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TYPHOID &  
OTHER INVASIVE  
SALMONELLOSES

December 5-7, 2023 | Kigali, Rwanda



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# **Efficacy of typhoid vaccines against culture confirmed *Salmonella* Typhi in typhoid endemic countries : A systematic review and meta-analysis**

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# Strategies to Improve Coverage of Typhoid Conjugate Vaccine (TCV) Immunization Campaign in Karachi, Pakistan

by Farah Naz Qamar <sup>1,\*</sup>, Rabab Batool <sup>1</sup>, Sonia Qureshi <sup>1</sup>, Miqdad Ali <sup>1</sup>, Tahira Sadaf <sup>1</sup>, Junaid Mehmood <sup>1</sup>, Khalid Iqbal <sup>2</sup>, Akram Sultan <sup>3</sup>, Noah Duff <sup>4</sup> and Mohammad Tahir Yousafzai <sup>1</sup>

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Vaccine

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## Effectiveness of typhoid conjugate vaccine against culture-confirmed typhoid in a peri-urban setting in Karachi: A case-control study

Rabab Batool <sup>a,b</sup>, Mohammad Tahir Yousafzai <sup>a,c</sup>, Sonia Qureshi <sup>a</sup>, Miqdad Ali <sup>a</sup>, Tahira Sadaf <sup>a</sup>, Junaid Mehmood <sup>a</sup>, Per Ashorn <sup>b,d</sup>, Farah Naz Qamar <sup>a</sup>

Article Category: Short Report

### Risk Factors Associated with Extensively Drug-Resistant Typhoid in an Outbreak Setting of Lyari Town Karachi, Pakistan

Rabab Batool, Sonia Qureshi, Mohammad Tahir Yousafzai, Momin Kazi, Miqdad Ali, and Farah Naz Qamar

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DOI: <https://doi.org/10.4269/ajtmh.21-1323>

Page(s): 1379-1383

Volume/Issue: Volume 106: Issue 5



Vaccine

journal homepage: [www.elsevier.com/locate/vaccine](http://www.elsevier.com/locate/vaccine)



## Parental acceptance of typhoid conjugate vaccine for children aged 6 months to 15 years in an outbreak setting of Lyari Town Karachi, Pakistan

Rabab Batool <sup>a,b</sup>, Mohammad Tahir Yousafzai <sup>a,c</sup>, Sonia Qureshi <sup>a</sup>, Sajid Muhammad <sup>a</sup>, Ibtisam Qazi <sup>a</sup>, Tahira Sadaf <sup>a</sup>, Per Ashorn <sup>b</sup>, Farah Naz Qamar <sup>a,\*</sup>

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# PLOS ONE

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

## Coverage survey of typhoid conjugate vaccine among children aged 6 months to 15 years in an urban slum settlement of Lyari Town Karachi, Pakistan

Rabab Batool, Sonia Qureshi, Zoya Haq, Mohammad Tahir Yousafzai, Rehana A. Salam, Rafey Ali, Tahira Sadaf, Miqdad Ali, Farah Naz Qamar

Published: August 7, 2023 • <https://doi.org/10.1371/journal.pone.0289582>



*Am J Trop Med Hyg.* 2020 Apr; 102(4): 705–706.

doi: [10.4269/ajtmh.19-0839](https://doi.org/10.4269/ajtmh.19-0839)

Story of Lyari

Rabab Batool\*

# Outline

- Background
- Objectives
- Methods
  - PICOS Framework
  - PRISMA
  - Data Collection
  - RoB
  - Statistical Analysis
- Results
- Conclusion



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# Background

**DAWN**

TODAY'S PAPER | NOVEMBER 05, 2019

## A virulent strain



## Drug-resistant superbug to blame for deadly typhoid outbreak in Pakistan

Researchers warn of limited treatment options as mutated strain of typhoid is blamed for surge in cases

**The Telegraph**

🏠 > News > Global Health Security > Science & Disease

## Typhoid superbug spreads throughout Pakistan

**THE EXPRESS**  
**TRIBUNE**

Friday, 15 Nov 2019 | Today's Paper | Advertise

## US issues travel alert for Pakistan over typhoid superbug outbreak



# Background

- Strategic Typhoid Alliance Across Africa and Asia (STRATAA) study reported azithromycin resistance of 21% in Bangladesh and 2.8% in Nepal.<sup>1,2</sup>
- Efficacious and safe typhoid vaccines have existed since the early 1990s but were not introduced into routine immunization.

1. Hooda Y, Sajib MS, Rahman H, Luby SP, Bondy-Denomy J, Santosham M, Andrews JR, Saha SK, Saha S. Molecular mechanism of azithromycin resistance among typhoidal Salmonella strains in Bangladesh identified through passive pediatric surveillance. *PLoS neglected tropical diseases*. 2019 Nov 15;13(11):e0007868.
2. Saha S, Sajib MS, Garrett D, Qamar FN. Antimicrobial resistance in typhoidal Salmonella: around the world in 3 days. *Clinical Infectious Diseases*. 2020 Jul 29;71(Supplement\_2):S91-5.

