

# 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**

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On behalf of

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# 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**<sup>1</sup>

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

# Background

- Methods for meta-analysis of economic evaluation (MAEE) recently developed to generate quantitative evidence<sup>1,2</sup> and inform decision makers<sup>3</sup> 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 on influenza vaccination
  - 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<sup>1</sup> and modified Economic Evaluations Bias checklist<sup>2</sup>

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<sup>1</sup>
- INB and its variance were calculated based on following equations:

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

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

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

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

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

- All cost data was converted to US dollars in 2019 using the consumer price index (CPI) and purchasing power parity (PPP)<sup>1</sup>

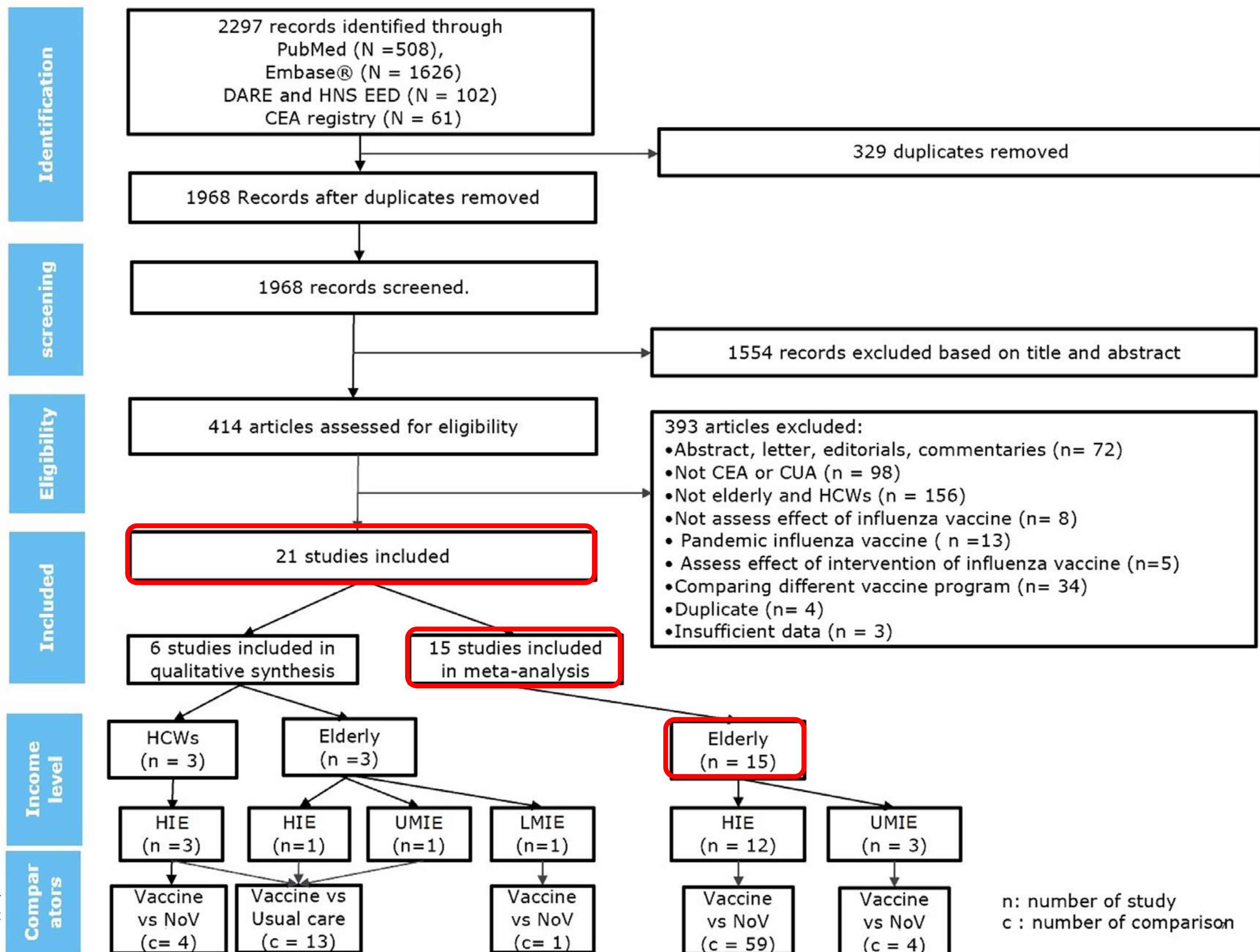
1. Bagepally BS. BMC Health Serv Res. 2022;22:202

