Meta-Analysis of Economic Evaluations of Vaccines to Support Decision Making Process

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3. Simon Procter and Mark Jit, London School of Hygiene and Tropical Medicine

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15th IHEA World Congress, Cape Town, 10 July 2023

Field: Economic evaluation of health and care interventions

Session ID: 2441

Session Type: Organized Sessions

Session background

- As vaccine costs rise and competing priorities increase, economic evidence plays an increasingly important role in vaccination decisions
- Decision makers including WHO SAGE on immunization are, however, often challenged by unmanageable amounts of information and conflicting findings from economic evaluations (EEs)
- Systematic reviews of EEs can provide an efficient mechanism to synthesize existing cost-effectiveness evidence to answer a specific value question, however, provide only descriptive and qualitative evidence
- **Meta-analysis of EEs (MAEEs)** using comparative efficiency research (COMER) to generate quantitative evidence*
- A step-by-step data harmonization process to conduct MAEEs has been applied in several therapeutic areas including vaccines, and has been endorsed by the **Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC)** of the World Health Organization (March 2021)

2021, 96, 133–144 No 17

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

30 APRIL 2021, 96th YEAR / 30 AVRIL 2021, 96e ANNÉE
No 17, 2021, 96, 133–144
http://www.who.int/wer

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Meeting of the Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC), March 2021

The IVIR-AC recommendations are based on discussions during a virtual meeting of the IVIR-AC held 1–5 March 2021.

COVID-19 vaccine modelling

The WHO COVID-19 Vaccine Impact Modelling Subgroup of the WHO Strategic Advisory Group of Experts on Immunization (SAGE) Working Group on COVID-19 Vaccines provides modelling guidance to inform global policy recommendations related to prioritization of COVID-19 vaccines. In September 2020, IVIR-AC reviewed an initial set of modelling questions developed by the Subgroup. These were part of a Request for Information that was shared with modelling groups which have since presented work on these topics to the SAGE Working Group and Subgroup. In January 2021, the Subgroup issued a Request for Proposals (RFP) that addressed priority questions and gaps in modelling evidence. The results of the RFP, expected in mid-2021, will enable SAGE to further develop vaccine product-specific guidance and policy recommendations. To inform this process, IVIR-AC was asked to identify additional priority areas for vaccine modelling and ways to incorporate additional evidence into the SAGE *Evidence to Recommendations* (E2R) process.[1]

Réunion du Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC), mars 2021

Les recommandations de l'IVIR-AC présentées ici sont basées sur les discussions qui ont eu lieu lors d'une réunion virtuelle du Comité qui s'est tenue du 1er au 5 mars 2021.

Modélisation des vaccins contre la COVID-19

Le sous-groupe de l'OMS chargé de la modélisation de l'impact des vaccins anti-COVID-19 au sein du groupe de travail sur les vaccins anti-COVID-19 du Groupe stratégique consultatif d'experts de l'OMS (SAGE) sur la vaccination fournit des conseils en matière de modélisation afin d'éclairer les recommandations stratégiques mondiales relatives à l'établissement des priorités de vaccination contre la COVID-19. En septembre 2020, l'IVIR-AC a examiné une première série de questions de modélisation préparées par le sous-groupe. Celles-ci faisaient partie d'une demande d'information partagée avec des groupes de modélisation qui ont depuis présenté des travaux sur ces sujets au groupe de travail et au sous-groupe du SAGE. En janvier 2021, le sous-groupe a émis un appel à propositions visant à répondre aux questions prioritaires et à combler les lacunes dans les données de modélisation. Les résultats de cet appel à propositions, attendus pour le milieu de l'année 2021, permettront au SAGE de poursuivre l'élaboration d'orientations et de recommandations stratégiques spécifiques aux différents vaccins. À cette fin, il a été demandé à l'IVIR-AC d'identifier d'autres domaines prioritaires pour la modélisation des vaccins et des moyens d'intégrer des données probantes supplémentaires dans le processus du SAGE pour élaborer des recommandations à partir des preuves scientifiques (*Evidence to Recommendations*).[1]

[1] Evidence to recommendations for COVID-19 vaccines: evidence framework (https://www.who.int/publications/i/item/WHO-2019-nCoV-SAGE-Framework-Evidence-2020-1; accessed March 2021).

