# Evidence map and interactive real-time meta-analyses to present results of a living systematic review (LSR) of COVID-19 vaccines during pregnancy

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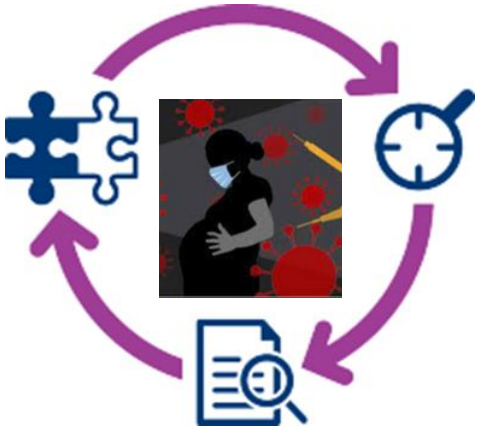

I have no conflict of interest concerning this presentation

Global Evidence Summit

**Prague, 10-13 Sept 2024**

# Introduction

- We conducted a LSR to evaluate safety and effectiveness of COVID-19 vaccines administered to pregnant persons.
- The great amount of evidence, the number of outcomes, and the subgroups of interest allow a large number of meta-analyses.
- We developed an interactive tool allowing tailored meta-analyses by selecting filters according and subgroups by outcome.

# Objective

To present the evidence map and the tool developed for interactive real-time meta-analyses using the shiny R library.

Drug Safety

# Safety and Effectiveness of COVID-19 Vaccines during Pregnancy: A Living Systematic Review and Meta-Analysis

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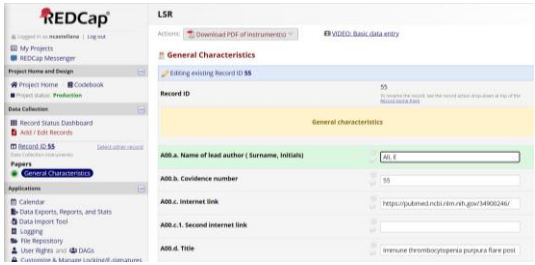
# LSR Methods

**Search every 2 weeks: 7872 records**

covidence

**177 studies**

REDCap




- Comparative MA (RE) of adjusted effect measures
- Proportion MA (RE)

R

Shiny

Power BI

For maps and descriptive statistics

**https://www.safeinpregnancy.org/**

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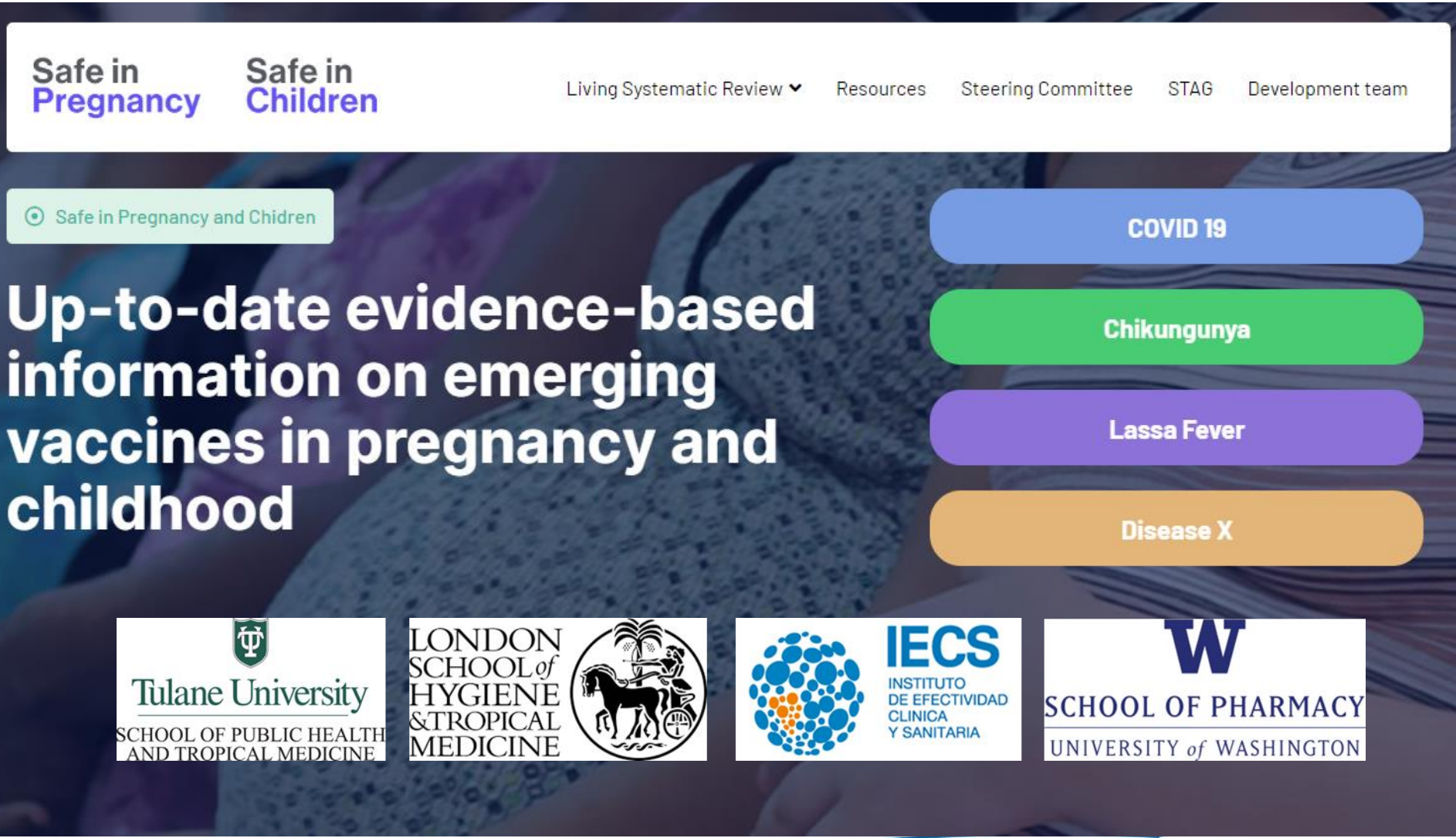
# Safety, effictiveness and immunogenicity of emerging vaccines during pregnancy & childhood: LSR