# 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



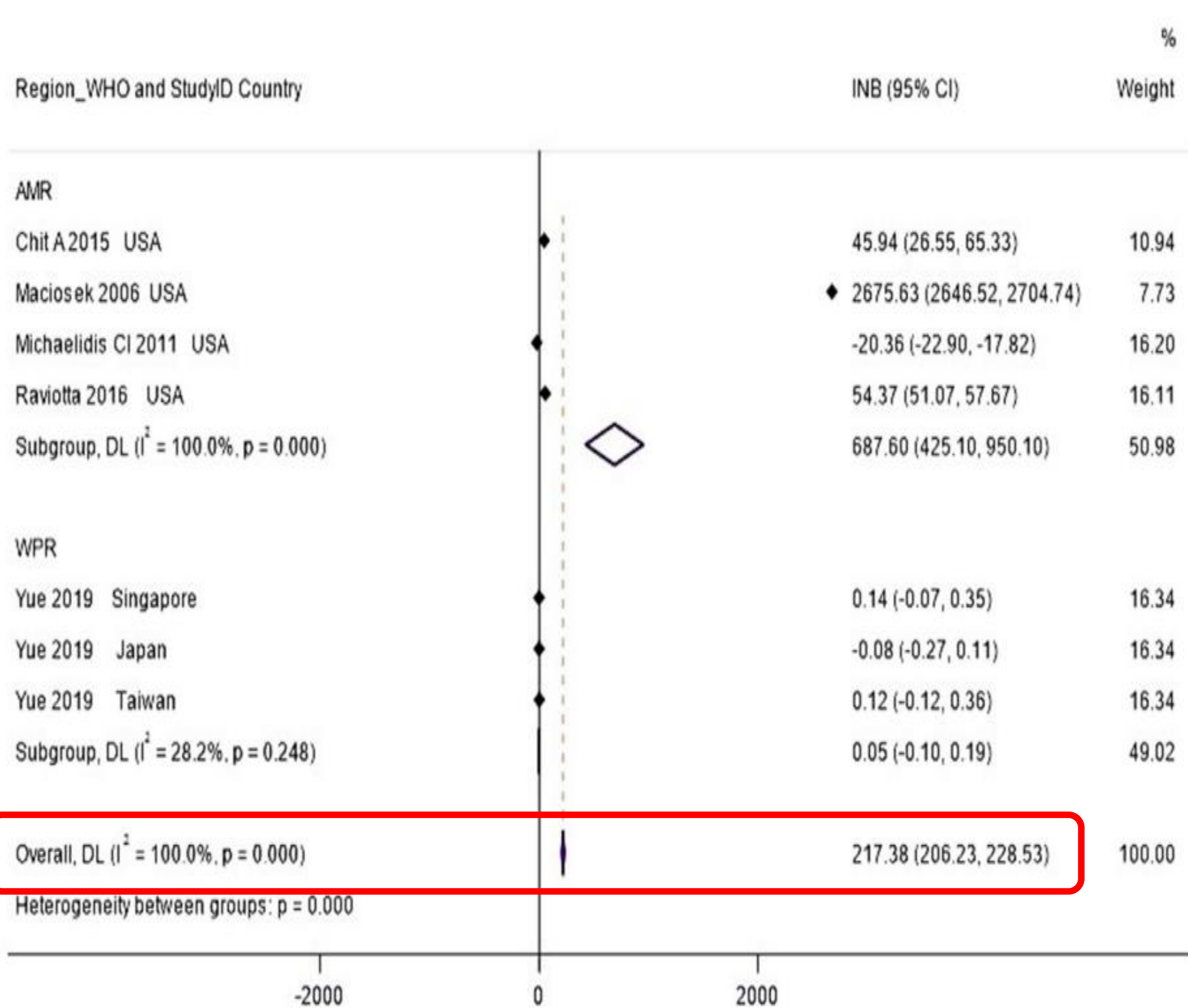
# Results

- 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

<b>Risk of bias</b>	<b>Low</b>	<b>Moderate</b>	<b>High</b>
Number of studies	7	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