# Characteristics of the 2 Typhoid Vaccines Recommended by the World Health Organization: Ty21a and Vi Polysaccharide



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	<b>Ty21a Vaccine</b>	<b>Vi Capsular Polysaccharide Vaccine</b>
Vaccine type	Live attenuated	Subunit
Composition	Chemically mutated Ty2 strain of <i>S. typhi</i>	Purified Vi capsular polysaccharide of Ty2 <i>S. typhi</i> strain
Immunogenic properties	<ul style="list-style-type: none"> <li>▪Elicits mucosal IgA and serum IgG antibodies against O, H, and other antigens, as well as cell-mediated responses</li> <li>▪No booster effect has been shown</li> </ul>	<ul style="list-style-type: none"> <li>▪Elicits serum IgG Vi antibodies</li> <li>▪T-cell independent (no booster response)</li> </ul>
Route of administration	Oral	Parenteral (subcutaneous or intramuscular)
Minimum age vaccine is licensed for use	2 years old for liquid formulation and 5 years old for capsule formulation	2 years old
Formulation	<ul style="list-style-type: none"> <li>▪Enteric-coated capsules, or</li> <li>▪Liquid suspension (lyophilized vaccine + buffer mixed with water upon use)</li> </ul>	Solution of 25 µg combined with buffer
Number of doses required for complete vaccine regimen	3 to 4	1
Storage requirements	Requires storage at 2° to 8°C	Requires storage at 2° to 8°C
Shelf life in higher temperature	14 days at 25 °C	6 months at 37 °C 2 years at 22 °C
Safety/tolerability	High	High
Efficacy at 3 years (95% CI)	51% (36–62%)	55% (30–70%)
Length of protection	At least 5–7 years	At least 3 years



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# Typhoid vaccine prequalified

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## New typhoid vaccine offers hope of protection for children

PUBLISHED

29 SEP 2017

[RESEARCH](#) [HEALTH](#) [SCIENCE](#)

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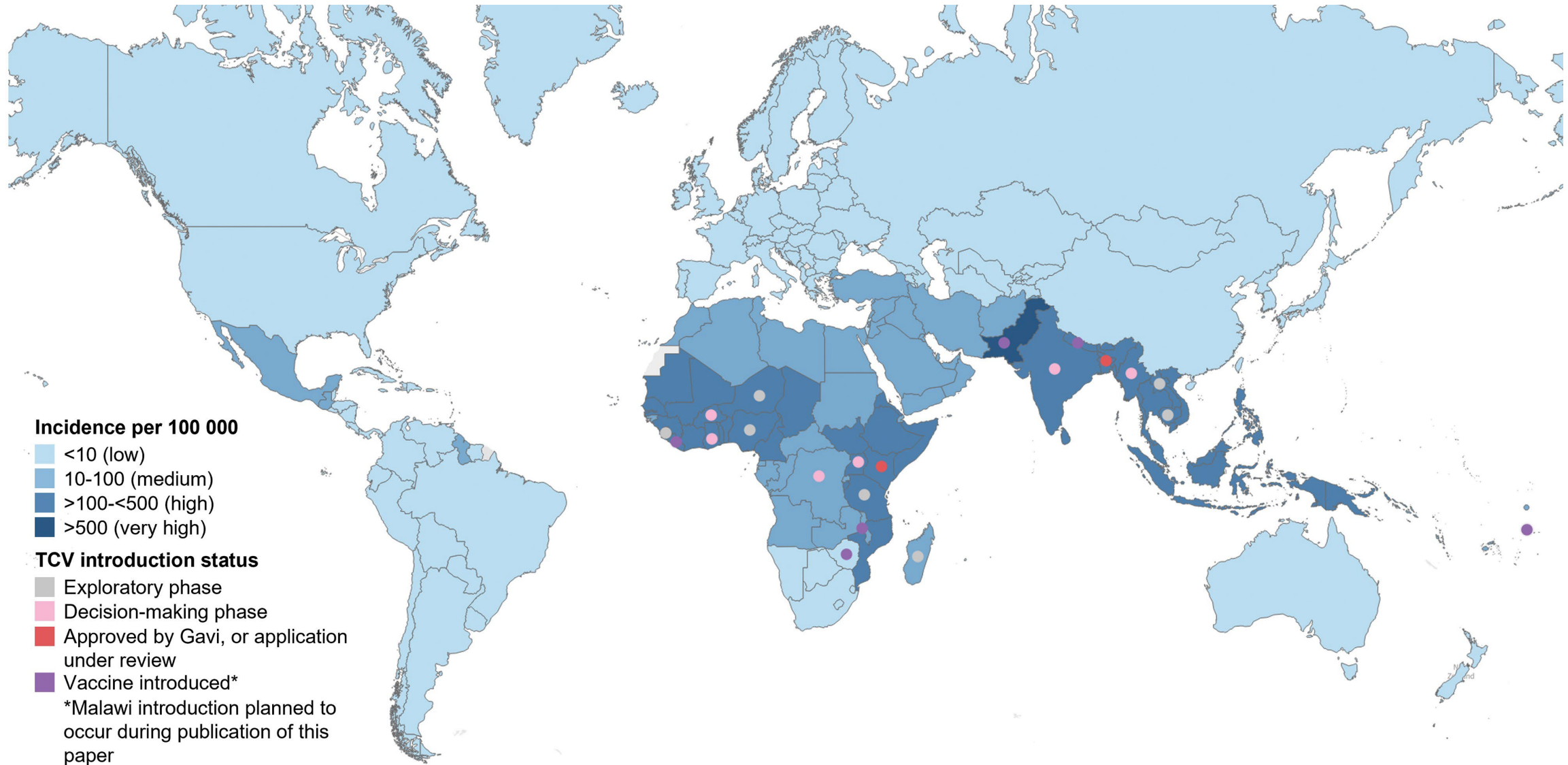
A new typhoid vaccine for both adults and children has been proven by Oxford researchers to be safe and effective in preventing the disease.

