding agencies are developing an evidence-based and transparent framework to evaluate and prioritize potential combinations[3]. In parallel are activities to identify the key value drivers for such priority combinations (e.g., enhanced coverage and/or timeliness of vaccination due to reduced injections, potentially increased equity, reduction in cold-chain and delivery costs) and translate them into transparent, relevant, and quantifiable metrics which capture the benefits described earlier and thereby allow the true value of potential combinations to be estimated. The results of these activities should become available in late 2026.

Secondly, and the subject of this article, are nascent efforts to reduce the risk, resources needed and complexity of clinical development programs underlying combination vaccine development by re-examining some of the licensing criteria established in the past and applied to combinations. The underlying premise of these efforts is that acceptability criteria should reflect the overall public health benefit-risk profile of each combination formulation. Moreover, such criteria are intended to be periodically reassessed as evidence and experience continue to accumulate.

The WHO-PATH project recently explored, in a one-day convening of vaccine developers, infectious disease experts, and regulators, whether innovative regulatory paradigms and criteria could be developed that would support the demonstration of the overall safety and efficacy of potentially valuable combination vaccines, rather than efficacy of the individual components. It is important to highlight that demonstration of "efficacy" of individual or combination vaccines is not limited to studies showing vaccine prevention of clinical disease, but in many cases may be inferred from studies relying on immunological endpoints. The overarching objective is not to lower regulatory standards, but to ensure that assessments are appropriately tailored to the vaccine formulation as a whole, thereby reducing unnecessary cost, time, and development risk. This article summarizes the highlights and insights from that convening.

3. The Regulatory Convening

Meeting goals and objectives:

1) Discuss current paradigm for regulatory assessment of multi-pathogen combinations, focusing on the US Food and Drug Administration (US FDA) and European Medicines Agency (EMA) guidelines and insights from licensure challenges with selected legacy combination vaccines;
2) Identify innovative clinical regulatory pathways currently being explored to expedite licensure without lowering the safety or efficacy "bar" for real-life combination vaccine candidates;
3) Within small working groups, solicit informal feedback from representatives of National Regulatory Agencies (NRAs) regarding the pros and cons of these pathways.

To encourage open discussion and creative input from meeting participants as individuals, the meeting was explicitly designed NOT to develop specific,

formal proposals of regulatory strategies nor to solicit official regulatory agency feedback. For similar reasons, this report employs the Chatham House rules in not attributing comments to specific participants.

The list of participants and their affiliations is listed in the *appendix.* Briefly, approximately 40 participants included current and former representatives from NRAs in Africa, Asia, Europe, North America, and South America, from several vaccine developers who were members of the International Federation Pharmaceutical Manufacturers and Associations and the Developing Countries Vaccine Manufacturers Network, as well as public health officials, immunization policy experts, and representatives from funding agencies.

4. Meeting summary.

This report is structured thematically. It first describes the essentials of the current regulatory guidelines most relevant to combination vaccines from major American and European agencies. It then discusses key lessons from experiences with existing combination vaccines, followed by consideration of how these might be applied and further enhanced for future combinations. It draws upon arguments and examples raised within individual presentations.

i) Relevance of current regulatory guidelines and paradigms to combination vaccines

Two speakers noted that most of the principles in current vaccine guidance by the European Medicines Agency (EMA) and US Food and Drug Administration (US FDA)[4,5] remain valid and relevant to combination formulations, although some of the specific wording may evolve over time. For example, the most recent US FDA guidance on combination vaccines, issued in 1997[5], states that, from a safety perspective, the combination vaccine should ideally be compared to its individual components administered separately and that its safety profile should be no worse. Nonetheless, regulators will consider the totality of the data in the benefit-risk assessment of the combination vaccine. Efficacy for combination vaccines should be demonstrated through randomized controlled clinical trials using endpoints that may range from clinical disease incidence to well-established correlates of protection where a corresponding protective threshold is available. Notably, immunogenicity data may be used to bridge to existing efficacy data, including through comparative immunobridging

studies to licensed comparator vaccines. Such data can provide supportive evidence of effectiveness even in the absence of a well-established correlate of protection.