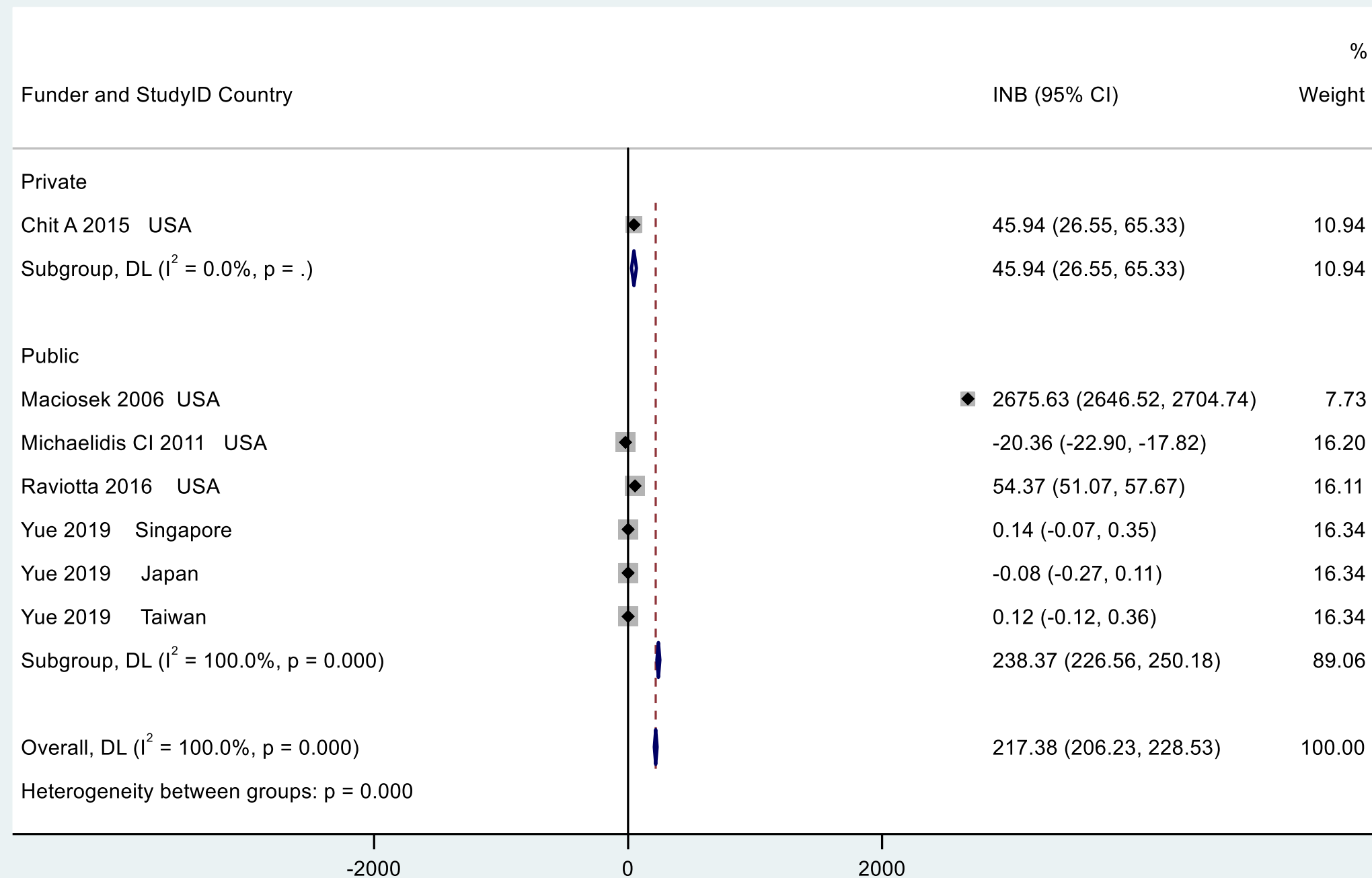
# Elderly – HIEs – societal perspective



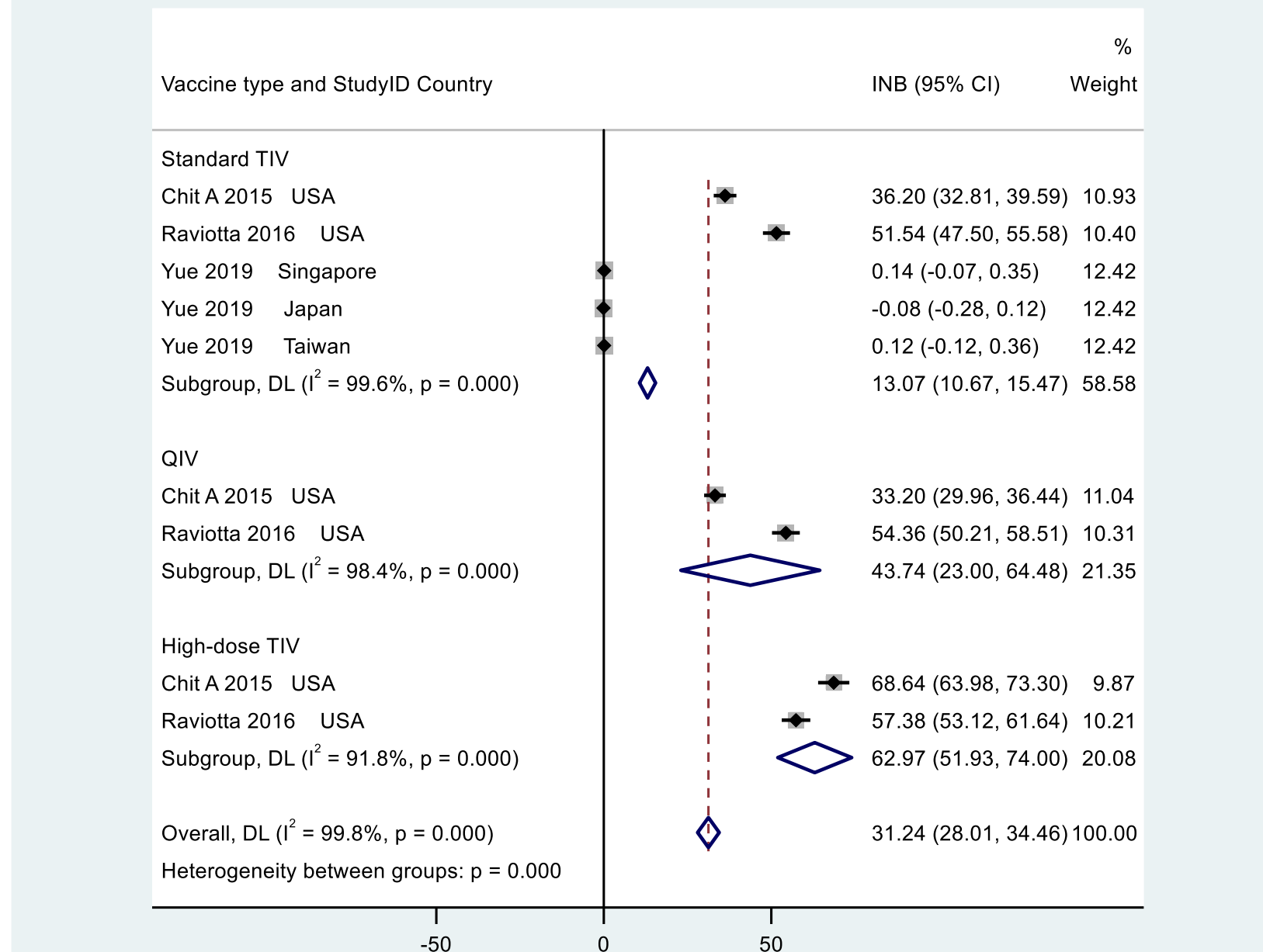
- **Cost-effective** compared to no vaccination
- Substantially **high heterogeneity**