# Our platform includes:

- LSR-based evidence syntheses
- Link to included studies
- Safety, effictiveness, and immunogenicity outcomes
- Real-time comparative and proportional meta-analyses customizable by subgroups and filters.

# Evidence map

All Studies

Outcomes

Methodology

Summary Tables

Comparative Meta Analyses

Proportional Meta Analyses

Filters

PUBLICATION DATE

COUNTRY / REGION

STUDY

OUTCOME

POPULATION

VACCINE

CLEAR ALL

| 224 | 1,176,433 | 6 | 42 | 10 |
|---|---|---|---|---|
| Collected Studies | Vaccinated Population | Published in the Last 6 Months | Number of Countries | Vaccine Products |

*The extraction of results from articles is currently in progress.*

## Studies Collected per Country

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

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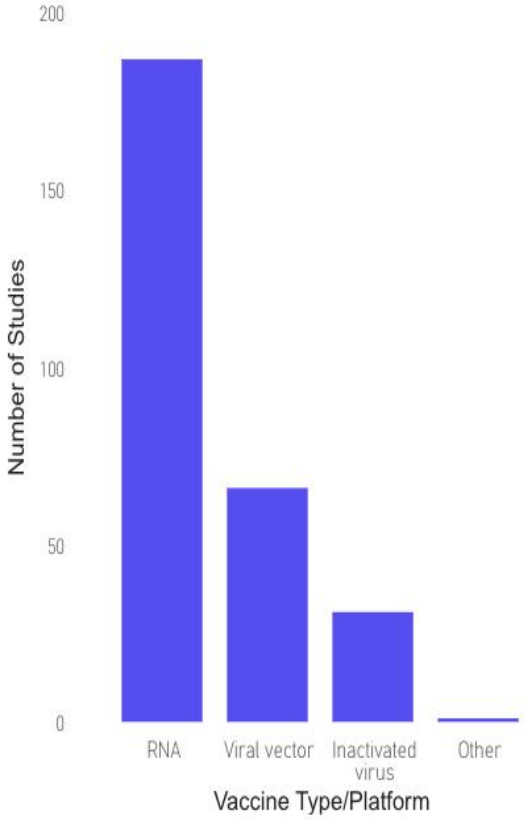
## Studies by Vaccine Type/Platform

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# Information when selecting a category

All Studies

Outcomes

Methodology

Summary Tables

Comparative Meta...

Proportional Meta...

