A Systematic Review and Meta-Analysis of Interventions Aimed at Delabeling Low-Risk Penicillin Allergies with Consideration for Sex and Gender

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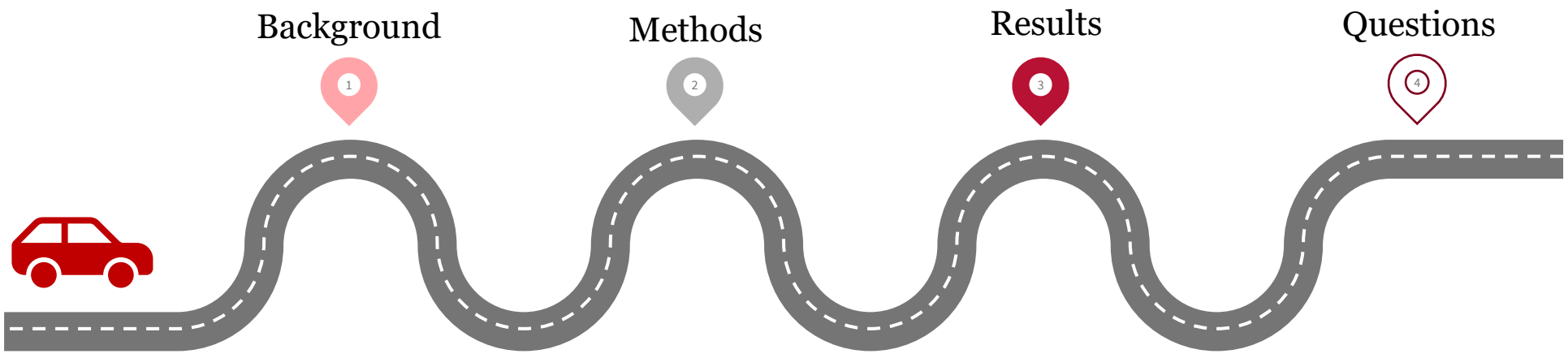
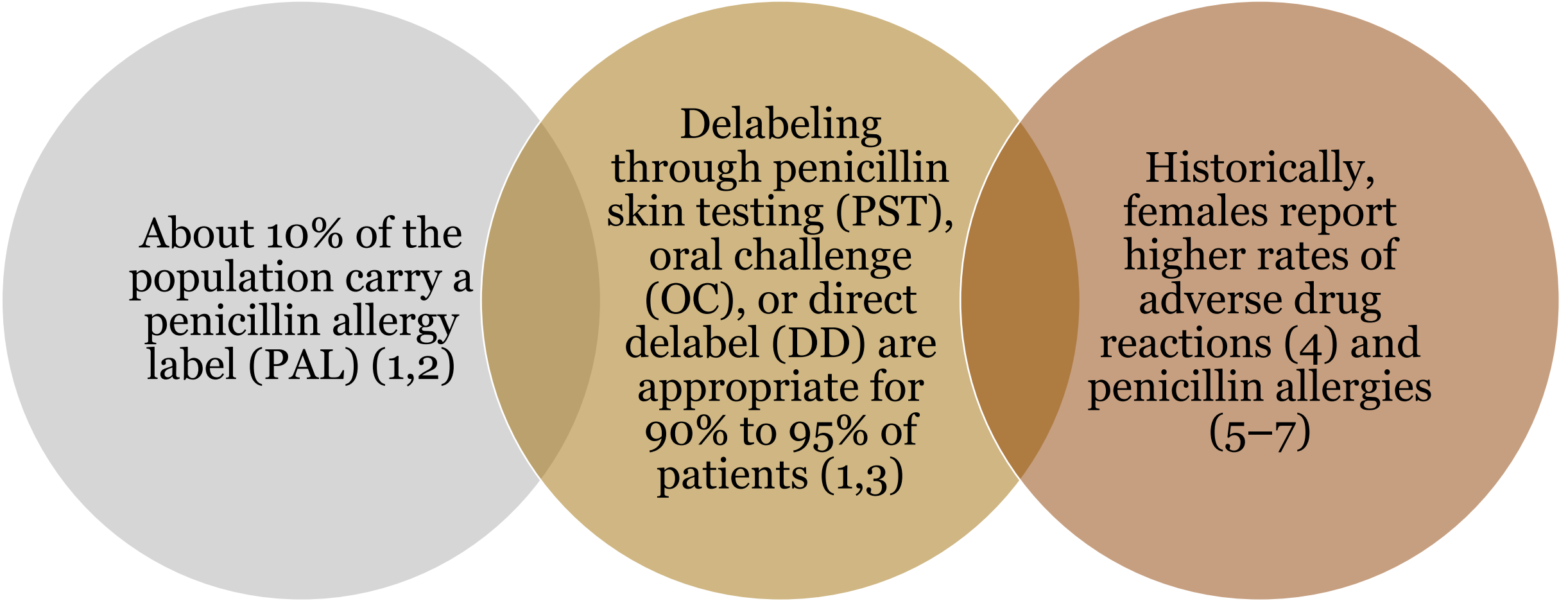
Overview and Plan