[1] Evidence to recommendations for COVID-19 vaccines: evidence framework (https://www.who.int/publications/i/item/WHO-2019-nCoV-SAGE-Framework-Evidence-2020-1; consulté en mars 2021).

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*Crespo et al. (2014)

Objective and content of this session

To present and share recent experiences on the methodological and practical viewpoint of performing MAEE, challenges, and its potential applications to guide healthcare decision-making around the following topic:

1. **Concept of MAEE** – discussion of overall concept and methodological approach of MAEE
2. **Case study of influenza vaccination in elderly and health workers** – demonstrating how MAEE allows policymakers make informed decisions based on pooled evidence of cost-effectiveness from EEs
3. **Advancing methodology by addressing potential challenges** – discussion of methodological challenges of MAEE and proposing of future mechanisms to address these challenges

Meta-Analysis of Economic Evaluations of Vaccines to Support Decision Making Process

Session 1: Concept of Meta-Analysis of Economic Evaluation

Raymond Hutubessy, World Health Organization
On behalf of
Nathorn Chaiyakunapruk, University of Utah

World Health Organization | IVB

Agenda

- Introduction to the overall concept and methodological approach of meta-analysis of economic evaluations
- Methodological Challenges
- Summary

Why Meta-analysis of Economic Evaluation (MAEE) Studies?

- **Economic evaluation (EE) studies** are important in providing evidence for policy decisions in healthcare including vaccination decisions
- The number of such evaluations is steadily increasing
- **Systematic review of EE studies (SREEs)** can provide an efficient mechanism to combine existing EEs to answer a specific value question[1]
- Globally, WHO has commissioned SREEs of various vaccines as part of Full Value of Vaccines Assessment

Limitation of SREEs: "provide only descriptive and qualitative evidence" **WITHOUT** quantitative evidence

- The idea of quantifying EEs with meta-analysis (MA) might provide policy makers with a clear policy recommendation

1. WHO Guide on Standardization of Economic Evaluations of Immunization Programmes (2019)

How do usually EE studies report findings?

Most EE studies apply an incremental cost-effectiveness ratio (ICER) for comparing cost and effectiveness.

$$ICER = \frac{Cost\ A - Cost\ B}{Effect\ A - Effect\ B}$$

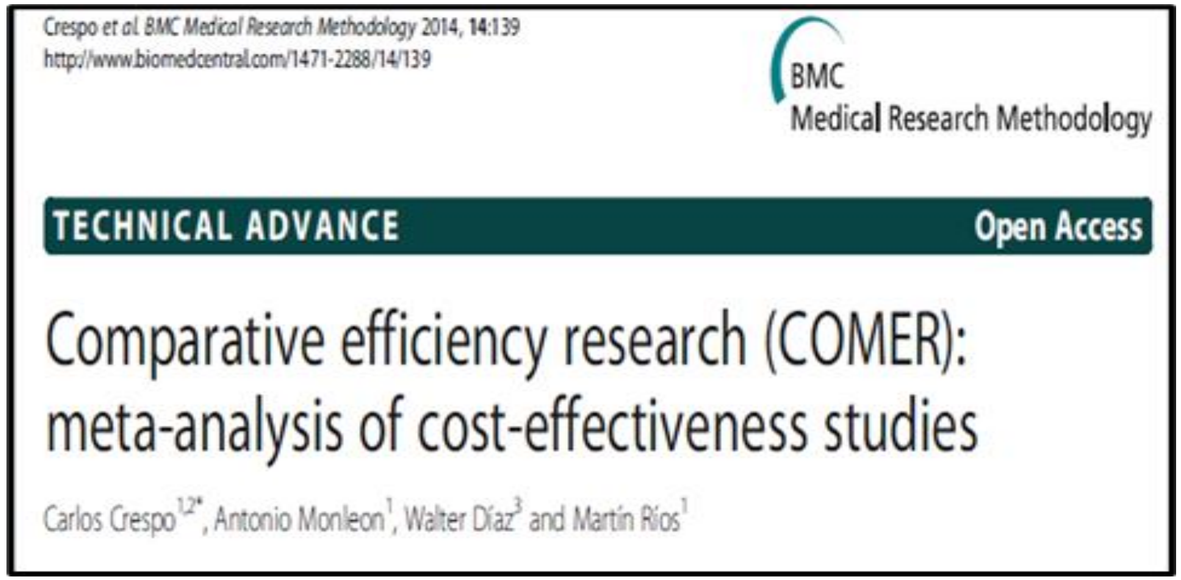
Effect: e.g., Quality adjust life year (QALY) or Life years gained

Can studies reporting ICERs be pooled?

