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

Moderator: Philipp Lambach, World Health Organization

Presenters: 1. Raymond Hutubessy, World Health Organization and Nathorn Chaiyakunapruk, University of Utah

2. Karene Hoi Ting Yeung, World Health Organization and Sajesh Kalkandi Veettil, University of Utah

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

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Contact: VoVteam@who.int

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.

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

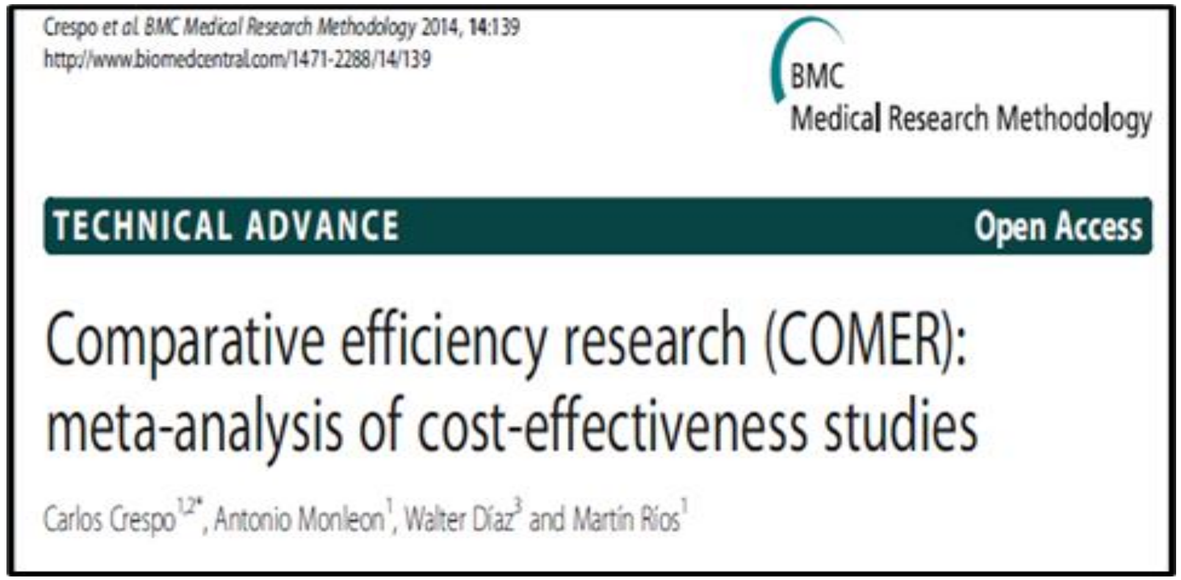
Effect: e.g., Quality adjust life year (QALY) or Life years gained

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.

RESEARCH

Meta-analysis of economic evaluation studies: data harmonisation and methodological issues

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.