The NEW ENGLAND  
JOURNAL of MEDICINESUBSCRIBE  
OR RENEW**IMAGE CHALLENGE**  
What is the diagnosis?**NEJM GROUP PODCASTS**  
DISCOVER NOW **ORIGINAL ARTICLE**  
Prehospital Tranexamic Acid for Severe Trauma**ORIGINAL ARTICLE**  
Base-Edited CAR7 T Cells for Relapsed T-Cell Acute Lymphoblastic Leukemia**EDITORIAL**  
Antagonizing the Leptin Receptor in Obesity

## Perspective

### Extensively Drug-Resistant Typhoid — Are Conjugate Vaccines Arriving Just in Time?

Jason R. Andrews, M.D., Farah N. Qamar, F.C.P.S., Richelle C. Charles, M.D., and Edward T. Ryan, M.D.



**Incidence per 100 000**

- <10 (low)
- 10-100 (medium)
- >100-<500 (high)
- >500 (very high)

**TCV introduction status**

- Exploratory phase
- Decision-making phase
- Approved by Gavi, or application under review
- Vaccine introduced\*

\*Malawi introduction planned to occur during publication of this paper





# Objectives

- To synthesize evidence on the efficacy and safety of typhoid vaccines against culture-confirmed *S. Typhi*.



# Methods

## Literature search

- January 1986, and January 2023
- Cochrane (CENTRAL), MEDLINE, and Embase

Search updated on November 2<sup>nd</sup>, 2023.