LIMITATION: "**ICER is a ratio** as shown in the equation, which leads to incorrect estimation of the confidence interval, the fact that it is not normally distributed, and it can have a negative value, which causes ambiguity in interpretation[1]"

1. Shields GE, Elvidge J. Challenges in synthesising cost-effectiveness estimates. Syst Rev. 2020;9(1):289.

Statistical Approach: MAEE



- Originally developed by Crespo et al. 2014[1]
- Known as **COM**parative **E**fficiency **R**esearch, [**COMER**]
- Proposed pooling **incremental net benefit (INB) not ICER**

1. Crespo C, et al. Comparative efficiency research (COMER): meta-analysis of cost-effectiveness studies. BMC Med Res Methodol. 2014;14:139.

Incremental net benefit (INB)

$$INB = \Delta E\,(K - ICER) \qquad \text{Equation 1}$$

$$Var(INB) = K^2\sigma^2_{\Delta E} + \sigma^2_{ICER}$$

$$INB = (K \times \Delta E) - \Delta C \qquad \text{Equation 2}$$

$$Var(INB) = K^2\sigma^2_{\Delta E} + \sigma^2_{\Delta C} - 2K\rho_{\Delta C \Delta E}$$

ICER=incremental cost-effectiveness ratio; ΔC= incremental cost; ΔE=incremental effectiveness; K =Willingness-to-pay (WTP) threshold; ICER=σ^2_{ICER} is variance of ICER; $\sigma^2_{\Delta C}$,$\sigma^2_{\Delta E}$,$\sigma_{\Delta E \Delta C}$ are variances of ΔC and ΔE and their covariance

- Positive pooled INB = Intervention is cost-effective
- Negative pooled INB = Intervention is not cost-effective

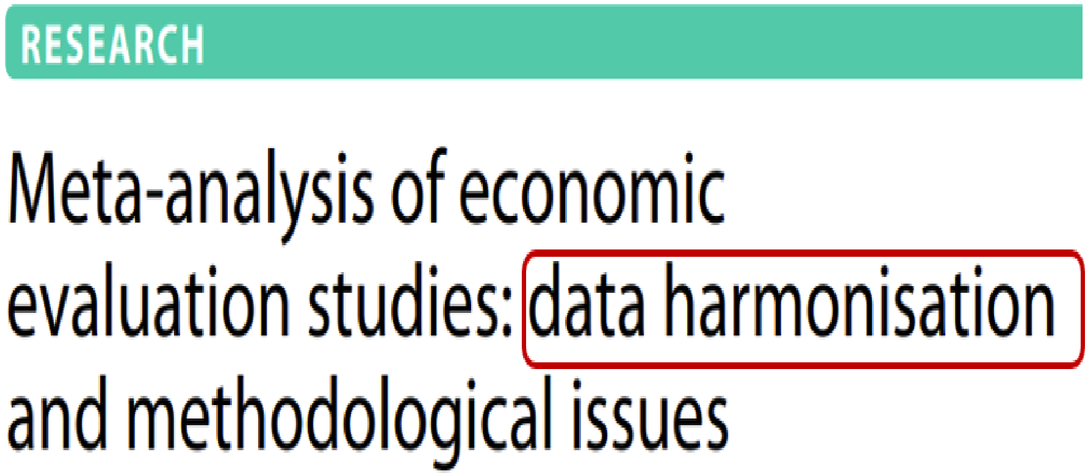
Reference: Crespo C, Monleon A, Díaz W, Ríos M. Comparative efficiency research (COMER): meta-analysis of cost-effectiveness studies. BMC Med Res Methodol. 2014;14:139.

Data harmonization: MAEE

In this context, "**data harmonization** is an approach to bringing together inconsistently reported or missing data from different EE studies and transforming them into one cohesive dataset that allows researchers to perform a meaningful meta-analysis".

Bagepally *et al. BMC Health Services Research* (2022) 22:202
https://doi.org/10.1186/s12913-022-07595-1

Our research team has further modified COMER methods and **devised a step-by-step data harmonization process** to facilitate performing MAEEs.