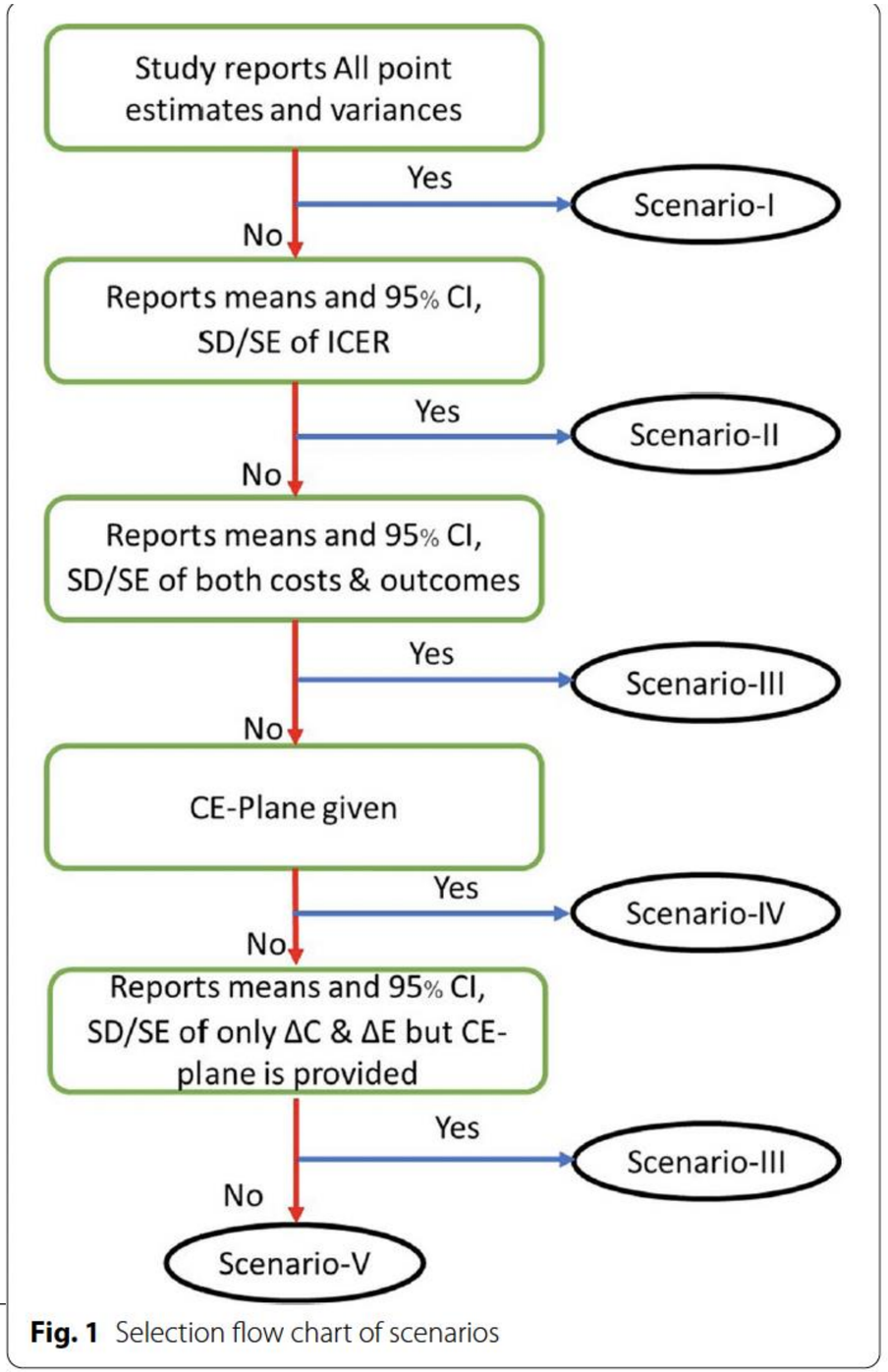


Fig. 1 Selection flow chart of scenarios

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

Session 2: Systematic review and meta-Analysis of economic evaluation studies: A case study of seasonal influenza vaccination in elderly and health workers

Karene Hoi Ting Yeung, World Health Organization
On behalf of
Sajesh Veettil, University of Utah

World Health Organization | IVB

Funding: United States Centers for Disease Control and Prevention
Protocol registered at PROSPERO (CRD42021246746)

Agenda

- Background
- Methods
- Results
- Limitations and summary

Background

- Seasonal influenza virus infection is associated with substantial morbidity and mortality worldwide
- Influenza vaccination is effective against influenza infection in high-risk population (health workers (HWs) and elderly)
- A number of cost-effectiveness analyses (CEAs) of influenza vaccination have been conducted to estimate its value
- Previous systematic reviews of economic evaluation of influenza vaccination have been conducted providing descriptive and qualitative evidence **WITHOUT quantitative evidence**[1]

1. P Dilokthornsakul. EClinicalMedicine. 2022 Apr 21;47:101410.

Background

- Methods for meta-analysis of economic evaluation (MAEE) recently developed to generate quantitative evidence[1,2] and inform decision makers[3] with
  1. an overall summary of all economic evidence quantitatively, and
  2. a summary stratified by perspective, country income-level, and herd-effect

- Aim
  - Summarize cost-effectiveness evidence by pooling the incremental net monetary benefit (INB) of influenza vaccination in elderly and HWs

1. Crespo C. BMC Med Res Methodol. 2014;14:139.
2. Bagepally BS. BMC Health Serv Res. 2022;22:202
3. Bagepally BS. BMC Health Serv Res. 2022;22:202

Methods

- Systematic review + meta-analysis
- Searched 5 electronic databases: PubMed, Embase, CEA Registry, NHS-EED, and DARE
- Inclusion criteria:
  - Cost-effectiveness studies
  - Published before February 2022
  - Conducted in elderly or HWs
  - Compared with no vaccination or current situation
  - Reported disability-adjusted life-years (DALY), quality-adjusted life year (QALY), or life year (LY)
- Followed PRISMA, CHEERS checklist[1] and modified ECOBIAS checklist[2]

CHEERS: Consolidated Health Economic Evaluation Reporting Standard checklist
DARE: Database of Abstracts of Reviews of Effects
NHS-EED: NHS Economic Evaluation Database
PEISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses

1. Husereau D. Value in Health. 2013;16(2):231-250
2. Adarkwah C.C. Expert Rev Pharmacoecon Outcomes Res. 2016; 16: 513-523

Data Preparation

- Data were prepared according to 5 scenarios as discussed in our first session[1]
- INB and its variance were calculated based on following equations:

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

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

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

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

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

- All cost data was converted to US dollars in 2019 using the consumer price index (CPI) and purchasing power parity conversion (PPP)[1]

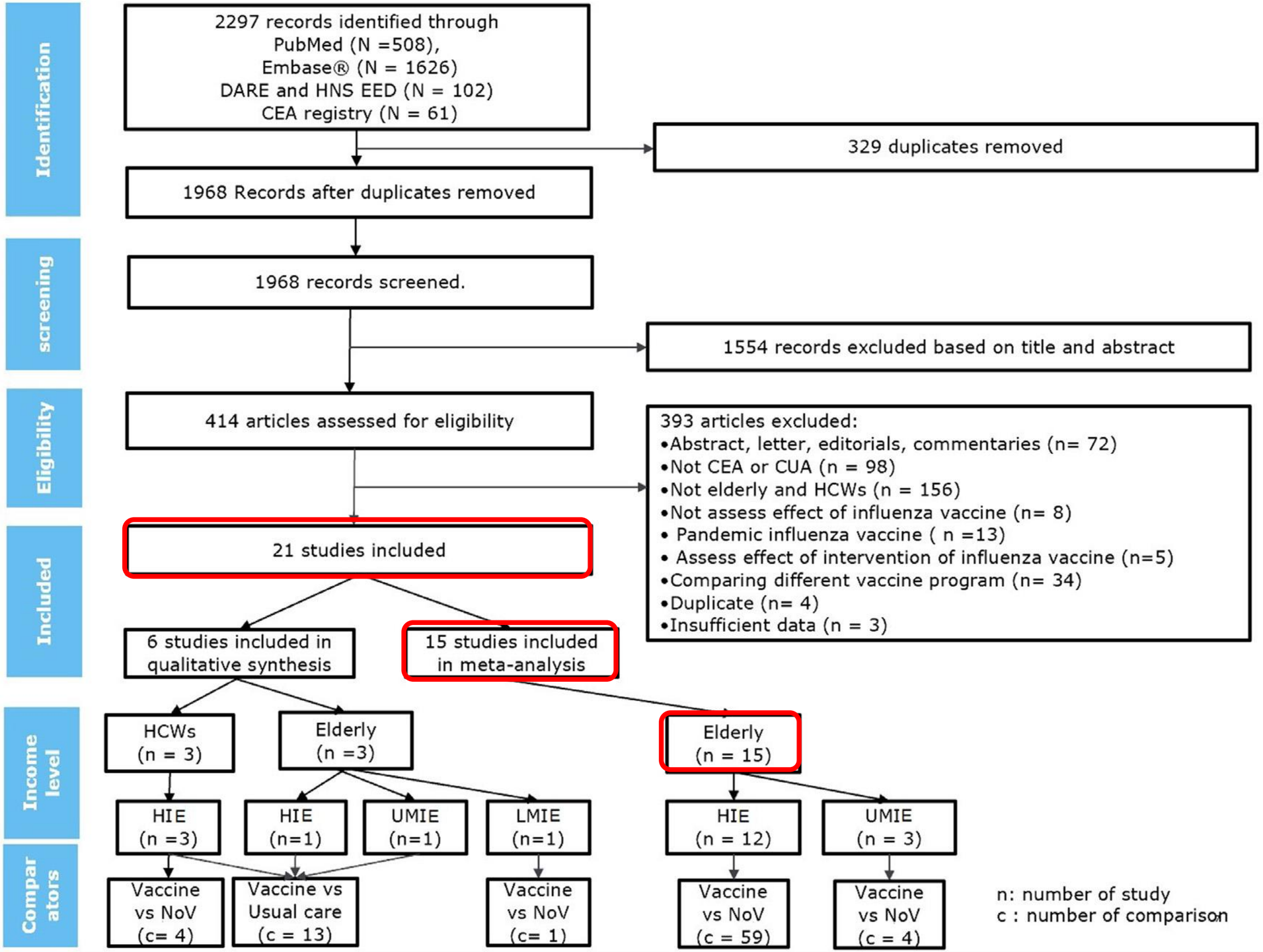
1. Bagepally BS. BMC Health Serv Res. 2022;22:202