Filters

PUBLICATION DATE

COUNTRY / REGION

STUDY

OUTCOME

POPULATION

VACCINE

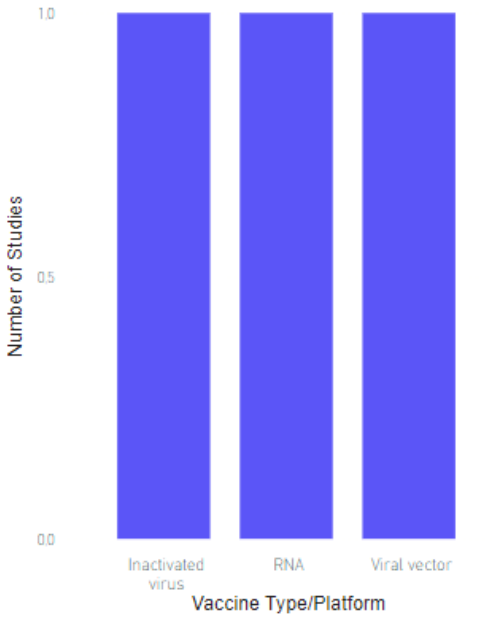
CLEAR ALL

| 1 | 2.886 | - | 1 | 10 |
|---|---|---|---|---|
| Collected Studies | Vaccinated Population | Published in the Last 6 Months | Number of Countries | Vaccine Products |

*The extraction of results from articles is currently in progress.*

## Studies Collected per Country

## Studies by Vaccine Type/Platform




## Detailed Information Of Collected Studies

| Lead author | Title | Publication date | Outcome / Measurement Type | Study Design | Center | Vaccinated Population | Countries | Vaccines |
|---|---|---|---|---|---|---|---|---|
| Villar, J. | Pregnancy outcomes and vaccine effectiveness during the period of omicron as the variant of concern, INTERCOVID-2022: a multinational observational study | 17/01/2023 | Efficacy/Effectiveness Outcomes, Infant Safety Outcomes Following COVID-19 Vaccination During Pregnancy, Maternal - Pregnancy Related Outcomes | Cohort | Multicenter | 2886 | Argentina, Brazil, Egypt, Arab Rep., France, Indonesia, Israel, Italy, Japan, Mexico, Nigeria | Sinovac (Coronavac), Moderna (mRNA-1273), Oxford/AstraZeneca (AZD1222 Vaxzevria), Janssen/Johnson&Johnson(Ad26.COV2.S), Covishield (ChAdOx1_nCoV-19), Pfizer/BioNTech (BNT162b2/Comirnaty), Sputnik V, Sinopharm, CanSinoBIO (Ad5-nCoV), Bharat Biotech (Covaxin) |

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# Outcome Information

All Studies

Outcomes

Methodology

Summary Tables

Comparative Meta...

Proportional Meta...

Filters

PUBLICATION DATE

COUNTRY / REGION

STUDY

OUTCOME

POPULATION

VACCINE

CLEAR ALL

**171** Studies with Complete Extraction

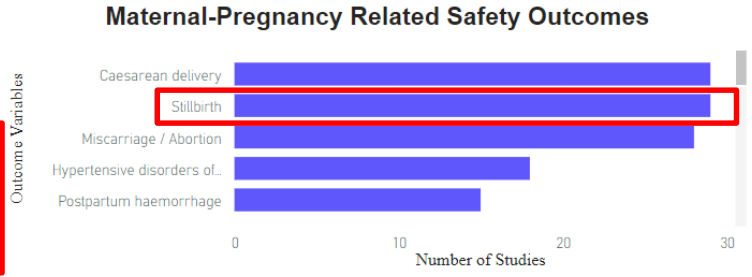
**71** Studies Reporting Maternal Pregnancy Related Outcomes

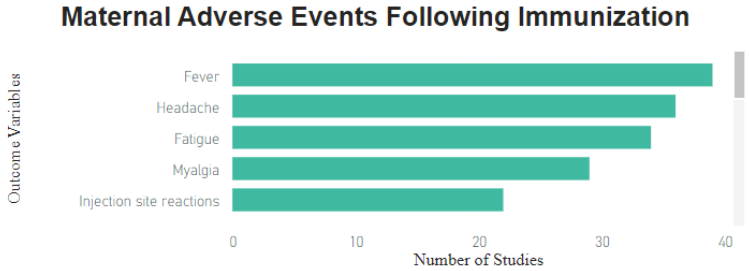
**59** Studies Reporting Maternal Adverse Events Following Immunizations