Data harmonization: example

1. Currency conversion

Standardize different money units (e.g., US $, €, £, ¥) and years by converting to purchasing power parity (PPP) adjusted to US$ for the latest year of analysis

For example, a study reported cost, ICER, and thresholds in Euros for 2012 and researchers plan to pool for the current year (e.g., 2023)

Step 1: Currency is firstly converted to 2023 Euros using the historical consumer price index (CPI) of that country

Step 2: Then, the Euro 2023 value will be converted to PPP adjusted US$ rate using conversion rates from the International Monetary Fund

Bagepally BS, et al. Meta-analysis of economic evaluation studies: data harmonisation and methodological issues. BMC Health Serv Res. 2022;22:202.

Data harmonization: example

2. Estimation of variance for INB

$$Equation\ 1\text{: } Var(INB) = K^2\sigma^2_{\Delta E} + \sigma^2_{\Delta C} - 2K\sigma_{\Delta E \Delta C}$$

$$Equation\ 2\text{: } Var(INB) = K^2\sigma^2_{\Delta E} + \sigma^2_{ICER}$$

K is the WTP, ΔC and ΔE are incremental cost and incremental effectiveness; $\sigma_{\Delta E \Delta C}$ are covariance of ΔC and ΔE and $\sigma^2_{\Delta E}, \sigma^2_{\Delta C}$ are their variances, σ^2_{ICER} is variance of ICER

Five scenarios developed to obtain variances

Bagepally BS, et al. Meta-analysis of economic evaluation studies: data harmonisation and methodological issues. BMC Health Serv Res. 2022;22:202.

Scenarios developed to obtain variance

Scenario-1: EE studies ideally reports the point estimates & variances for every parameter required for calculation

Scenario-2: The study reports the means and 95% CIs of incremental costs & outcomes, and ICER

Scenario-3: The study reports means and 95% CI of costs/outcomes, or ΔC& ΔE, but not ICER or its variance.

- Monte Carlo simulation with a gamma and normal distributions for ΔC and ΔE was performed to estimate covariance between ΔC and ΔE.

$$95\%CI \text{ of } \mu_{ICER} = \hat{\mu}_{ICER} \pm Z_{\alpha/2} xSE$$

$$UL_{ICER} = \hat{\mu}_{ICER} + Z_{\alpha/2} xSE$$

$$SE = \frac{UL_{ICER} - \hat{\mu}_{ICER}}{Z_{\alpha/2}}$$

$$\hat{\sigma}^2_{ICER} = SE^2$$

$$UL_{ICER} = \text{Upper limit of ICER}$$

$$Z_{\alpha/2} = \text{Standardize normal} = 1.96$$

$$\hat{\mu}_{ICER} = \text{mean ICER}$$

Bagepally BS, et al. Meta-analysis of economic evaluation studies: data harmonisation and methodological issues. BMC Health Serv Res. 2022;22:202.

Scenarios developed to obtain variance

Scenario-4: The study does not report any dispersion, but does provide the CE plane graphs, in which data can be directly extracted from the CE plane using Web-Plot-Digitizer software.

- The means of ΔC, ΔE, and their variances and co-variance can be estimated accordingly. Finally, the INB and its variance can be estimated.

Scenario-5: The study reports only the means (or point estimates) of costs, outcomes, and ICER.

- The measures of dispersions can be borrowed from another similar study if they fulfil the following criteria:
- They are in the same stratum of country income level, perspective, intervention, comparator, time period, country region, model type, and inputs (i.e., discounting, time horizon).
- Their ICERs are not much different, e.g., ±50% to 75%

Bagepally BS, et al. Meta-analysis of economic evaluation studies: data harmonisation and methodological issues. BMC Health Serv Res. 2022;22:202.