Data Analysis

- A random-effects model by Der-Simonian and Laird method to **pool INB and its variance** across studies
- **Stratification** by income level, WHO region, perspective, comparator, and herd effect
- **Subgroup analyses** by types of vaccine (TIV or QIV) and funders (public vs private)
- I^2 statistic to **assess heterogeneity** across studies
- Meta-regression to explore **sources of heterogeneity**
- Prespecified sensitivity analyses to **assess robustness** of findings
- A funnel plot and Egger's test to **assess publication bias**

TIV: trivalent influenza vaccine
QIV: quadrivalent influenza vaccine

Results


Identification
screening
Eligibility
Included
Income level
Comparators
2297 records identified through PubMed (N =508), Embase® (N = 1626) DARE and HNS EED (N = 102) CEA registry (N = 61)
329 duplicates removed
1968 Records after duplicates removed
1968 records screened.
1554 records excluded based on title and abstract
414 articles assessed for eligibility
393 articles excluded:
•Abstract, letter, editorials, commentaries (n= 72)
•Not CEA or CUA (n = 98)
•Not elderly and HCWs (n = 156)
•Not assess effect of influenza vaccine (n= 8)
• Pandemic influenza vaccine (n =13)
• Assess effect of intervention of influenza vaccine (n=5)
•Comparing different vaccine program (n= 34)
•Duplicate (n= 4)
•Insufficient data (n = 3)
21 studies included
6 studies included in qualitative synthesis
15 studies included in meta-analysis
HCWs (n = 3)
Elderly (n =3)
Elderly (n = 15)
HIE (n =3)
HIE (n=1)
UMIE (n=1)
LMIE (n=1)
HIE (n = 12)
UMIE (n = 3)
Vaccine vs NoV (c= 4)
Vaccine vs Usual care (c = 13)
Vaccine vs NoV (c= 1)
Vaccine vs NoV (c = 59)
Vaccine vs NoV (c = 4)
n: number of study
c : number of comparison