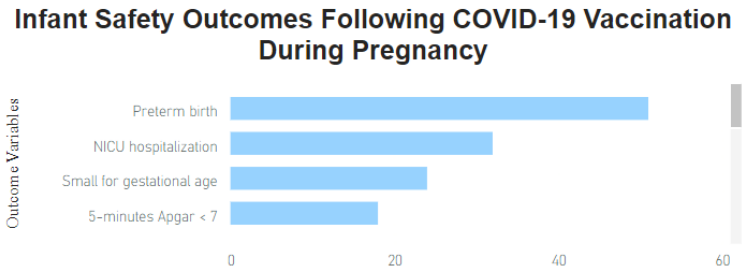
**64** Studies Reporting Infant Safety Outcomes Following COVID-19 Vaccination During Pregnancy

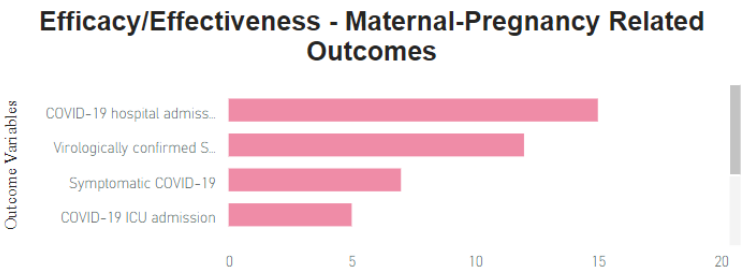
**28** Studies Reporting Vaccine Efficacy / Effectiveness Outcomes

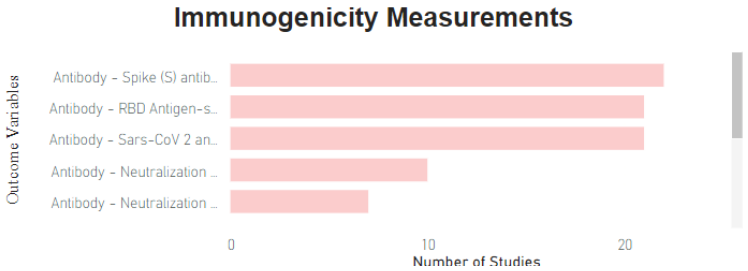
**67** Studies Reporting Immunogenicity Measurements

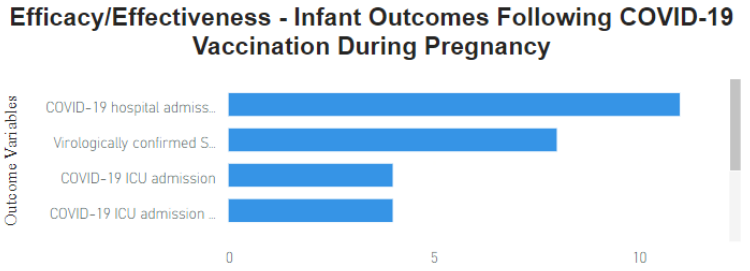
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Stillbirth