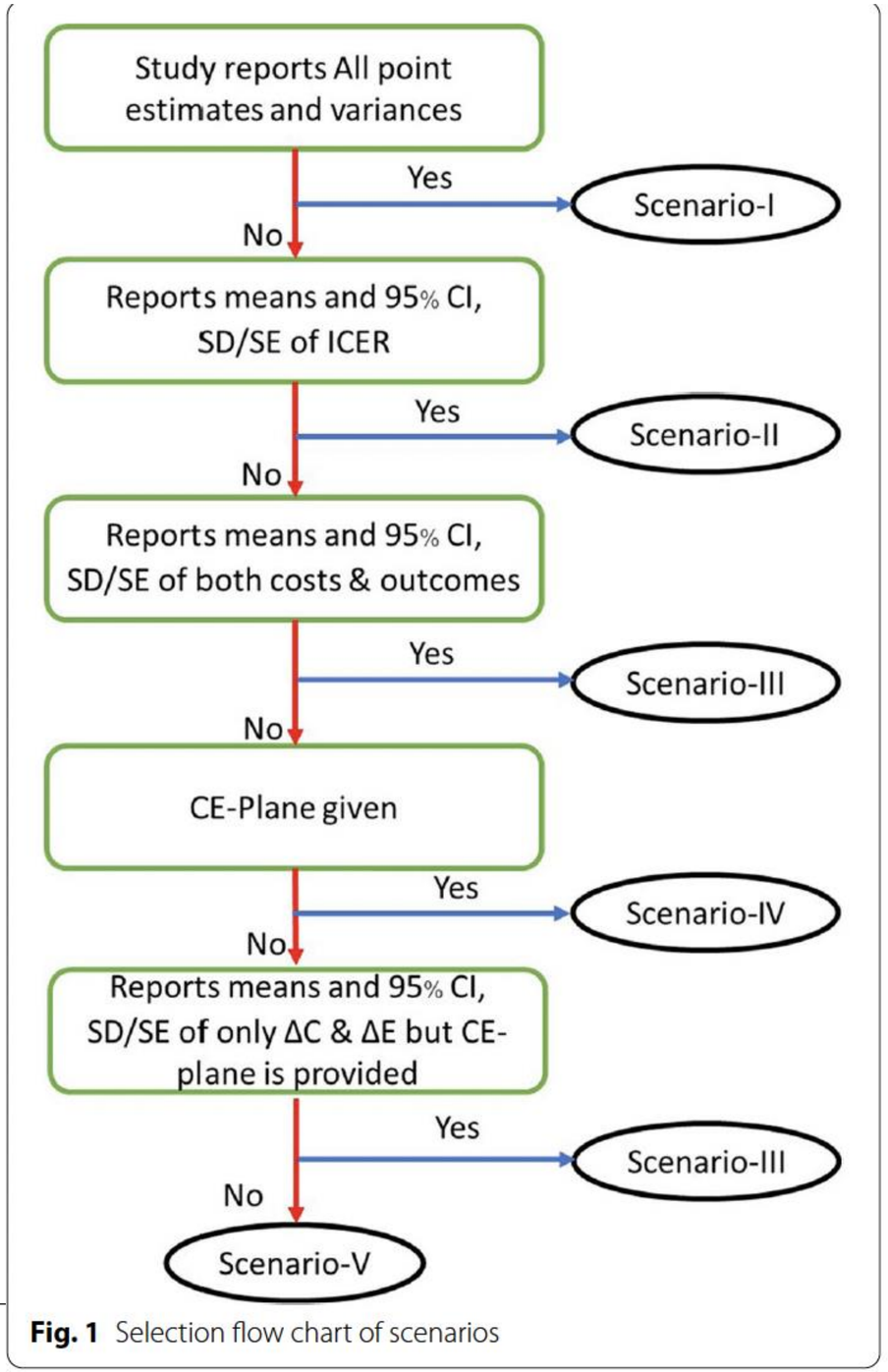


Fig. 1 Selection flow chart of scenarios

Bagepally BS, et al. Meta-analysis of economic evaluation studies: data harmonisation and methodological issues. BMC Health Serv Res. 2022;22:202.