In reality, each of the components of the most prominent multi-pathogen combination vaccines in that era, DT(a)P-Hib-HepB and M(M)R, had already been licensed separately as a standalone formulation, and the clinical efficacy of each had been previously demonstrated separately. However, to dispel any uncertainty regarding novel combination vaccines, it was emphasized there is no *a priori* requirement that each individual component be first licensed separately. Furthermore, there is no requirement that the efficacy of each component of a combination be first demonstrated as a standalone vaccine—i.e., efficacy can, in theory, be established in a study evaluating only the larger combination. Similarly, there is no requirement that efficacy of each component within a combination be compared to efficacy of a corresponding standalone formulation if the latter does not already exist as a licensed product *(Table 1).*

Table 1. Common misconceptions surrounding licensure of combination vaccines

Misconception	Reality
Each individual component of a combination needs to be separately licensed first.	While individual components of combination vaccines in the past were previously licensed as standalone products, this is not a requirement.
The efficacy of each component of a combination needs to first be demonstrated as a standalone formulation.	There is no requirement to demonstrate efficacy of a standalone formulation that is not intended to be licensed as such.
Efficacy of each component within a combination must always be compared to efficacy of a standalone formulation.	Such comparisons are likely to be requested if the standalone is already licensed. However, one could also establish efficacy of an individual component in a study evaluating only the larger combination.

It is generally considered desirable for any new vaccine component to demonstrate a clinical efficacy of at least 80 or 90%, and with a high degree of certainty (i.e., with a lower bound of the 95% confidence interval (CI) well above 0%). In the case of COVID-19 vaccines, for example, a lower bound of 30% was generally agreed upon by many NRAs. However, current licensure guidelines from the US FDA or EMA do not contain any statutory or regulatory requirement to demonstrate a specific level of vaccine efficacy or threshold of protection. Furthermore, a lower bound of the 95% CI just above 0% has been accepted in the past. One notable case is that of the RTS,S malaria vaccine, which was deemed acceptable for EMA licensure given the tremendous public health benefit of a projected 31-56% decrease in disease and a lower bound of the CI above 0%.[6]

Furthermore, while the regulators must conclude that there is ‘substantial evidence of effectiveness’ to approve a product, the degree of certainty necessary to support such a conclusion may differ depending on the incidence and severity of disease, the anticipated target population, the availability of other therapies (or lack thereof) and the vaccine’s safety profile. Indeed, for several regulatory authorities, a requirement for the lower bound of the 95% confidence interval to be greater than 0% (and not tighter)

could still be acceptable with proper justification. The above considerations may have particular relevance when evaluating evidence of efficacy for "incremental" components of combination vaccines (see later section).

Post-marketing surveillance (PMS) studies were highlighted as means to demonstrate effectiveness of vaccine formulations and thereby complement pre-licensure immunogenicity and efficacy data, especially where robust assessment of clinical efficacy may be precluded by low case numbers[7-8]. It was also noted that such studies are not always feasible in many settings, especially in LMICs, given the dearth of robust PMS systems. Furthermore, it was clarified that licenses based on immunological correlates/markers may constitute full licenses in their own right, i.e., they are not necessarily "provisional" and contingent on confirmatory PMS data. Given the relative paucity of clinical trials in LMIC settings, it is crucial that post-authorization studies (ranging from active surveillance to effectiveness studies) are conducted in those settings to support the safe use of these products.

The presenters highlighted regulatory agencies' openness to extending regulatory flexibilities where scientifically justified. The overarching principle is that regulatory data needs and requirements should be commensurate with the benefit-risk ratios of a specific combination vaccine formulation, taken as a whole.

ii) Lessons from previously licensed combination vaccines

The early US FDA guidance referenced above[5] stated that "the data required to support each indication will be the same as for single component vaccines." At the same time, however, it was acknowledged that such an approach may not be feasible for certain combination vaccine formulations, particularly when disease caused by the individual pathogens is rare or when the number of immunological comparisons is prohibitively large, as these could necessitate a clinical trial with an impractically large sample size. For instance, the large number of pneumococcal serotypes in pneumococcal conjugate vaccines (PCV) made it impractical to generate robust efficacy data for each serotype through a logistically feasible trial. Both US FDA and EMA accepted aggregate vaccine serotype efficacy as the primary endpoint in the pivotal clinical studies supporting licensure of the 7-valent Prev(e)nar™.[9]