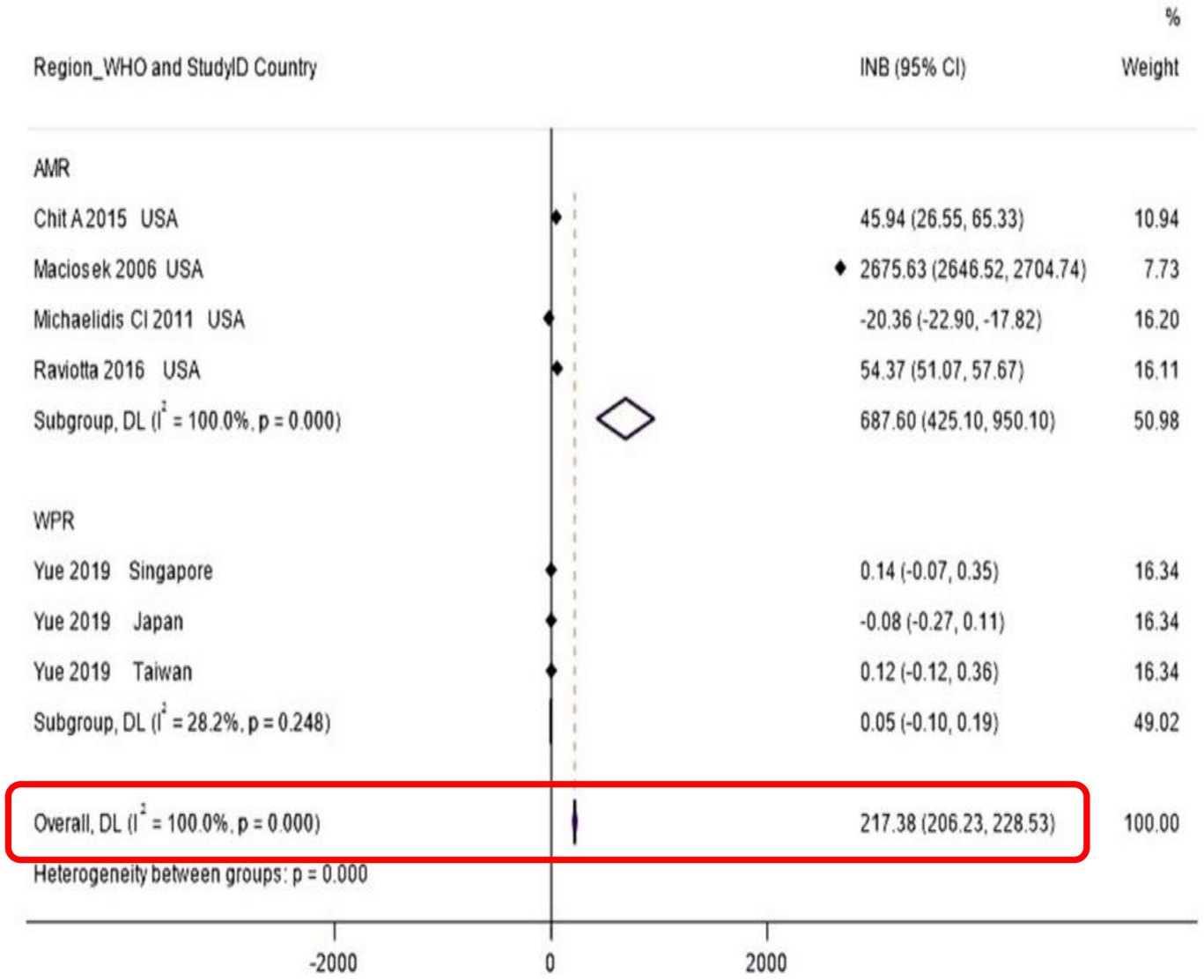
Results

- Meta-analysis performed for **elderly** studies **without herd effect** in
  - **High-income economies (HIEs)** from **societal perspective**
  - **HIEs** from **healthcare provider/ payer perspective**
  - **Upper-middle income economies (UMIEs)** from **societal perspective**
- Risk-of-bias assessment
  - Limited sensitivity analysis bias
  - Wrong model bias
  - Bias related to treatment effects

Risk of bias	Low	Moderate	High
Number of studies	4	4	4

Societal perspective: the perspective which identify all relevant costs occurred in a society including direct medical cost, direct non-medical cost, and indirect cost
Healthcare provider/ payer perspective: the perspective which identify cost occurred in healthcare system which including only direct medical cost

Elderly – HIEs - societal perspective

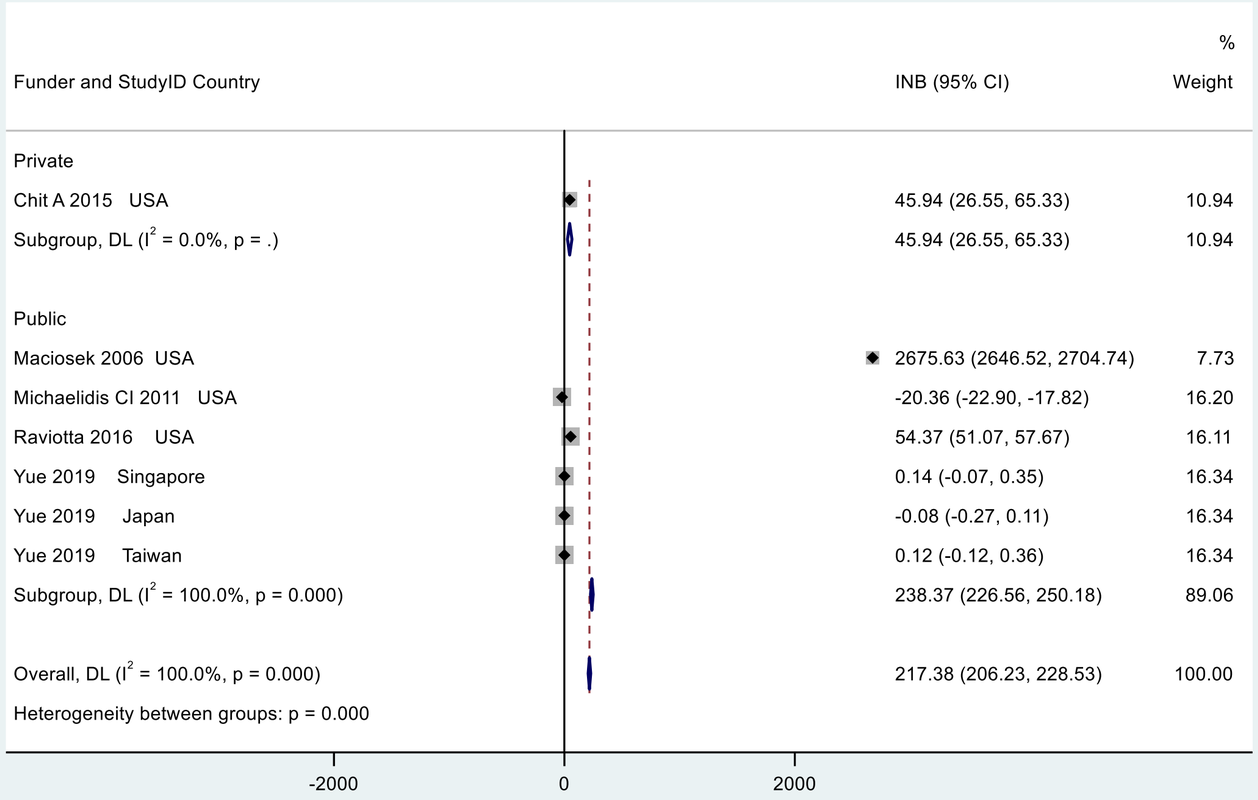


- **Cost-effective** compared to no vaccination
- Substantially **high heterogeneity**