Pooling INB

- The INB can be pooled across studies using a fixed-effect or a random-effect model depending on the degree of heterogeneity
- Analysis should be **stratified** by **country income level** (e.g., low, lower-middle, upper-middle, and high), **perspective** (e.g., societal, health care or payer, etc.), **model type** (Markov, decision tree, discrete event simulation, or others) etc.
- Heterogeneity can be visualized by inspection of the forest plot and quantitated using the Cochrane-Q test and the I^2 statistic
- Exploring sources of heterogeneity is strongly recommended: meta-regression, sub-group and sensitivity analyses
- Reporting bias: Funnel plot and Egger's test

Advocacy: MAEE

World Health Organization

Meeting of the Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC), March 2021

IVIR-AC WHO (March 2021) **AGREES** that "the quantitative evidence generated from MAEEs may be useful to **support clear policy recommendations** and can facilitate decision-making in **resource-strained settings where context-specific EEs are not available"**

The World Health Organization Meeting of the immunization and vaccine related implementation research advisory committee (IVIR-AC), March 2021. Wkly Epidemiol Rec. 2021; 96: 133-144

Examples of MAEE in the Vaccination Area

ELSEVIER

Value in Health
Volume 26, Issue 4, April 2023, Pages 598-611

Systematic Literature Review

Pneumococcal Vaccination in Children: A Systematic Review and Meta-Analysis of Cost-Effectiveness Studies

M. Sakil Syeed MD [1], Priyanka Ghule MS [1], Lan M. Le PhD [1], Sajesh K. Veettil PhD [1], Emily K. Horn MSc [2], Johnna Perdrizet MPH [2], Matt Wasserman MSc [2], Ammarin Thakkinstian PhD [3], Nathorn Chaiyakunapruk PhD [1 4]

eClinicalMedicine
Part of THE LANCET *Discovery Science*

Economic evaluation of seasonal influenza vaccination in elderly and health workers: A systematic review and meta-analysis

Piyameth Dilokthornsakul,[a,b] Le My Lan,[c] Ammarin Thakkinstian,[d] Raymond Hutubessy,[e] Philipp Lambach,[e] and Nathorn Chaiyakunapruk[c,f**]*

Open Forum Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Systematic Review and Meta-Analysis of Cost-effectiveness of Rotavirus Vaccine in Low-Income and Lower-Middle-Income Countries

Sabbir Haider,[1,2] Usa Chaikledkaew,[1,3] Montarat Thavorncharoensap,[1,3] Sitaporn Youngkong,[1,3] Md. Ashadul Islam,[2] and Ammarin Thakkinstian[1,4]

[1]Mahidol University Health Technology Assessment (MUHTA) Graduate Program, [3]Social and Administrative Pharmacy Excellence Research Unit, Department of Pharmacy, Faculty of Pharmacy, and [4]Section for Clinical Epidemiology and Biostatistics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [2]Health Economics Unit, Ministry of Health and Family Welfare, Bangladesh, Bangladesh

Vaccines

Incremental net monetary benefit of herpes zoster vaccination: a systematic review and meta-analysis of cost-effectiveness evidence

Sariya Udayachalerm, Maranda G. Renouard, Thunyarat Anothaisintawee, Ammarin Thakkinstian, Sajesh K. Veettil & Nathorn Chaiyakunapruk

Pages 26-37 | Received 09 Sep 2021, Accepted 16 Nov 2021, Accepted author version posted online: 18 Nov 2021, Published online:08 Dec 2021

Summary

- The step-by-step approach of data harmonization is demonstrated for facilitating the process of MAEE
- MAEE makes SREEs more meaningful and can provide an efficient mechanism to quantitatively summarize cost-effectiveness findings
- MAEE is useful and could facilitate decision-making especially in countries where context-specific EEs are not available
- The methodology of MAEE is evolving. There is a critical need to address the current methodological challenges to advance the field of MAEE

Thank you

Meta-Analysis of Economic Evaluations of Vaccines to Support Decision Making Process

Discussion

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World Health Organization | IVB

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MODELLING & SIMULATION HUB, AFRICA

Themes for discussion

- Evidence of benefit
  - When is it appropriate to conduct a MAEE compared to a qualitative scoping review?
  - Have validation studies been conducted to demonstrate the benefit of MAEE?
  - Consider different contexts and settings
- Insufficient data
  - To what extent does expert consultation have a role in applications of MAEE where little data is available? How will this affect weighting on quality vs quantity?
- Process of implementation
  - Should there be guidance on how to combine estimates and related uncertainties without relying on statistical methods to do it automatically.
  - Transparency of evidence synthesis (qualitatively and quantitatively)
- In clinical trials, meta-analyses group n samples into 1 large sample to reduce uncertainty, but MAEE requires additional methodology to combine uncertainty from heterogenous samples.
  - What is needed to bring MAEE to the point where it is mature enough to be used routinely?