**Subgroup analysis**
- (•) Trimester
- ( ) Dominant variant
- ( ) Vaccine type
- ( ) Dose

**Vaccine type**
- [x] Inactivated virus
- [x] RNA
- [x] Viral vector

**Dose**
- [x] 1
- [x] 2
- [x] Booster
- [x] Not specified

**Dominant Variant**
- [x] Alpha
- [x] Beta
- [x] Delta
- [x] Omicron

**Effect measure**
- ( ) OR
- (•) RR

**Type of Pregnant Population Exposed to COVID-19 vaccination**

General pregnant population vaccinated

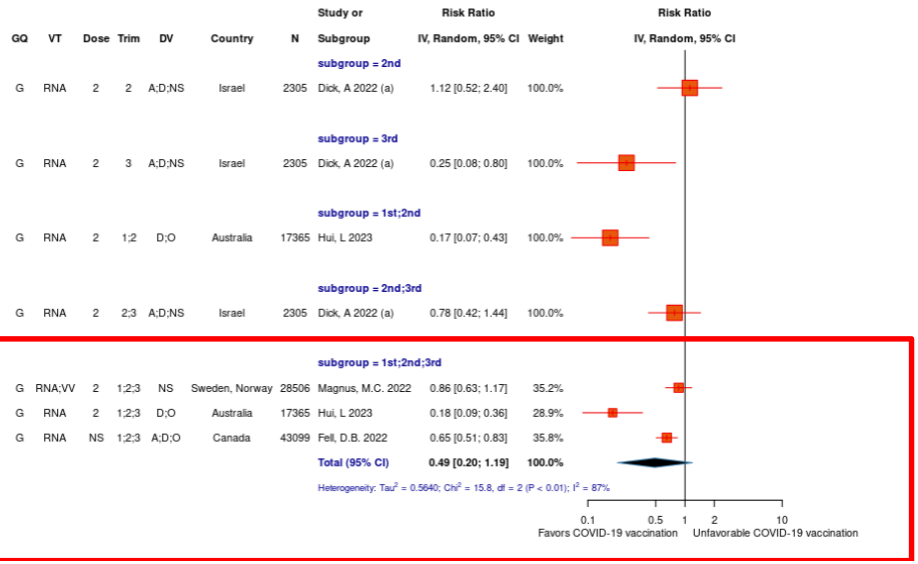
**Comparator**

Unvaccinated

Forest Plot / Meta-analysis | Summary table

We identified 32 studies reporting this outcome. Based on the methodology described, only 4 studies reported adjusted effect measures for this outcome: Dick, A (2022) (a), Fell, D.B. (2022), Magnus, M.C. (2022), Hui, L 2023. Finally, 4 were included in the meta-analysis based on the selected filters. The meta-analysis included a total of 113,250 patients exposed to the vaccine in 5 countries: Australia, Canada, Israel, Norway and Sweden.

**Maternal safety of COVID-19 vaccines during pregnancy versus unvaccinated pregnant population: Stillbirth.**




Para cualquier trimestre las vacunas ARNm/vector viral mostraron un RR de 0,49 (0,20 a 1,19)

## Analysis parameters

**Outcome type**

- ○ Infant safety outcomes following COVID-19 vaccination during pregnancy
- ◉ Maternal-Pregnancy related outcomes
- ○ Maternal-Adverse events following immunizations

**Outcome**

Stillbirth

**Subgroup analysis**

- ○ Vaccine type
- ◉ Trimester

Video Guide to Interpreting Proportional Meta-analyses (2.36 min)

Por tipo de vacuna o por trimestre de exposición, la incidencia de muerte fetal en embarazadas vacunadas es similar a las tasas históricas.