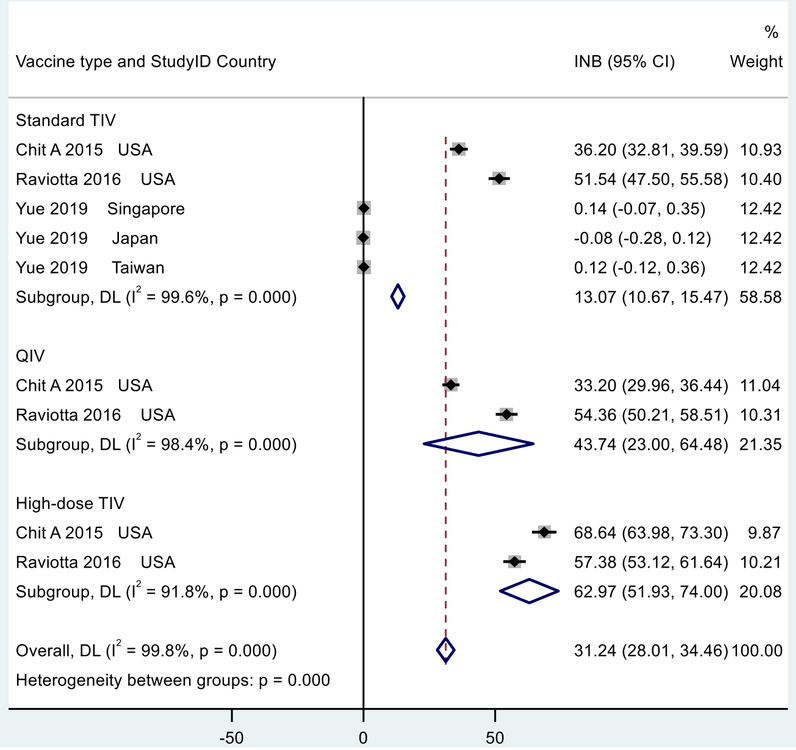
AMR: Regions of the Americas
WPR: Western Pacific Region

Elderly – HIEs - societal perspective: subgroup analyses

Vaccination for elderly vs No vaccination by funder



Vaccination for elderly vs No vaccination by vaccine type



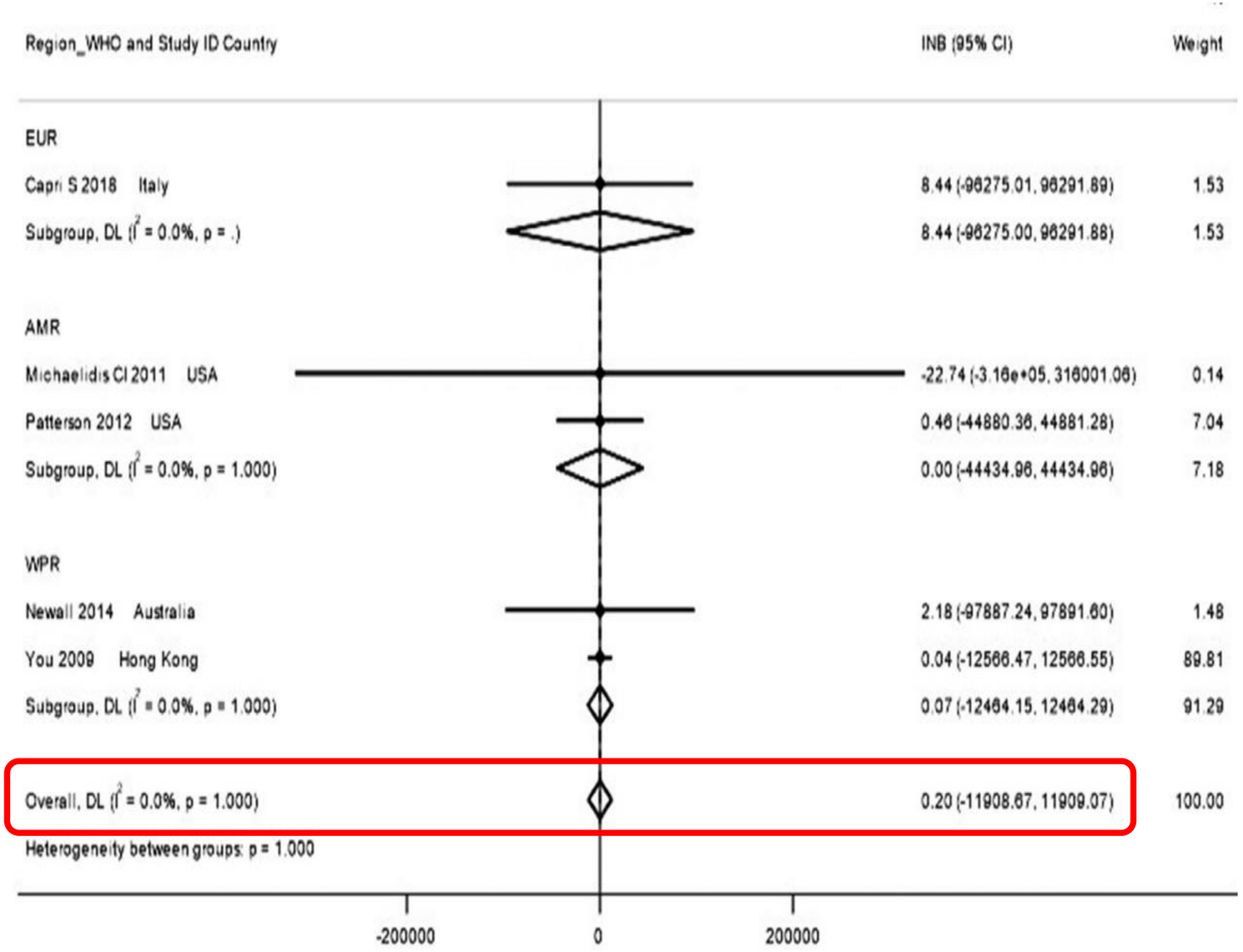
- **Cost-effective** compared to no vaccination in all analyses

TIV: trivalent influenza vaccine
QIV: quadrivalent influenza vaccine

Elderly – HIEs - societal perspective: exploring heterogeneity

- Sources of heterogeneity
  - Univariate meta-regression of the following variables
    - Funder, type of vaccine, model type, vaccine efficacy, vaccine price, and type of economic evaluation
  - **None were found to explain heterogeneity**
    - I^2 ranged from 99.9% to 100% in meta-regressions
- **Robust**ness of findings
  - Confirmed by a series of prespecified sensitivity analyses
- Publication bias
  - A contour-enhanced funnel plot
  - The asymmetry was more likely due to heterogeneity, **not publication bias**