Two presenters described how the use of multiple immunological endpoints based on the anti-capsular polysaccharide responses were necessary to provide sufficient confidence that inclusion of multiple pneumococcal serotypes in higher-valent PCVs (compared with the original 7-valent formulation) or of Hib within DTaP penta- and hexavalent (compared with standalone Hib) would not compromise efficacy. Non-inferiority comparisons using serotype-specific IgG geometric mean titers (GMT) as the primary endpoint were used to demonstrate the effectiveness of the investigational combination vaccines. These were supported by secondary endpoints including titers of functional antibodies. While not all serotypes met the non-inferiority criteria, a holistic evaluation of the immune responses induced was used to infer vaccine effectiveness. For both Hib and individual pneumococcal serotypes, these included immune parameters such as the percentage of vaccinees achieving a putative protective antibody threshold, as well as other antibody levels reflecting boostability or durability of protection.

Given the multiplicity of statistical comparisons to be undertaken to license complex multivalent vaccines, it is possible that some “failures” to demonstrate non-inferiority may occur by chance. Therefore, an important additional regulatory consideration for PCVs was that the requirement to achieve a given efficacy or immunogenicity threshold for a particular pneumococcal serotype may depend on its perceived benefit/epidemiological importance. In other words, vaccine approval may still be possible even if some components are deemed “inferior” compared to the licensed products and that inclusion of these components is justified by the overall benefit of the combination vaccine. Furthermore, the level of evidence required to infer clinical efficacy of any given serotype might be in direct proportion to its epidemiological importance relative to other serotypes[10].

The above considerations were taken into account during licensure of the PCV13 vaccine by the US FDA. Three of the 13 serotypes failed at least one of the primary immunogenicity objectives in a study with primary series at 2,4, 6 months, with serotype 3 notably failing the primary and all secondary endpoints. However, regulators acknowledged that IgG antibody concentrations ≥ 0.35 ug/ml is not a well-established and uniform correlate of protection for each serotype, and that the putative protective threshold would likely vary depending on the serotype. In addition, they considered opsonophagocytic titer (OPA) response rates as important for protection against invasive pneumococcal disease (IPD) and there were no differences

in OPA response rates, including for serotype 3, between PCV13 and the licensed comparator, PCV-7. Thus, PCV -13 was deemed acceptable for licensure[11].

In this context, it is noteworthy that the 1997 US FDA combination vaccine guidance explicitly encompassed both multi-pathogen combination vaccines such as DTP and MMR, as well as (then forthcoming) mono-pathogen multivalent combinations (such as PCV). PCV is thus an example where the principle of ensuring that regulatory criteria are appropriate for the combination vaccine as a whole may have been prioritized over ensuring that each (pneumococcal serotype) component individually passed "the same" efficacy criteria as if it were being considered as an individual standalone vaccine.

Demonstration of immunological non-inferiority of each of the components within a combination vaccine to the separate, licensed components, as measured by a relevant biomarker, is often assumed to be necessary to infer comparable efficacy. However, the example of a recently licensed meningococcal ABCWY combination vaccine, illustrated that regulatory agencies will also consider and accept innovative immunological parameters more closely linked to clinical protection. In this case, immune responses as measured by human serum bactericidal activity (hSBA) elicited by the four major antigens within the B serogroup component of the combination formulation were NOT statistically non-inferior to those in the standalone vaccine. However, the applicant successfully argued that comparable levels of protection against MenB strains in the combination vaccine were demonstrated by using an alternative killing assay (endogenous-complement hSBA). This assay was used with a 110-isolate panel of diverse MenB strains[12] to demonstrate comparable protection in the combination vaccine, permitting licensure despite reporting lower hSBA results to the four indicator strains.[13]