PROSPERO protocol ID: CRD42021241043

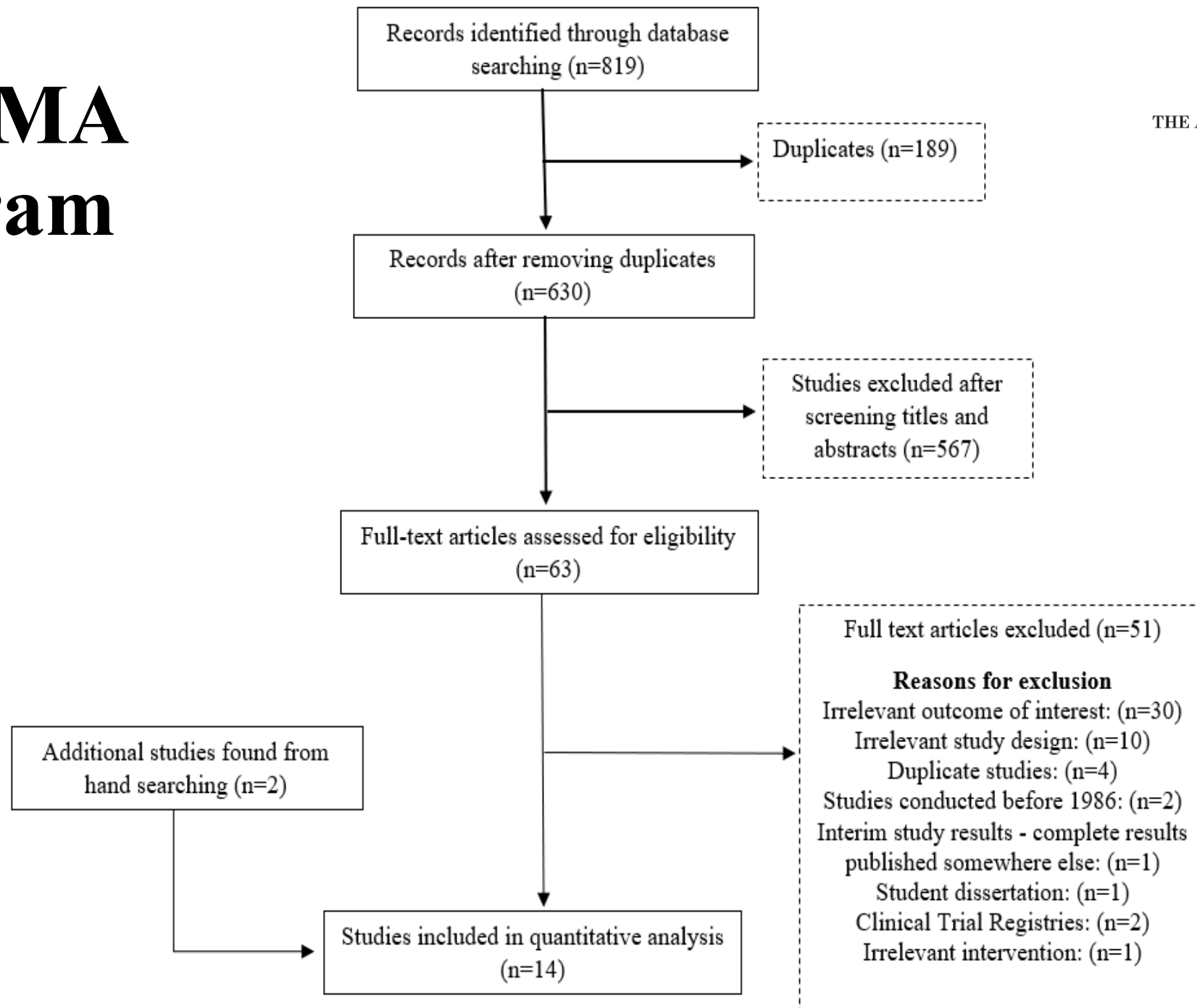


# Description of the PICOS strategy

Population	All age groups
Intervention	<b>All typhoid vaccines:</b> The Live Attenuated Ty21a, Vi capsular polysaccharide, Vi-tetanus toxoid conjugate vaccine, Vi polysaccharide conjugated to recombinant Pseudomonas aeruginosa exotoxin A vaccine (Vi-rEPA)
Comparison	<b>Control:</b> Placebo , Typhoid-inactive agents , Vaccines other than Typhoid
Outcome	<b>Vaccine efficacy:</b> calculated as $(1 - IRR) \times 100\%$ <b>Adverse events:</b> within 7 days following vaccination.
Study Type	<b>Included:</b> Randomized control trials (RCTs) (individually, cluster and quasi-randomized trials) <b>Excluded:</b> <ul style="list-style-type: none"><li>- Observational studies</li><li>- Modeling studies, human challenge studies, studies with sample size &lt;30</li><li>- Studies in languages other than English</li><li>- Trials that aimed to assess only the immunogenicity of vaccine, or side effects</li><li>- Studies older than 1986</li></ul>



# The PRISMA flow diagram





EndNote™

# Data collection

- Covidence Systematic Review Software >> screening
- Data were extracted on:
  - Type of vaccine, number of shots or doses, follow-up duration, nature of vaccine formulation
  - Mode of administration (oral, IM)
  - Type of surveillance method for vaccine efficacy
  - Age of trial participants
  - Outcomes reported (vaccine efficacy and adverse events).





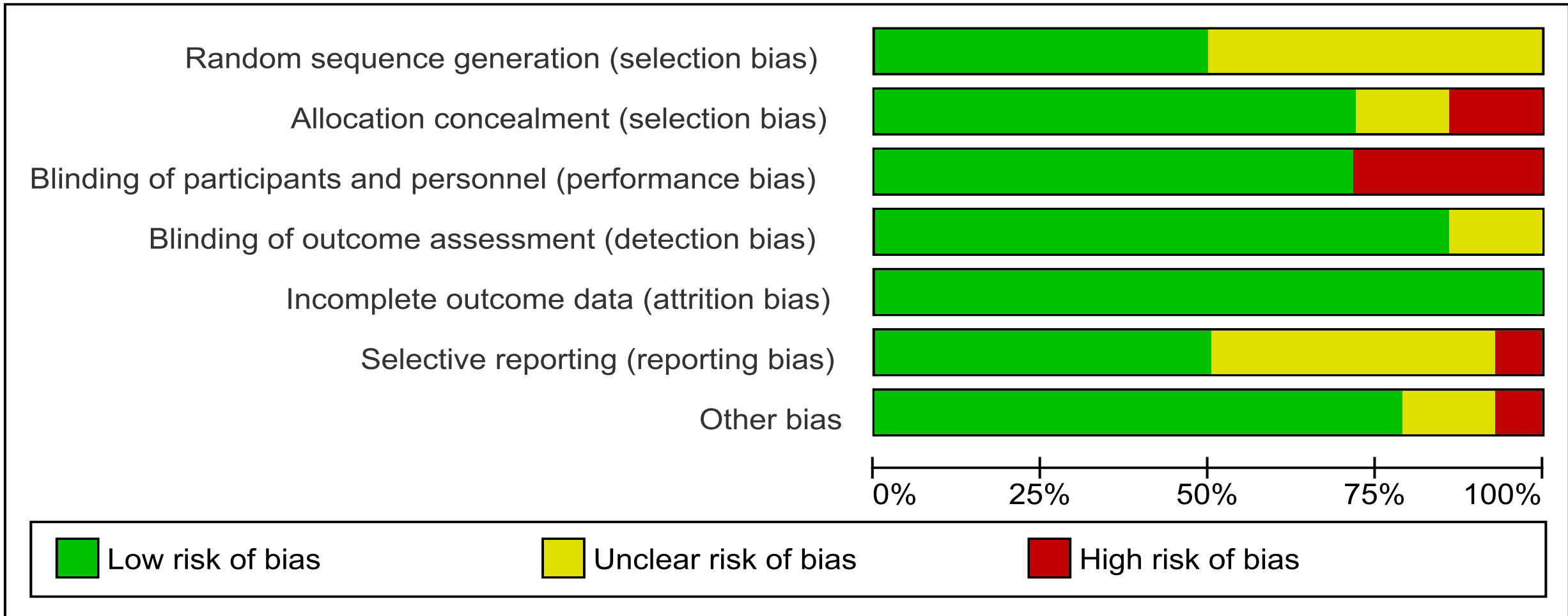


# Data collection

- For cluster-RCTs , effective sample sizes was calculated.
- The estimates from the individually randomized and cluster adjusted RCTs were pooled using GIV method.
- Methodological quality of articles was assessed using RoB 2.0.
- Quality of evidence for outcomes of interest was summarized as per (GRADE) criteria.



# Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



# Risk of bias summary for each risk of bias item for each included study

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Acharya 1987	?	+	+	+	+	?	+
Black 1990	?	+	+	+	+	?	+
Khan 2012	+	+	+	+	+	+	+
Klugman 1987	?	+	+	+	+	?	+
Levine 1987	?	+	+	+	+	?	?
Levine 1990	?	+	+	+	+	?	?
Lin 2001	?	+	+	+	+	+	+
Mitra 2016	+	-	-	?	+	-	-
Patel 2021	+	?	-	+	+	+	+
Qadri 2021	+	?	-	+	+	+	+
Shakya 2021	+	+	+	+	+	+	+
Simanjuntak 1991	+	+	+	?	+	?	+
Sur 2009	+	-	-	+	+	+	+
Yang 2001	?	+	+	+	+	+	+



# Statistical analysis

## Meta-analysis

- RevMan software (5.4.1).
- Random effects model
  - data were heterogeneous.
- Statistical heterogeneity
  - $\tau^2$ ,  $I^2$ , and the significance of the  $\chi^2$  test.
- Publication bias
  - funnel plots by assessing asymmetry.
- Subgroup analysis
  - Age groups

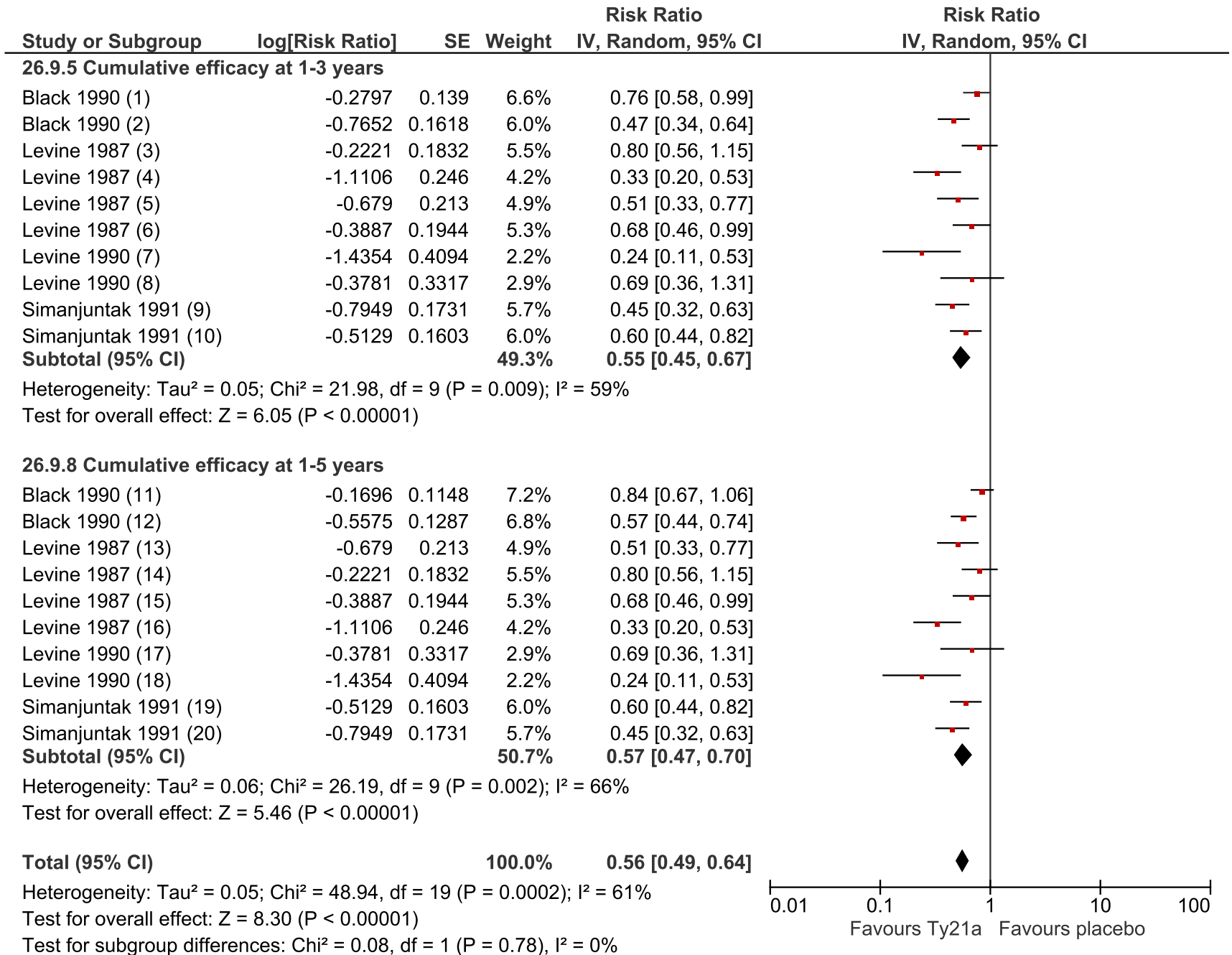
# Results



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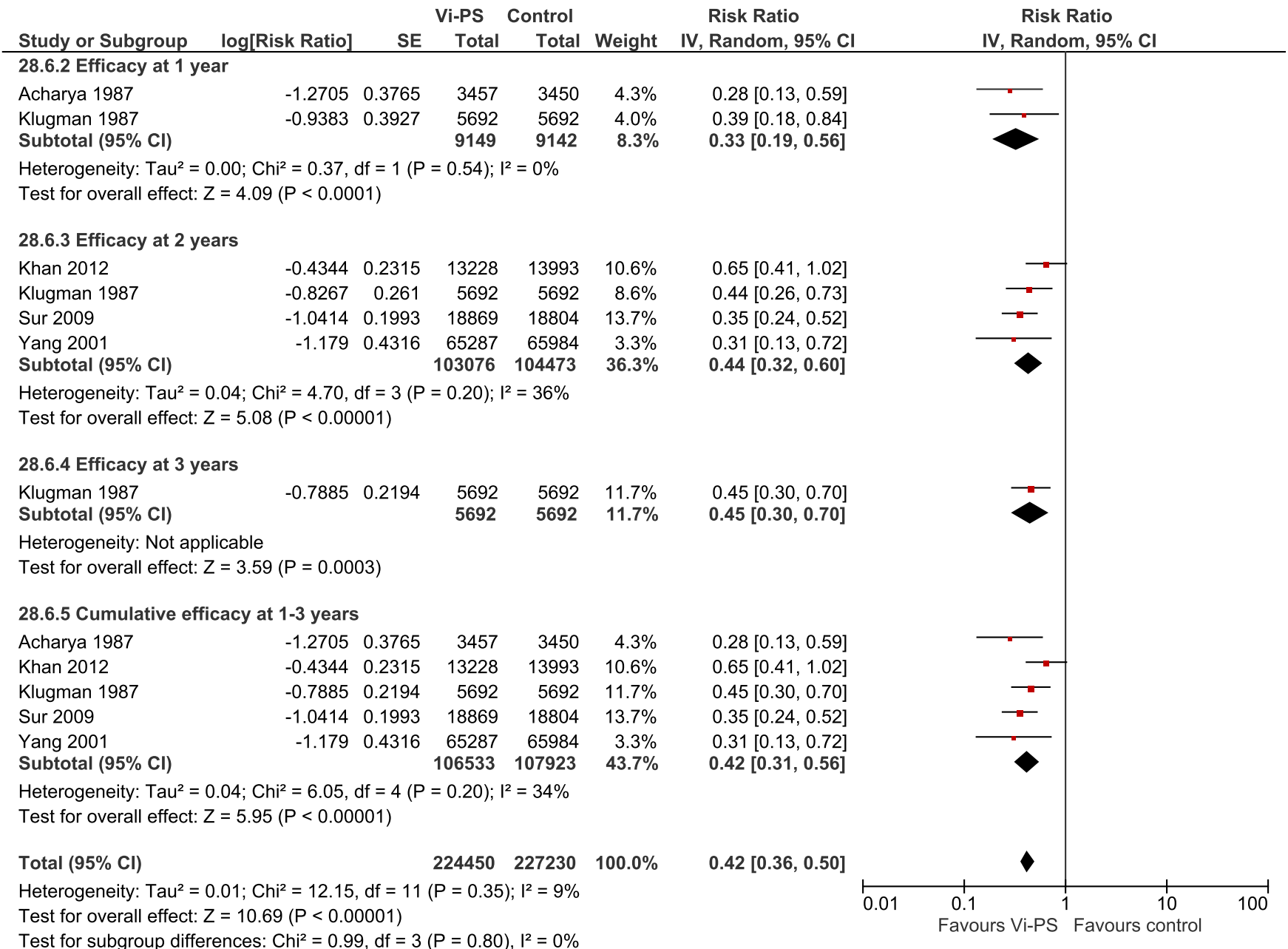
# Ty21a versus control



# Summary of findings: Ty21a versus control for preventing Typhoid fever

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	Risk with vaccine			