Elderly – HIEs - healthcare provider/ payer perspective

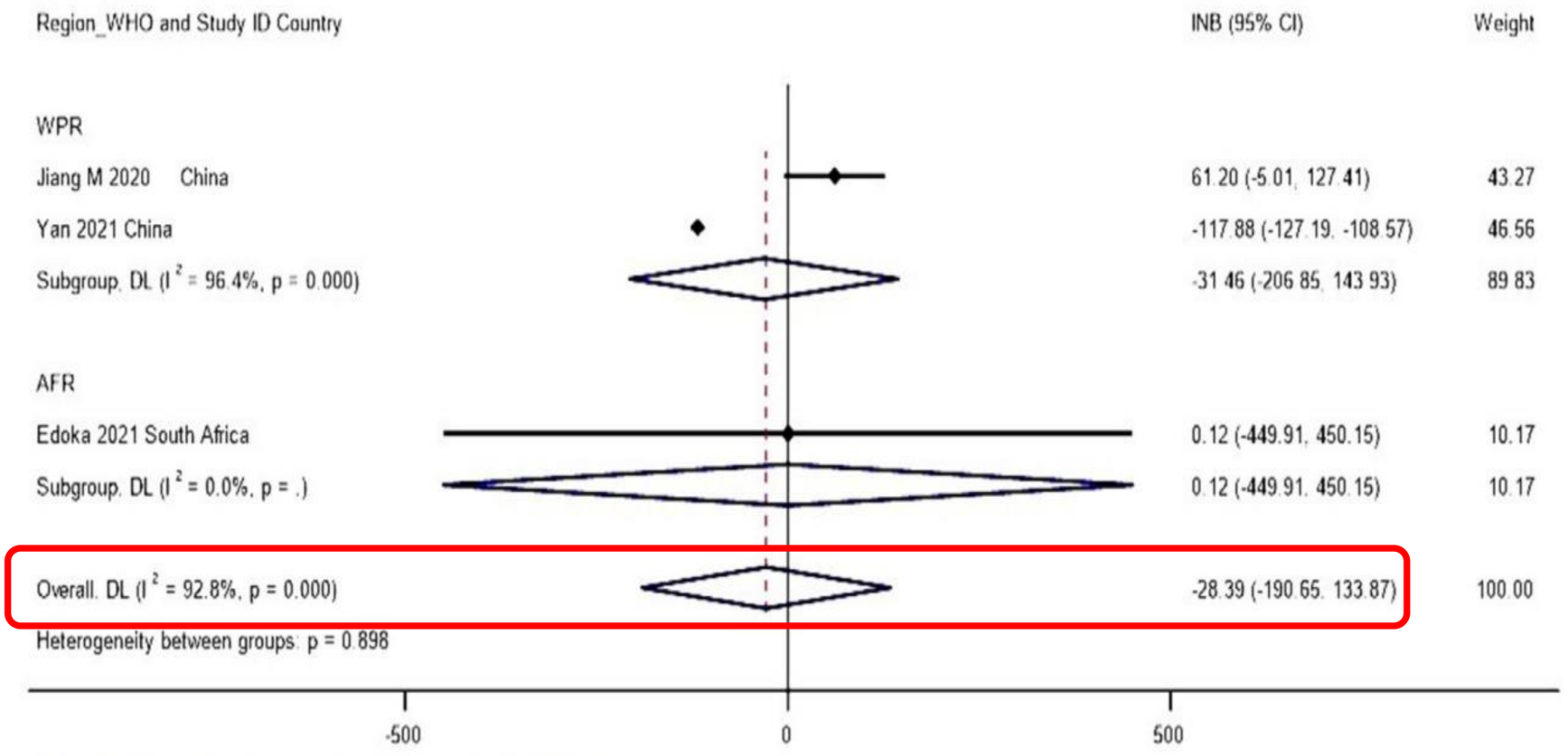


- **Likely not cost-effective**

  compared to no vaccination

AMR: Regions of the Americas
EUR: European Region
WPR: Western Pacific Region

Elderly – UMIEs – societal perspective



- **Not cost-effective** compared to no vaccination

AMR: Regions of the Americas
WPR: Western Pacific Region

Limitations

- A large heterogeneity in most of the analyses observed
  - No explanations of its sources could be found
- **Critical need to explore sources of heterogeneity in MAEE and to develop a standardized approach to address it**
- Limited number of studies across WHO regions
- Generalizability of the findings in terms of the precision of cost-effectiveness findings should be for HIEs only
  - Could not be applied for countries with different income levels

Summary

- Our quantitative findings in elderly demonstrated favorable INBs from influenza vaccination under a societal perspective with relatively robust results in HIEs
- Limited evidence for healthcare provider/ payer perspective and for low- and middle-income economies
- Further evidence is warranted

Thank you

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

Session 3: Meta-Analysis of Economic Evaluation Studies: Advancing methodology by addressing potential challenges

Simon Procter & Mark Jit

London School of Hygiene & Tropical Medicine

World Health Organization | IVB

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Agenda

- Overview
- Heterogeneity in MAEE
- Combining estimates (variance weighting)
- Summary

Overview of approaches to MAEE

Three potential approaches to meta-analysis of economic evaluations:

1. **Direct meta-analysis of ICERs** – problematic (session 1) as it's a ratio measure that doesn't meet normality assumptions and ambiguity of negative values

2. **Meta-analysis of INB** – overcomes the problem of using a ratio measure, but requires an explicit assumption about the cost-effectiveness threshold

3. **Meta-analysis of incremental costs and effects** – separately analyze the numerator and denominator then re-combine into an ICER, risk of bias?

Most published analyses have focused on 2.