Although most of the discussion at the convening focused on ways to evaluate the efficacy of combination formulations, the participants emphasized that the safety of any vaccine formulation is of paramount importance. One presenter referred to the slightly but significantly increased fever rates observed with MMR-V vs MMR and V given separately.[14-15] He suggested that conclusions regarding the acceptability of the benefit-risk ratio may depend on whether the data are presented as relative changes between the two groups or as the absolute increase expressed as the

number of children with high fever, which was reassuringly low. Accordingly, he proposed that there should be no automatic rejection of any combination that shows a statistically significant relative increase in reactogenicity compared to the corresponding standalone vaccines; the decision should instead depend on the absolute magnitude of the increase and severity of the reactogenicity. It was noted that tolerance for any increased reactogenicity whatsoever for a combination may be less within settings where vaccine uptake of a component vaccine is already sub-optimal. Regardless of the setting, it is the overall impact on the benefit-risk balance of the combination vaccine as a whole that matters, not the comparison with stand-alone vaccines.

iii) Opportunities to apply lessons and new paradigms to new vaccine combinations.

The overall standards and principles for demonstrating efficacy and safety are the same for any preventive vaccine, including combination vaccines. However, there will be additional specific considerations in the development of these products that will depend on whether one is considering a combination of two or more licensed vaccines, a licensed vaccine with one or more novel candidates, or a vaccine consisting of two or more novel vaccine components. For example, if two licensed vaccines were combined in a single formulation, there may be limited benefit in regulators requiring a clinical study to show lot-to-lot consistency of manufacture of the combined product since consistency of the licensed standalone vaccines would already have been demonstrated. In fact, demonstration of lot-to-lot consistency is not a universal regulatory requirement. It was further suggested that for a combination product that is well-characterized (e.g. vaccines manufactured using the mRNA platform), it may be possible to forego demonstration of Lot-to-lot consistency, even if it had not already been demonstrated for the individual components.

When one or more novel candidates is included in a combination, the lack of a regulatory requirement for demonstrating efficacy of each component separately does not preclude a developer from nonetheless deciding to do so. For example, given the advanced status of *Shigella* vaccine development, it may be most expedient and risk-mitigating to first demonstrate efficacy with a standalone *Shigella* vaccine even though it may need to be ultimately included within a combination formulation to become sufficiently cost-effective.

In contrast, for other vaccine candidates at early stages of development, one might choose to demonstrate efficacy using only the combination itself. For example, a combined typhoid conjugate vaccine (TCV)-paratyphoid formulation was used to demonstrate efficacy against paratyphoid disease in a CHIM. The possibilities of demonstrating invasive non-typhoidal *Salmonella* (iNTS) efficacy using co-formulated TCV-invasive non-typhoidal *Salmonella* (iNTS) or TCV-iNTS-*Shigella* formulations were also described. Similarly, it was suggested that an RSV-human metapneumovirus combination vaccine (indicated for older adults) might be used to demonstrate efficacy of the metapneumovirus component rather than evaluating the efficacy of the latter by itself.

The definition of "incremental" combination vaccine components and its regulatory implications

The discussion of specific combination vaccine formulations led to extensive discussion at the convening as to whether certain vaccine components proposed to be combined with a vaccine targeting a pathogen of major public health importance might be considered "incremental." By "incremental," it was meant that the additional components would have been unlikely to be licensed and marketed as stand-alone formulations because they protect against pathogens responsible for a lower mortality burden (but nonetheless significant morbidity) relative to the primary vaccine. By giving greater consideration to the context of use and feasibility of evidence generation in their decision making, regulatory authorities may justify and exercise greater flexibility in accepting innovative strategies (e.g. enhanced reliance on CHIM models and clinical bridging studies) and alternate thresholds for clinical efficacy (level of vaccine efficacy and lower limit of the 95% CI) for the incremental components of the combination vaccine.

To some extent, regulatory precedent has already been set: regulators applied flexibility in the licensure of higher valent PCVs, where the relative contribution of each additional serotype in protecting against IPD is relatively minor, though in aggregate they are impactful.