<b>Ty21a versus placebo for blood culture confirmed <i>S. Typhi</i></b>					
Incidence of Typhoid fever at 1 year	54 per 10,000	<b>32 per 10,000</b> (25 to 41)	<b>RR 0.59</b> (0.46 to 0.76)	129757 (3 RCTs)	⊕⊕⊕⊕ High
Incidence of Typhoid fever at 2 years	99 per 10,000	<b>50 per 10,000</b> (39 to 65)	<b>RR 0.50</b> (0.39 to 0.65)	129757 (3 RCTs)	⊕⊕⊕○ Moderate <sup>a</sup>
Incidence of Typhoid fever at 1 to 3 years	116 per 10,000	<b>64 per 10,000</b> (52 to 78)	<b>RR 0.55</b> (0.45 to 0.67)	247649 (4 RCTs)	⊕⊕⊕○ Moderate <sup>b</sup>
Incidence of Typhoid fever at 4 years	108 per 10,000	<b>71 per 10,000</b> (47 to 108)	<b>RR 0.66</b> (0.44 to 1.00)	82544 (1 RCT)	⊕⊕○○ Low <sup>c,d</sup>
Incidence of Typhoid fever at 5 years	120 per 10,000	<b>84 per 10,000</b> (58 to 123)	<b>RR 0.70</b> (0.48 to 1.02)	82544 (1 RCT)	⊕⊕○○ Low <sup>e,f</sup>
Cumulative incidence of Typhoid fever at 1 to 5 years	130 per 10,000	<b>74 per 10,000</b> (61 to 91)	<b>RR 0.57</b> (0.47 to 0.70)	247649 (4 RCTs)	⊕⊕⊕○ Moderate <sup>g</sup>