Heterogeneity in MAEE

- Two key methodological challenges for MAEE of INB

Challenge 1: Heterogeneity in MAEE – in particular unexplained heterogeneity

- Approximately two-thirds of analyses in recently published MAEEs showed evidence of substantial heterogeneity[1]
- However, most analyses provide no explanations of the potential sources of heterogeneity
- "As long as this substantial heterogeneity remains unexplained, the credibility of MAEEs findings will be questioned" – *experts' opinion*

1. Veettil SK, et al. Does meta-analysis of economic evaluations have the potential to play a role in healthcare decision-making in the United States? J Med Econ. Published online May 27, 2022:1-8.

Heterogeneity (methodological factors)

Many factors can contribute to heterogeneity between studies

Methodological factors

- The comparator!
- Model structure e.g. static vs dynamic model
- Inclusion of all disease outcomes/consequences
- Time-horizon
- Discount rates
- Perspective e.g. healthcare payer vs societal (and what this includes in practice)
- Spill-over effects

Methodological choices will be influenced by technical and normative guidance.

Heterogeneity (model parameterization)

Many factors can contribute to heterogeneity between studies

Model parameters

- Efficacy and Effectiveness of the intervention and comparator
- Cost estimates (and their adjustment over time)
- Measures of health outcomes: DALYs, QALYs, Life Years
- Demography and other population characteristics (e.g. risk factors, contact patterns)

Heterogeneity

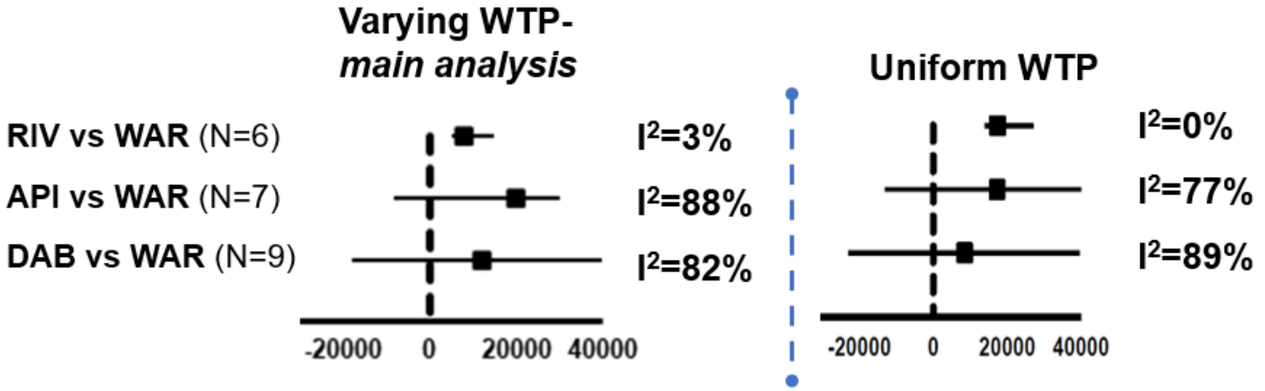
Approaches to reduce MAEE heterogeneity:

- Data harmonization
- Restriction to specific subset of studies (e.g. one country / region)
- Applying fixed willingness-to-pay threshold when calculating INB
- Stratification / Meta-regression

Alternative: full model harmonization (e.g. Malaria, HPV, Dengue, PCV)

HPV https://doi.org/10.1186/1741-7015-9-54
Dengue https://doi.org/10.1371/journal.pmed.1002181
PCV https://doi.org/10.1186/1741-7015-9-53
Malaria https://doi.org/10.1016/s0140-6736(15)00725-4

MAEEs comparing DOACs vs Warfarin in patients with atrial fibrillation in the US setting



Abbreviations: API, Apixaban; DAB, dabigatran; INB, Incremental net benefit; N, number of studies included in MAEE; RIV, rivaroxaban; WAR, warfarin. Note: A positive INB favors intervention

In many instances, other factors, in addition to WTP, might contribute to heterogeneity. There is a strong need to explore other sources of heterogeneity in addition to the WTP threshold.

Reference: Veettil SK, Syeed MS, Noviyan R, Thakkinstian A, Chaiyakunapruk N. Does meta-analysis of economic evaluations have the potential to play a role in healthcare decision-making in the United States? J Med Econ. Published online May 27, 2022:1-8.

Study weighting in MAEE

Challenge 2: Weighting studies by variance is not appropriate

- Current approach: Like traditional meta-analysis of clinical outcomes, EE studies are weighted according to the variance. Thus, studies with higher uncertainty are given less weight.
- There is a distinction between MA of empirical studies (where sample size determined variance) and MA of models (where variance is driven by analysis assumptions)
- For EE studies uncertainty intervals depend on how thoroughly the modelers have investigated uncertainty; therefore, larger intervals may reflect relatively better-quality studies that should not be down-weighted
- Alternatives could be unweighted pooling or weighting base on study quality.