For some combinations, such as DTP-hexavalent or a hypothetical RSV-Group B Streptococcal (GBS) formulation, there is no obvious incremental component. However, for some other examples, described below, such terminology may be applicable, although the magnitude of the perceived

incremental epidemiological benefit of additional components may vary by geographic setting or by the age range of the target population. For example, a component may be considered “incremental” for young children but not for older adults/elderly due to population-specific differences in disease rates. Participants agreed that the paratyphoid component in the context of a future TCV-paratyphoid vaccine, as previously discussed, might be a good example of a “incremental” component as paratyphoid disease is considerably less common than typhoid. Another example might be human metapneumovirus in a combination with RSV.

Clinical disease endpoint efficacy studies for a paratyphoid vaccine would be prohibitively large (60,000 to >100,000 children), given the low incidence of paratyphoid disease (personal communication, A. Pollard). Therefore, if regulators were to consider the paratyphoid component as “incremental,” they may more easily accept as primary evidence of clinical efficacy a CHIM study involving adult volunteers (accompanied by immunological bridging of the immune responses between the CHIM volunteers and the target pediatric population).

A similar rationale could support reconsideration of whether a lower bound of the 95% CI for clinical efficacy of the paratyphoid component of a typhoid-paratyphoid vaccine within the CHIM model needs to be set substantially higher than zero, e.g. above 20%. Where the lower bound is set has substantial implications for the sample size required to provide sufficient statistical power, potentially entailing a significant increase in cost and time needed. In a benefit-risk calculation, the greater confidence that the true efficacy is substantially high needs to be balanced against the knowledge that the contribution of the paratyphoid component is incremental to an already highly effective vaccine against the more significant pathogen.

Some meeting participants noted that, even if regulators granted licensure based on an alternative efficacy measure for the incremental component of a combination vaccine, national, regional, or global immunization advisory committees may still require demonstration of effectiveness before issuing a recommendation for use.

Clinical syndromic endpoints may prove critical for registration of certain combination formulations

There may be significant public health value to developing a combination vaccine that targets the major pathogens responsible for a given clinical syndrome[1]. Demonstration of substantial clinical efficacy of such a combination against the common clinical syndrome via a composite endpoint would be highly desirable. Ideally, in the absence of a well-accepted immunological correlate of protection, one would seek to demonstrate high clinical efficacy against each of the individual components using discrete clinical endpoints. However, due to low incidence of disease caused by one or more of the pathogens, it may be impossible for logistical and financial reasons to ensure a study is large enough to have sufficient power to reveal a statistically significant clinical efficacy result for each of the individual pathogens targeted. In those cases, efficacy against the composite syndromic endpoint might serve as the primary endpoint of a study.

Reliance on a syndromic clinical endpoint has rarely been utilized for vaccine studies. (One notable exception was the demonstration of clinical efficacy by PCVs against radiologically-confirmed lobar pneumonia in children in the absence of any etiological diagnosis.[16]) Nonetheless, it was noted that such trial designs—not demonstrating efficacy against every individual causative pathogen—are not uncommon in pivotal licensure studies of antibiotics and other pharmaceutical therapeutics including prophylactic interventions. Two presentations discussed how combination vaccine studies using a clinical syndromic endpoint with a strict, well-defined case definition might be designed in consultation with regulators.

A few common prerequisites were described. First and foremost, the developers must provide convincing justification that obtaining sufficient statistical power to demonstrate efficacy is simply not practical for each component. Secondly, it was assumed that each vaccine component could be shown to elicit substantial and putatively protective immune responses. In addition, it would be desirable, if feasible, for robust, well-defined post-licensure studies to subsequently demonstrate vaccine effectiveness against each component.

Two different scenarios were offered. In the first, it is feasible to obtain etiological confirmation of each of the causative pathogens using microbiological or molecular approaches, and so an overall aggregate efficacy value can be obtained. This was the case with IPD, influenza, and dengue and is anticipated to be the case with moderate-severe diarrhea caused by *Shigella*. However, due to the relatively low incidence of most

individual pneumococcal or *Shigella* serotypes, an etiologically based, statistically powered confirmation of clinical efficacy by a multi-serotype targeting vaccine may only be possible for one or two serotypes.