# Vi-PS versus control



# Summary of findings: Vi-PS versus control for preventing Typhoid fever

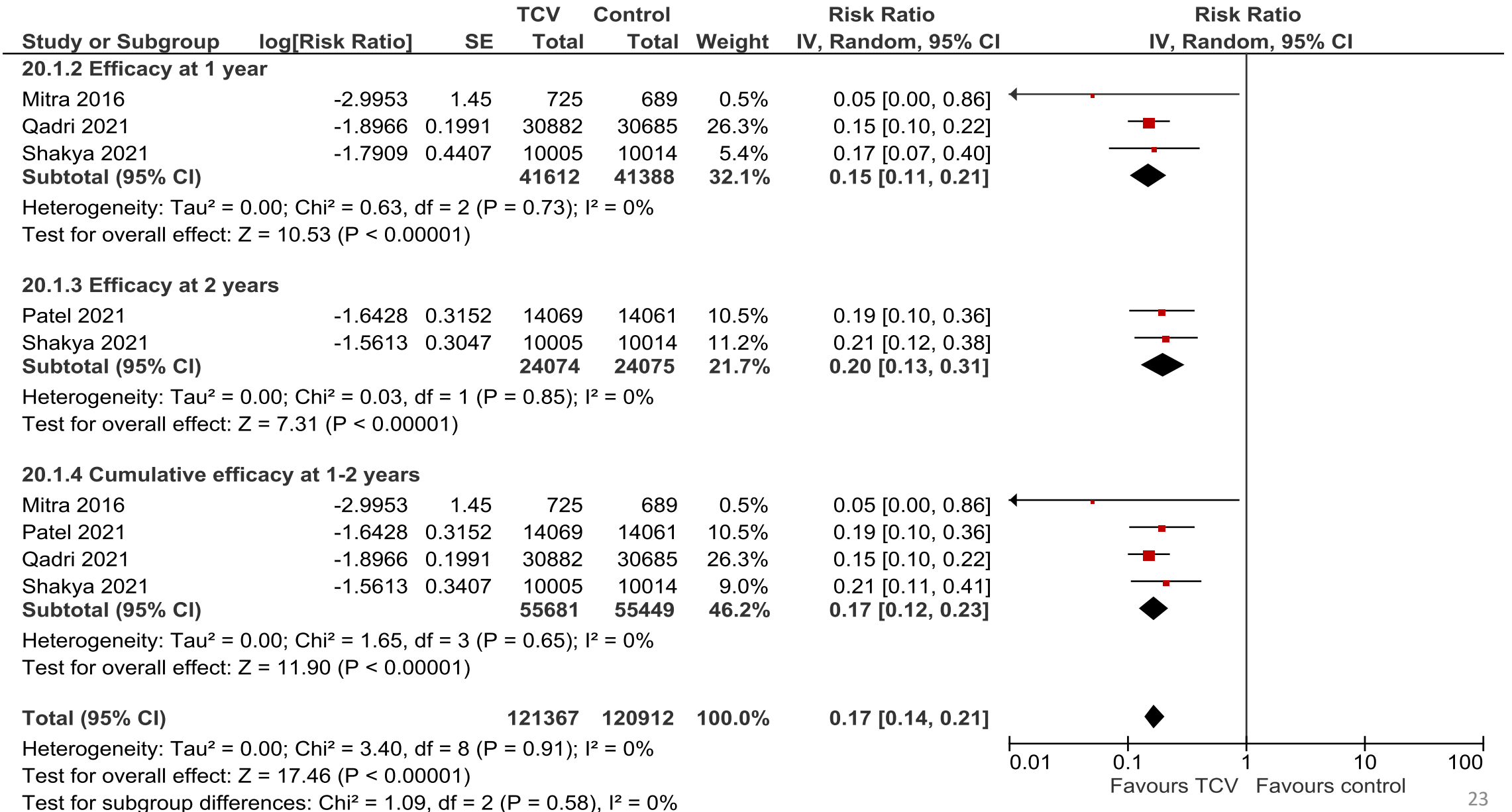


Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	Risk with vaccine			
<b>Ty21a versus placebo for blood culture confirmed <i>S. Typhi</i></b>					
<b>Vi-PS versus control for blood culture confirmed <i>S. Typhi</i></b>					
Incidence of Typhoid fever at 1 year	60 per 10,000	<b>20 per 10,000</b> (11 to 34)	<b>RR 0.33</b> (0.19 to 0.56)	18291 (2 RCTs)	⊕⊕⊕⊕ High
Incidence of Typhoid fever at 2 years	21 per 10,000	<b>9 per 10,000</b> (7 to 12)	<b>RR 0.44</b> (0.32 to 0.60)	207549 (4 RCTs)	⊕⊕⊕○ Moderate <sup>h</sup>
Cumulative incidence of Typhoid fever at 1 to 3 years	25 per 10,000	<b>10 per 10,000</b> (8 to 14)	<b>RR 0.42</b> (0.31 to 0.56)	214456 (5 RCTs)	⊕⊕⊕○ Moderate <sup>h</sup>

*Footnotes*

h. High risk of bias was observed in one study (Sur 2009) as the two vaccines (control & typhoid vaccine) were not packaged in an identical fashion therefore allocation concealment and blinding were compromised.

# TCV versus control







# Summary of findings: TCV versus control for preventing Typhoid fever

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	Risk with vaccine			
<b>TCV versus control for blood culture confirmed S. Typhi</b>					
Incidence of Typhoid fever at 1 year	57 per 10,000	<b>9 per 10,000</b> (6 to 12)	<b>RR 0.15</b> (0.11 to 0.21)	83000 (3 RCTs)	⊕⊕⊕○ Moderate <sup>i</sup>
Incidence of Typhoid fever at 2 years	52 per 10,000	<b>10 per 10,000</b> (7 to 16)	<b>RR 0.20</b> (0.13 to 0.31)	48149 (2 RCTs)	⊕⊕⊕○ Moderate <sup>i</sup>
Cumulative incidence of Typhoid fever at 1 to 2 years	59 per 10,000	<b>10 per 10,000</b> (8 to 13)	<b>RR 0.17</b> (0.13 to 0.23)	111130 (4 RCTs)	⊕⊕⊕○ Moderate <sup>i</sup>