# Elderly – HIEs – societal perspective: subgroup analyses

Vaccination for elderly vs No vaccination by funder



Vaccination for elderly vs No vaccination by vaccine type



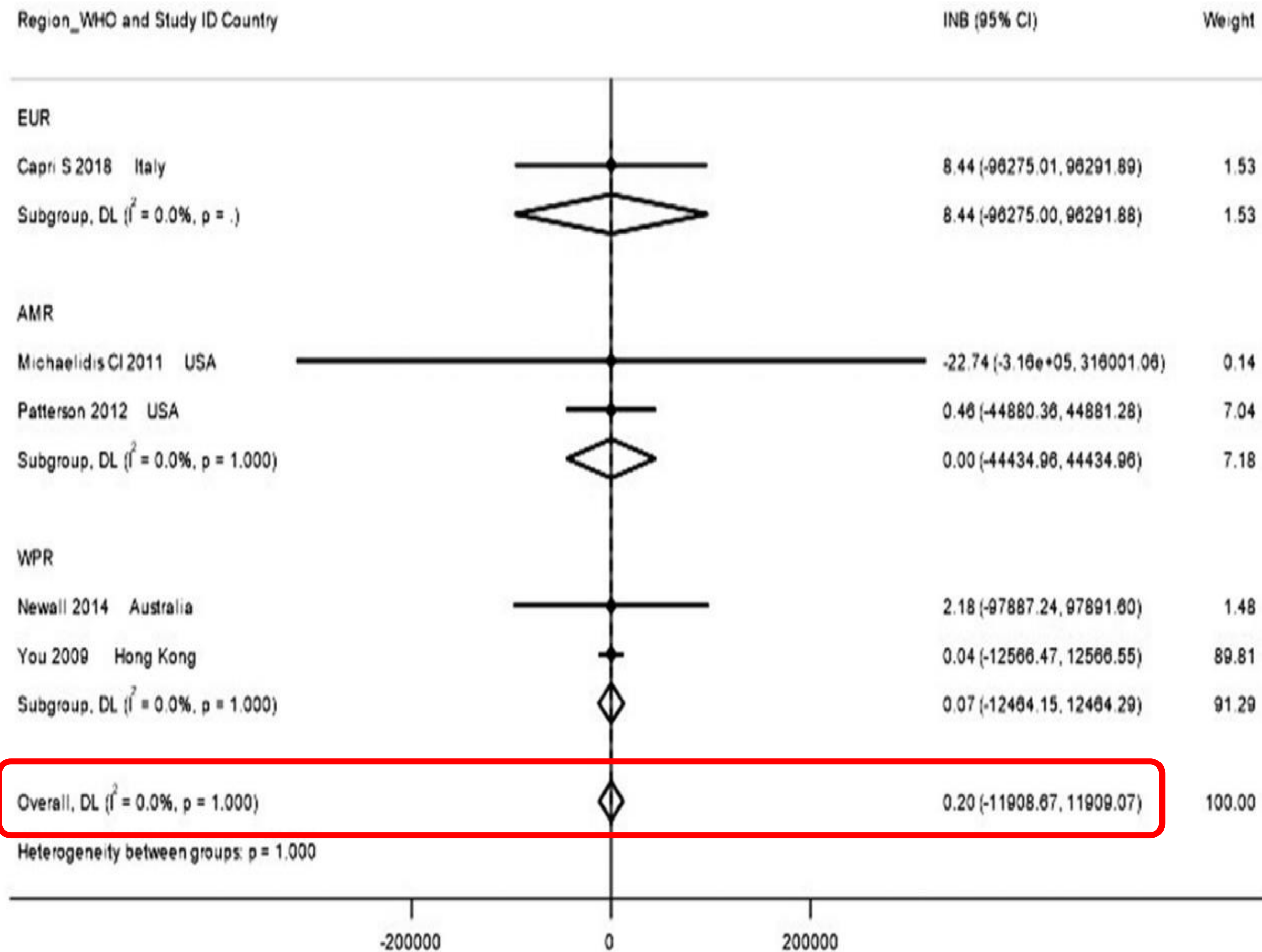
- **Cost-effective** compared to no vaccination in all analyses