A quality framework for weighting studies in MAEE

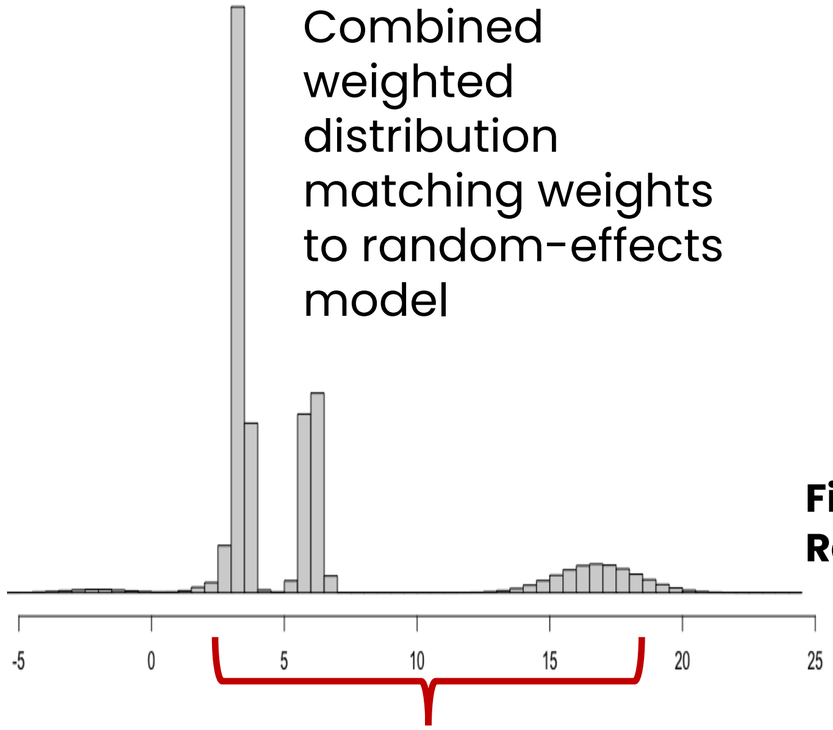
- There is a need to “develop a grid of criteria for assessing study quality to enable quantitative assessment and weighting” – *IVIR-AC*
- Possible factors to consider:
  - Quality of uncertainty assessment - how were parameter distributions chosen – particularly for those most influential on the ICER
  - Comprehensiveness of model
  - Multiple studies that use some of the same underlying assumption/epirical data
  - Risk of bias
- Methodology to convert these into a study weight?

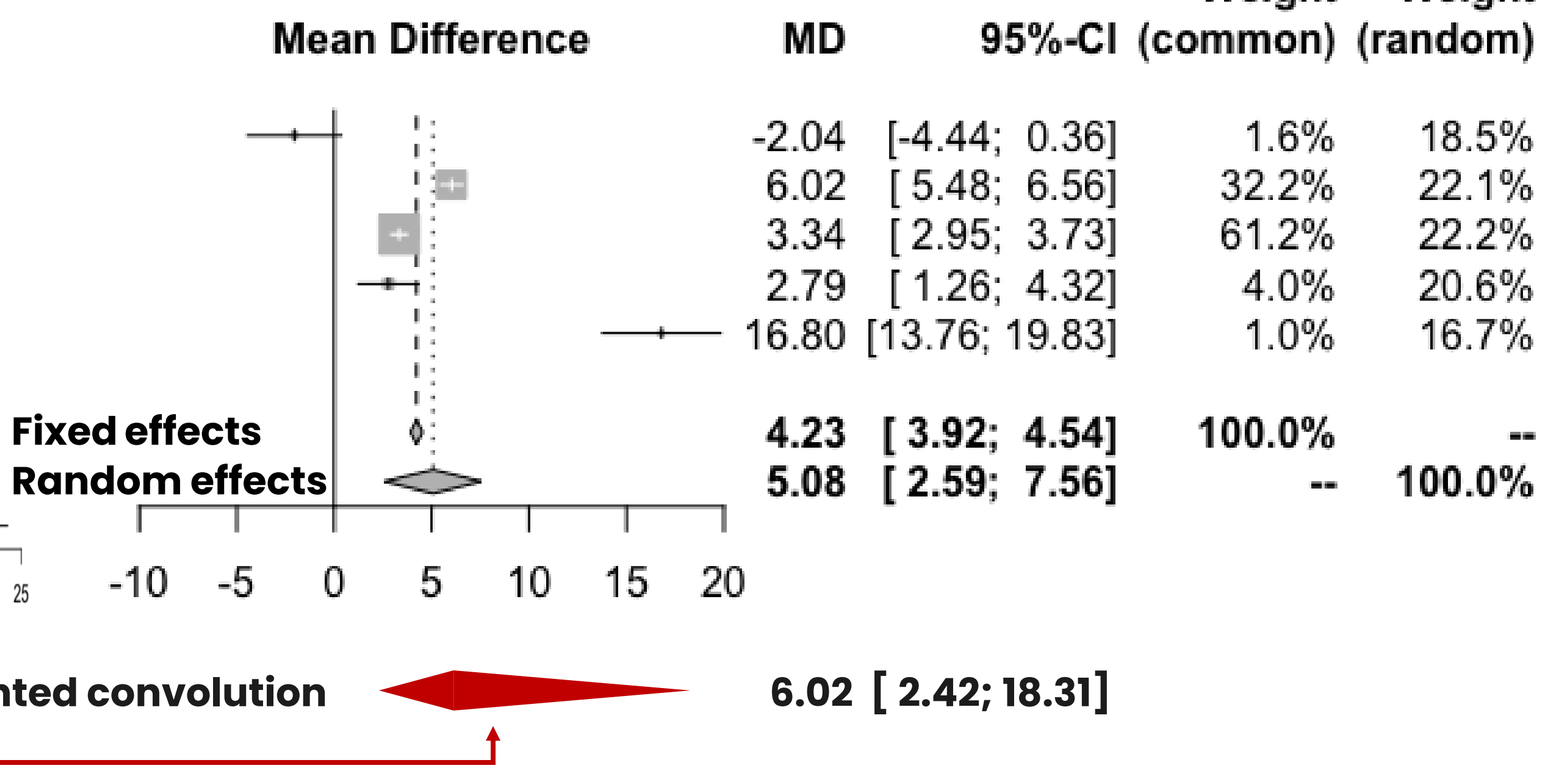
https://www.who.int/publications/i/item/weekly-epidemiological-record-no-17-2021-96-133-144

A complementary approach to representing uncertainty

- Complementary approach to MAEE using random-effects model could be combining uncertainty distributions from studies through weighted convolution.

Hypothetical example:





Summary

- Two policy contexts in which MAEE might be used:
  - Pool results into a summary finding where multiple studies exist in a specific setting
  - Provide quantitative insight for countries without cost-effectiveness studies
- If meta-analysis in not done explicitly then it is likely to happens implicitly.
- Current approaches to MAEE face challenges around heterogeneity and methods for pooling of estimates.
- What kind of methodology would be sufficiently robust in order for MAEEs to be useful to inform-policy making?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Thank you

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

Discussion

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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?