**Esta ruta se puede replicar para cada resultado.**

| Country | Study or Subgroup | Events | Total | Events per 1000 observations IV, Random, 95% CI | Weight | Global quality | Vaccine type | Vac. Prod. | Dose | Events per 1000 observations IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|
| | **subgroup = 1st;2nd** | | | | | | | | | |
| Australia | Hui, L 2023 | 6 | 2442 | 2.457 [ 0.902; 5.340] | 100.0% | Good | RNA | Pfz | 2 | |
| | **subgroup = 1st;2nd;3rd** | | | | | | | | | |
| Australia | Hui, L 2023 | 15 | 9682 | 1.549 [ 0.867; 2.554] | 13.6% | Good | RNA | Pfz | 2 | |
| USA | Cassidy, A 2023 | 0 | 76 | 0.000 [ 0.000; 47.379] | 3.4% | Fair | RNA | Mod Pfz | Not specified | |
| Canada | Fell, DB 2023 | 54 | 18491 | 2.920 [ 2.195; 3.809] | 13.8% | Good | RNA | Mod Pfz | Booster | |
| Canada | Fell, DB 2023 | 89 | 14198 | 6.268 [ 5.037; 7.708] | 13.7% | Good | RNA | Mod Pfz | 2 | |
| Canada | Fell, D.B. 2022 | 107 | 43099 | 2.483 [ 2.035; 2.999] | 13.9% | Good | RNA | Mod Pfz | Not specified | |
| Netherlands | Zilver, S.J.M. 2023 | 0 | 130 | 0.000 [ 0.000; 27.977] | 4.9% | Fair | RNA | Mod Pfz | Not specified | |
| USA | Theiler, R N 2021 | 0 | 140 | 0.000 [ 0.000; 26.005] | 5.2% | Good | RNA; Viral vector | Mod Pfz J&J | 1 | |
| India | Tripathy, G 2023 | 2 | 127 | 15.748 [ 1.913; 55.729] | 4.9% | Fair | Inactivated virus; Viral vector | AZDi BBV | Not specified | |
| UK | Stock, S. 2021 | 11 | 2364 | 4.653 [ 2.325; 8.310] | 12.7% | Fair | RNA; Viral vector | Mod Pfz AZD | 2 | |
| veden, Norway | Magnus, M.C. 2022 | 50 | 28506 | 1.754 [ 1.302; 2.312] | 13.9% | Good | RNA; Viral vector | Mod Pfz AZD | 2 | |
| | **Total (95% CI)** | | | **1.606 [ 0.560; 3.019]** | **100.0%** | | | | | |
| | Heterogeneity: $Tau^2 = 0.0002$; $Chi^2 = 67.72$, df = 9 (P < 0.01); $I^2 = 87\%$ | | | | | | | | | |
| | **subgroup = 2nd** | | | | | | | | | |
| Israel | Dick, A 2022 (a) | 10 | 964 | 10.373 [ 4.985; 18.994] | 100.0% | Good | RNA | Mod Pfz | 2 | |
| | **subgroup = 2nd;3rd** | | | | | | | | | |
| Israel | Dick, A 2022 (a) | 20 | 2305 | 8.677 [ 5.308; 13.369] | 19.0% | Good | RNA | Mod Pfz | 2 | |
| Israel | Kugelman, N. 2022 (c) | 2 | 930 | 2.151 [ 0.261; 7.747] | 16.7% | Fair | RNA | Pfz | 2 | |
| Israel | Goldshtein, I 2021 | 1 | 7530 | 0.133 [ 0.003; 0.740] | 20.3% | Good | RNA | Pfz | 1 | |
| Israel | Dick, A 2022 (b) | 0 | 294 | 0.000 [ 0.000; 12.469] | 11.6% | Good | RNA | Mod Pfz | Booster | |
| Israel | Dick, A 2022 (b) | 20 | 2845 | 7.030 [ 4.299; 10.836] | 19.3% | Good | RNA | Mod Pfz | 2 | |
| USA | Trostle, ME 2021 | 0 | 85 | 0.000 [ 0.000; 42.470] | 5.5% | Fair | RNA | Mod Pfz | 2 | |
| UK | Blakeway, H 2021 | 0 | 133 | 0.000 [ 0.000; 27.355] | 7.5% | Good | RNA; Viral vector | Mod Pfz AZD | 1 | |
| | **Total (95% CI)** | | | **1.579 [ 0.000; 5.362]** | **100.0%** | | | | | |
| | Heterogeneity: $Tau^2 = 0.0010$; $Chi^2 = 70.3$, df = 6 (P < 0.01); $I^2 = 91\%$ | | | | | | | | | |
| | **subgroup = 3rd** | | | | | | | | | |
| Israel | Rottenstreich, M 2021 | 5 | 712 | 7.022 [ 2.284; 16.311] | 25.6% | Good | RNA | Pfz | 2 | |
| Vietnam | Vuong, L.N. 2022 | 1 | 513 | 1.949 [ 0.049; 10.813] | 23.3% | Poor | RNA | Pfz | 2 | |
| Vietnam | Vuong, L.N. 2022 | 2 | 441 | 4.535 [ 0.550; 16.286] | 22.2% | Poor | Viral vector | AZD | Not specified | |
| Israel | Dick, A 2022 (a) | 4 | 1329 | 3.010 [ 0.821; 7.688] | 28.9% | Good | RNA | Mod Pfz | 2 | |
| | **Total (95% CI)** | | | **3.705 [ 1.665; 6.398]** | **100.0%** | | | | | |
| | Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.16$, df = 3 (P = 0.54); $I^2 = 0\%$ | | | | | | | | | |
| | **subgroup = Not specified** | | | | | | | | | |
| Thailand | Nguanboonmak, A 2023 | 0 | 99 | 0.000 [ 0.000; 36.576] | 28.9% | Fair | Not specified | | Not specified | |
| Israel | Rottenstreich, M. 2022 | 24 | 626 | 38.339 [24.716; 56.510] | 71.1% | Good | RNA | Pfz | Booster | |
| | **Total (95% CI)** | | | **14.523 [ 0.000; 72.258]** | **100.0%** | | | | | |
| | Heterogeneity: $Tau^2 = 0.0096$; $Chi^2 = 7.61$, df = 1 (P < 0.01); $I^2 = 87\%$ | | | | | | | | | |

0 10 20 30 40 50 60

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# Should vaccination vs. no vaccination be used in pregnancy?