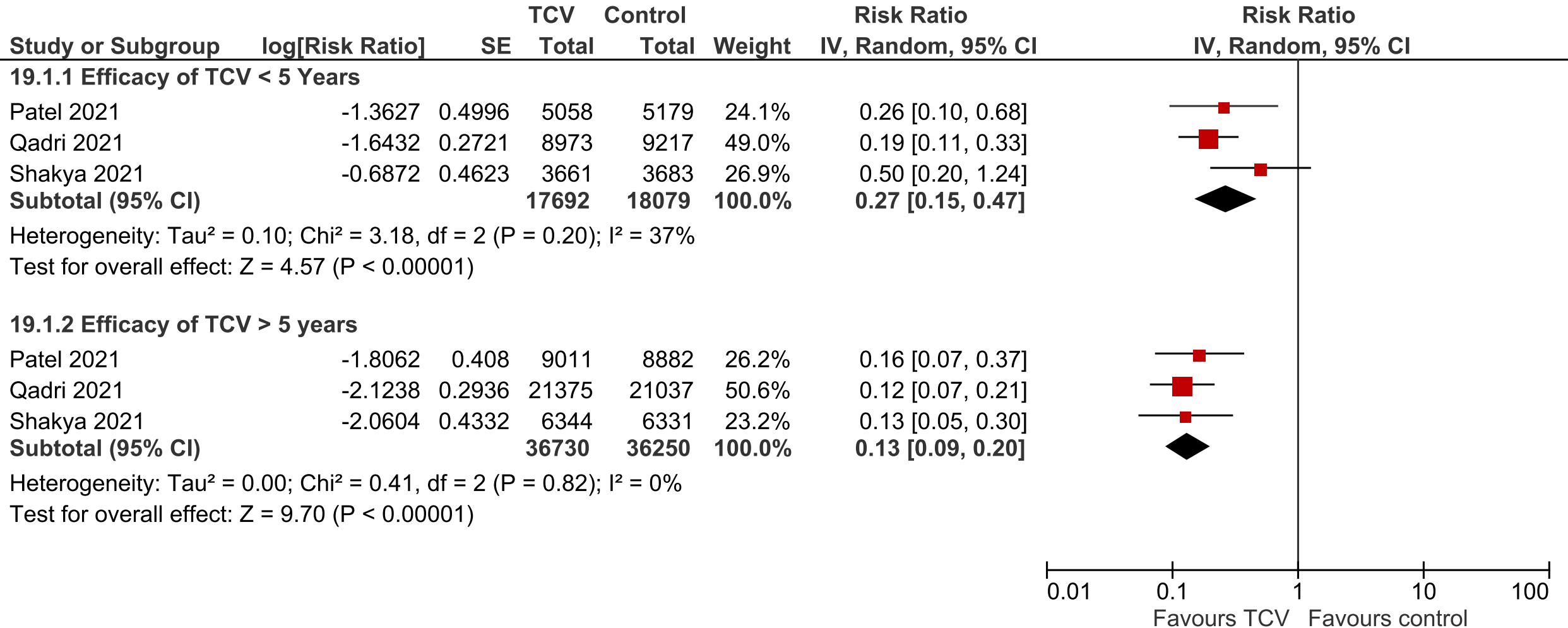
*Footnotes*  
 i. High risk of bias was observed in one study (Mitra 2016) in multiple domains including allocation concealment, blinding selective reporting and other biases (analysis not adjusted for clustering, results might have been affected due to seasonal variations and baseline differences were observed between demographics of vaccines versus control group. High risk of bias in blinding was observed in two studies (Patel 2021, Qadri 2021). 24



# Subgroup Analysis



# Results



Test for subgroup differences: Chi<sup>2</sup> = 3.94, df = 1 (P = 0.05), I<sup>2</sup> = 74.6%



# Summary of findings: TCV versus control for preventing Typhoid fever in different age groups

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	Risk with vaccine			
<b>TCV versus control for blood culture confirmed <i>S. Typhi</i> in different age groups</b>					
Incidence of Typhoid fever - children <5 years	7 per 1,000	<b>2 per 1,000</b> (1 to 3)	<b>RR 0.27</b> (0.15 to 0.47)	35771 (3 RCTs)	⊕⊕⊕○ Moderate <sup>d</sup>
Incidence of Typhoid fever - children ≥5 years	5 per 1,000	<b>1 per 1,000</b> (0 to 1)	<b>RR 0.13</b> (0.09 to 0.20)	72980 (3 RCTs)	⊕⊕⊕○ Moderate <sup>d</sup>

*Footnotes:*

d. High risk of bias due to lack of blinding in two studies (Patel 2021, Qadri 2021)



# Conclusions

- The data from included trials provide promising results regarding the efficacy of TCV in typhoid endemic countries.
- The efficacy of TCV is found to be higher than that of the previously licensed vaccines.
- The longer-term efficacy of TCV and the need for booster dose for younger children must be assessed.

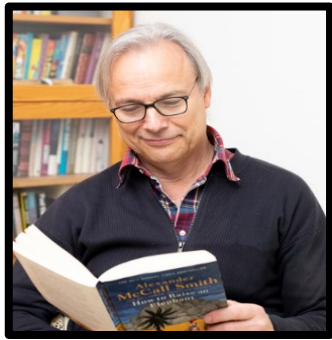


# Acknowledgments

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Zoya Haq



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