For multi-pathogen vaccines, examples could include aggregate efficacy determination of a neonatal sepsis vaccine for pregnant women in LMICs containing multiple serotype-specific conjugates of GBS and of *Klebsiella pneumoniae* and perhaps also extraintestinal pathogenic *E.coli* (ExPEC), or a respiratory viral combination for adults including RSV and human metapneumovirus. Participants emphasized that it would still be important to show that there was no indication, even if statistically insignificant, of a negative point estimate for efficacy of one or more components.

In the second case, a definitive etiological determination is simply not possible without an impractical, highly invasive procedure, and it is only feasible to measure the aggregate efficacy of the combination vaccine. Examples could include combination vaccines targeting acute otitis media (since tympanocentesis is practically impossible to perform in most settings), or consolidated pneumonia (where lung puncture sampling is currently considered the only sufficiently specific way to determine the causative pathogen but is rarely performed).

An obvious drawback to either of these aggregate efficacy approaches is less confidence, compared with individual pathogen efficacy measurements, that each individual component is highly efficacious and/or contributed significantly to the overall efficacy.

In each case, it would be important to conduct periodic epidemiological monitoring to ensure that each pathogen continues to circulate as a potential cause of disease. However, one speaker cautioned that decisions by regulatory authorities to require vaccine developers to rapidly remove a component from a combination formulation due to year-to-year fluctuations in pathogen circulation—as was the case with the US FDA's recent requirement for manufacturers to remove the B/Yamagata component from quadrivalent influenza vaccine formulations—should not be taken lightly. As such a move would entail the need to develop and license what would be considered a new product, this could adversely affect willingness of developers to assume the development costs and risks of combination vaccine development in the first place.

The potential value of CHIM studies for combination vaccine licensure
In the absence of field efficacy information, CHIM studies in immunologically naïve populations can provide critical data, especially for incremental/minor pathogens, if coupled with immunological bridging to the target population. The role and value of the CHIM study will depend on the ultimate target population[17]. If it is conducted in the target population itself (e.g., *Shigella* in adult travelers), the CHIM results may be sufficient to represent primary evidence of efficacy. However, if the ultimate target differs (e.g., infants in LMICs), there will more likely be a requirement for efficacy data in that population (or if not possible, immunological bridging to that population using a correlate of protection or acceptable immune marker).

In light of the relatively low incidence of paratyphoid disease, as described earlier a CHIM study of paratyphoid vaccine effectiveness will likely prove critical to allow licensure of paratyphoid-typhoid combination vaccines to proceed. Interestingly, a comparison of the TCV efficacy results seen in a CHIM *vs* results subsequently observed in efficacy studies in the target population suggest that some CHIM studies may actually be more stringent[18]; whether this will be generalizable to related pathogens and models (such as paratyphoid) remains to be seen.

In summary, there are a variety of regulatory "levers" that could be adjusted to better reflect the strong public health benefits of and need for combination vaccines, the greater complexity of determining efficacy of each element of multi-valent formulations, and the incremental value of some additional combination vaccine components. *Table 2* lists several of the clinical trial design elements, considerations, and parameters discussed at the convening. The relevance and value of each of these will depend on the perceived benefit-risk assessment of the specific combination and the strength of the scientific justification that adjustment of any individual lever will result in an adequate demonstration of vaccine efficacy.

Table 2. Clinical trial design elements and parameters with particular relevance for licensure of combination vaccines