TIV: trivalent influenza vaccine  
QIV: quadrivalent influenza vaccine

# Elderly – HIEs – societal perspective: exploring heterogeneity

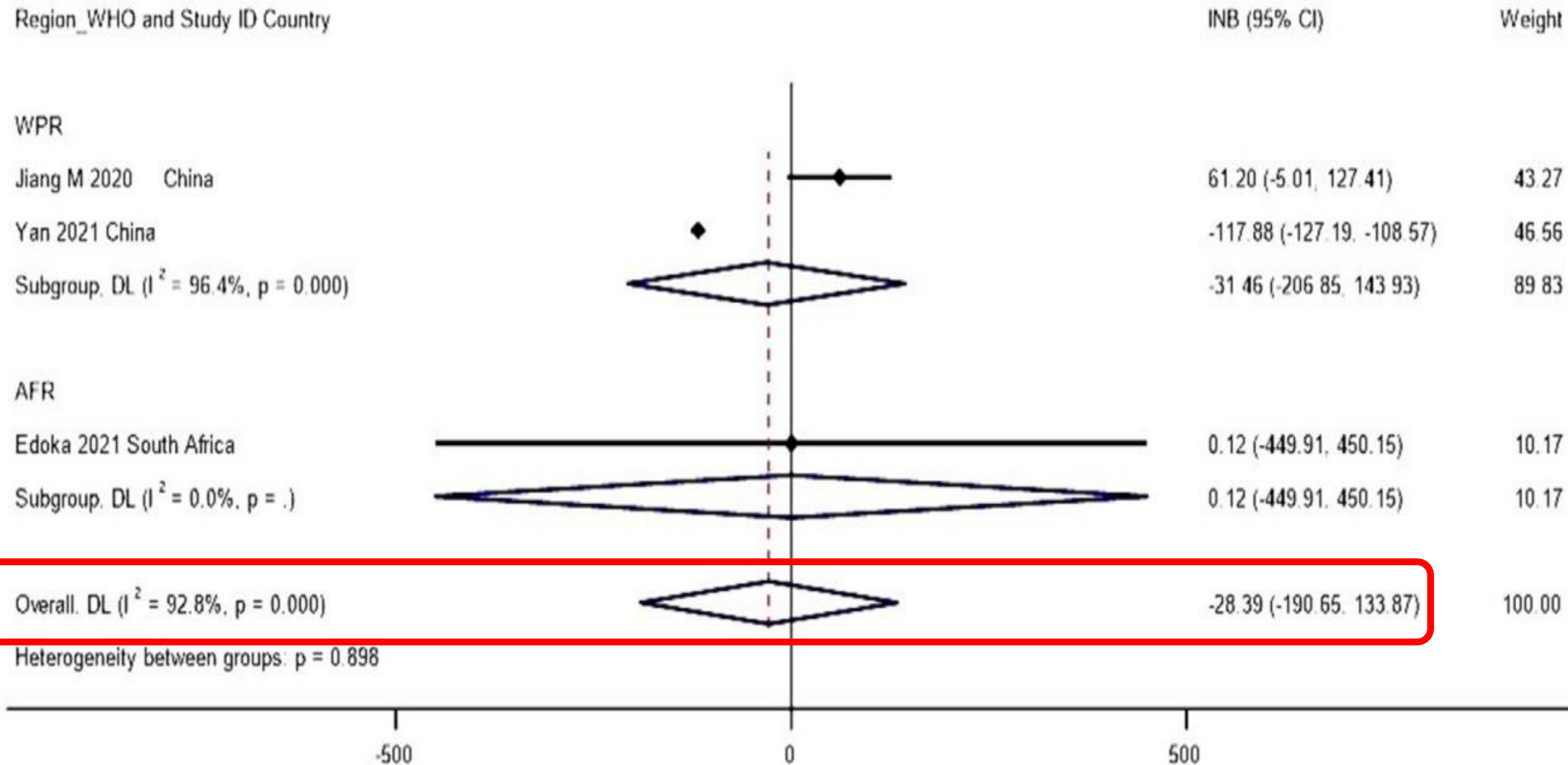
- Sources of heterogeneity
  - Univariate meta-regression of the following variables
    - Funder, type of vaccine, model type, vaccine efficacy, vaccine price, and type of economic evaluation
  - **None were found to explain heterogeneity**
    - $I^2$  ranged from 99.9% to 100% in meta-regressions
- **Robustness** 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

# 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



**World Health  
Organization**



**Thank you**

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

## Discussion

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Nuffield Department of Medicine, Oxford University



# 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 heterogeneous samples.
  - What is needed to bring MAEE to the point where it is mature enough to be used routinely?