| Outcomes | Absolute Effect: With no vaccination | Absolute Effect: With vaccination | Relative effect (95% CI) | Certainty of the evidence GRADE |
|---|---|---|---|---|
| **Stillbirth, after the mother's vaccination in 1st or 2nd trimester with mRNA or viral vector vaccine** | 5 per 1000 | 1 per 1000<br>Difference: 4 fewer per 1000 patients (95% CI: 4 to 3 fewer per 1000 patients)<br>Based on data from 7107 patients in 1 study | **RR 0.17** (0.07 to 0.43) | ⨁⨁◯◯ LOW |
| **Stillbirth, after the mother's vaccination in 2nd trimester with mRNA or viral vector vaccine** | | | | |
| **Stillbirth, after the mother's vaccination in 3rd trimester with mRNA or viral vector vaccine** | | | | |
| **Stillbirth, after the mother's vaccination in any trimester with mRNA or viral vector vaccine** | | | | |

Summary of findings

Maternal-Pregnancy related outcomes

Infant safety

Effectiveness

# Should vaccination vs. no vaccination be used in pregnancy?

| Outcomes | Absolute Effect: With no vaccination | Absolute Effect: With COVID-19 vaccination | Relative effect (95% CI) | Certainty of the evidence GRADE |
|---|---|---|---|---|
| NICU hospitalization - 1st trimester (mRNA vaccines) | 56 per 1000 | 48 per 1000 | RR 0.86 (0.674 to 1.097) | ⨁⨁◯◯ LOW |

Difference: 8 fewer per 1000 patients (95% CI: 18 fewer to 5 more per 1000 patients)

Based on data from 5602 patients in 1 study

NICU hospitalization - 2nd trimester (mRNA, Viral vector vaccines)

NICU hospitalization - 3rd trimester (mRNA, Viral vector vaccines)

NICU hospitalization - Any trimester (mRNA vaccines)

Summary of findings

Maternal-Pregnancy related outcomes

Infant safety

Effectiveness

# Should vaccination vs. no vaccination be used in pregnancy?

| Outcomes | Absolute Effect: With no vaccination | Absolute Effect: With COVID-19 vaccination | Relative effect (95% CI) | Certainty of the evidence GRADE |
|---|---|---|---|---|
| **Severe or hospitalized COVID-19 in mothers - mRNA vaccine (omicron/alpha/other dominance)** Follow-up: range 31 days to 365 days | 31 per 1000 | 1000 per 1000 | OTHER 72 (42 to 86) | ⨁⨁◯◯ LOW |

Difference: 969 more per 1000 patients (95% CI: 86 to 13 fewer per 1000 patients)
Based on data from 34495 patients in 4 studies

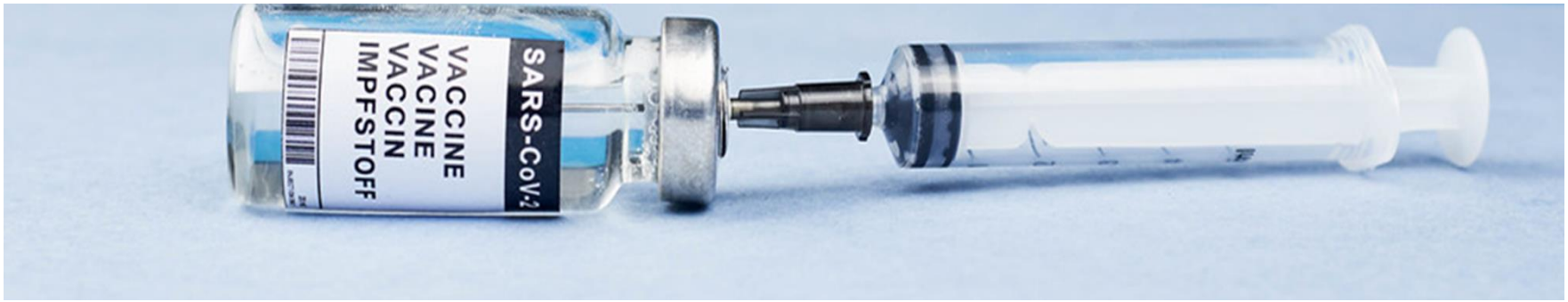
**Severe or hospitalized COVID-19 in mothers - Inactivated vaccine (omicron/delta/other dominance)**