Variable	**Description**	**Comments**	**Theoretical Vaccine Example**
Design Element			
Regulatory acceptance of data from CHIM studies	Determination of clinical efficacy of combination vaccine or novel component after deliberate challenge in adults in a controlled setting	Need immunological bridging of novel component with final combination vaccine in target population followed by PMS for effectiveness	Paratyphoid-containing combination vaccine
Use of clinical disease (syndromic) endpoint to determine aggregate efficacy of the combination vaccine	Expected to be useful especially where etiological confirmation not possible due to lack of access to clinical samples and/or insufficient incidence of disease due to one or more individual pathogen	Requires strict, clinically relevant case definition; and no trend against efficacy of any components (where etiological confirmation is possible)	Syndromic combination vaccine against acute otitis media (*S. pneumoniae* and non-typable *H. influenzae* and *M. catarrhalis*, acute viral respiratory disease (RSV, human MPV, parainfluenza virus), or neonatal sepsis (GBS and *K. pneumoniae*)
Parameters, particularly for "incremental" component			
Required threshold of vaccine efficacy	Consideration that values below 70-80% vaccine efficacy may still be acceptable for incremental component	A "default" high vaccine efficacy requirement for incremental component may preclude licensure of combinations with substantial public health value above standard of care	
Acceptable lower limit of 95% CI for VE point estimate determined in target population or CHIM	Need for flexible approach for acceptable lower limits above 0%	Confidence in efficacy value of incremental component may be less or cases fewer than that for major component	Paratyphoid-containing combination vaccines
Acceptable non-inferiority margins used as basis for comparisons between vaccines	Acceptable non-inferiority margins for immunological bridging might be more than the usual 10% for proportion of responders or seroconverters, or more than 25% for geometric mean titers	May be particularly valuable in bridging from component tested separately in a CHIM study to final combination	
Reliance on multiple immunological endpoints with focus on functional responses, to establish non-	In absence of established correlate of protection, clinical efficacy may be more reliably inferred using a variety of	Relative epidemiological importance of incremental component(s) may affect regulatory acceptability when one	Combination vaccines targeting pathogens with multiple serotypes, e.g., PCV and *Shigella*

inferiority	immunological endpoints rather than a single parameter if adequately justified	(or a few) comparisons fail to show non-inferiority	

5. Conclusions and Next Steps

At the same time that the benefits of vaccines along the life course are becoming widely recognized, the increasing number of vaccines is leading to concerns about their ease of administration, access, and acceptability especially in areas difficult to access. There was general agreement among participants at the convening that the additional advantages combination vaccines bring, i.e., beyond those of their individual components, should be explicitly recognized in public health decision-making. Their overall benefit-risk profiles relative to individual vaccines or vaccine candidates should be taken into account by regulators in their assessments. To this end, it was suggested that global, regional and national policy-makers should be involved in further discussions of combination vaccine regulatory considerations, alongside regulators.

Regulators welcome sound scientific and public health rationales to adapt, where necessary, existing guidelines and adopt innovative approaches to demonstrate clinical efficacy of combination vaccines. Experience with previous combinations, including mono-pathogen/multi-serotype formulations, shows that regulatory flexibility is possible. It was recognized that some regulatory authorities may have more experience and competence than others in evaluating combination vaccines.

Furthermore, some countries lack alternative regulatory pathways/frameworks which allow for acceptance, for example, of CHIM studies or for issuance of provisional licensure with flexible data requirements and ultimate approval contingent on PMS data.
It was also noted that the timely availability of WHO guidelines (Technical Review Series) on combination vaccines could guide and support local capacity building for regulatory review of combinations.

At the same time, it was agreed that regulatory review of combination vaccine dossiers can be improved and possibly expedited if conducted jointly by multiple regulatory authorities (both North-South and South-South) to take advantage of different expertise. Similarly, joint training workshops on combination vaccine issues, such as considerations for conditional

authorizations based on results of PMS, would increases regulatory certainty and support vaccines for which traditional efficacy studies are not suitable. Publication and dissemination of this peer-reviewed meeting report was also highlighted to increase awareness of some of the issues, challenges, and possible approaches to facilitating combination vaccine licensure.

Participants highlighted that this convening only addressed clinical regulatory considerations particularly relevant to combination formulations. Another key aspect of regulatory assessment is the chemistry, manufacturing, and controls (CMC) side. A separate convening focused on CMC challenges associated with combination vaccines might be quite valuable.

Finally, as noted in the Introduction, the ideas and suggestions discussed in this manuscript were specifically focused on licensure pathways for combinations, and thus complement ongoing activities under the WHO-PATH project that will provide analyses and information to better inform decision-making of NITAGs on whether to recommend introduction and use of combination vaccines once they are licensed.

Appendix (List of Invited Participants)

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