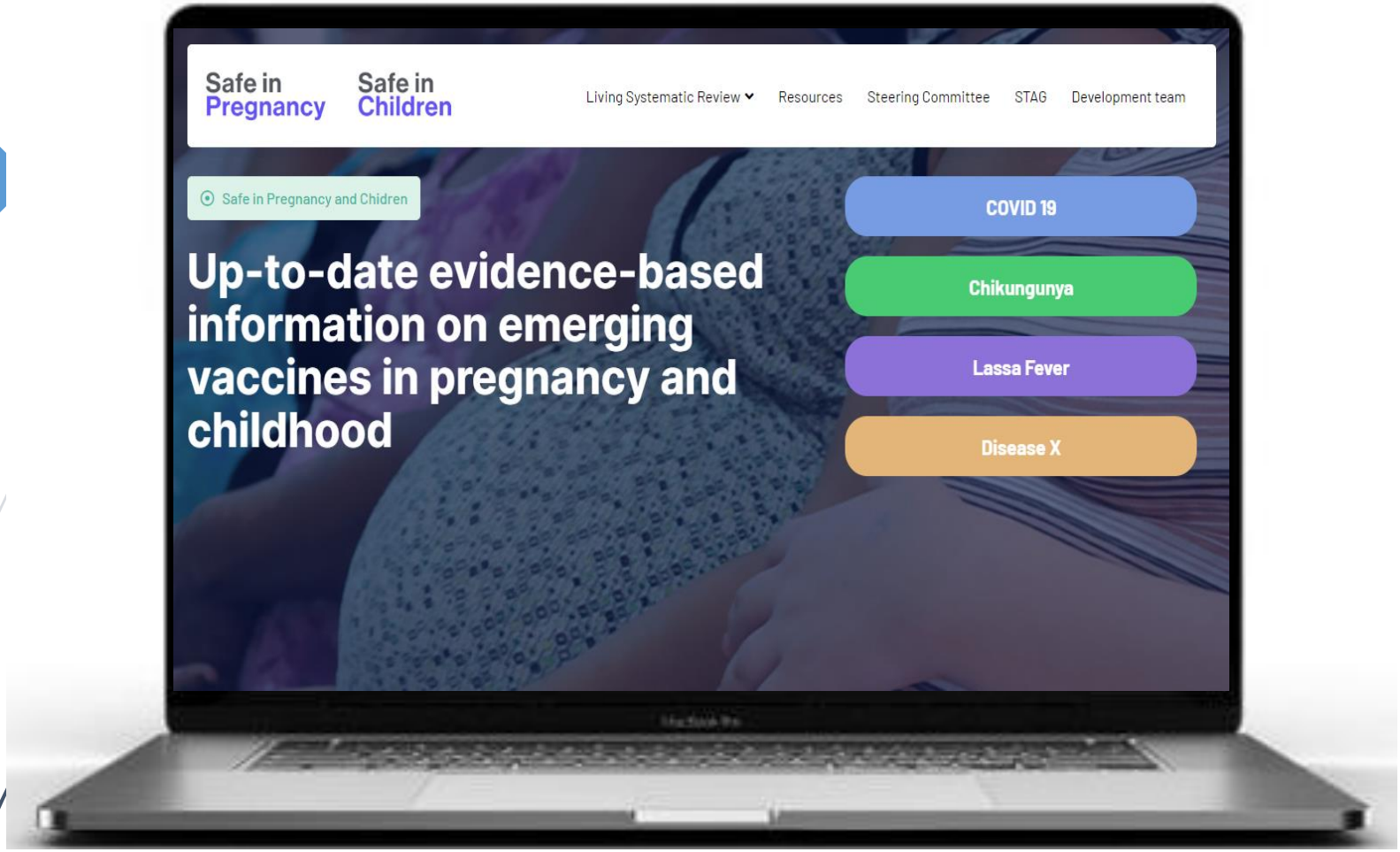
**Severe or hospitalized COVID-19 in mothers - Viral vector (omicron dominance)** Follow-up: range 1 months to 9 months

**Severe or hospitalized COVID-19 in mothers - mRNA/viral vector vaccine (omicron dominance)** Follow-up: range 13 days to 365 days

# Conclusions

We consider that the tool developed is useful for decision-makers in the area of health, since it allows to visualize and have the synthesis of relevant evidence, and specific according to their specific needs regarding the possible benefits and harms of vaccines against COVID-19 for pregnant people.



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