Background


About 10% of the population carry a penicillin allergy label (PAL) (1,2)
Delabeling through penicillin skin testing (PST), oral challenge (OC), or direct delabel (DD) are appropriate for 90% to 95% of patients (1,3)
Historically, females report higher rates of adverse drug reactions (4) and penicillin allergies (5–7)

Sex and Gender Based Analyses (SGBA) in Health Research

Biologic sex influences pharmacokinetics, pharmacodynamics, and drug response [8]

Female sex is associated with more adverse drug reactions and hypersensitivity [4-6]

Gender roles, stigma or discrimination **may lead to implicit bias in healthcare delivery** [9] and unintended biased decisions [10]

AIM OF THE SYSTEMATIC REVIEW AND META-ANALYSIS

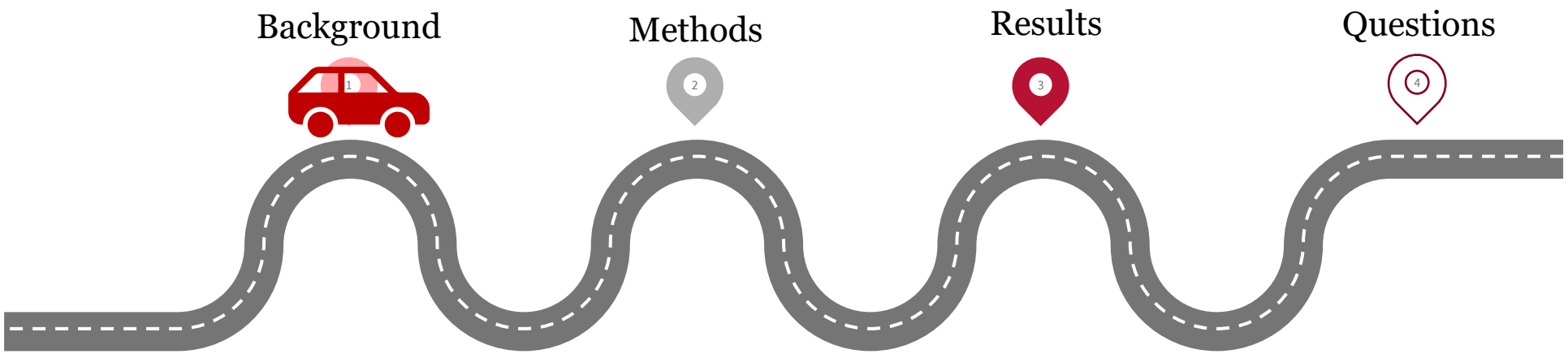
Identify, assess quality of, and synthesize results from studies reporting on the effectiveness and safety of delabeling interventions

Sex and Gender-Based Analysis Plus (SGBA+) information was extracted

Interventions and Outcomes of Interest

Population	Interventions	Comparator	Outcome
• Adult patients with low-risk penicillin allergies	• Direct Delabel (DD) • Oral Challenge (OC)	• Penicillin skin testing (PST) • Any other intervention • No intervention	• Successful delabeling defined as removal of the penicillin allergy label (PAL)

Overview and Plan



Methods

A co-design strategy involved clinicians, a public citizens' council, administrative and leadership personnel

RCTs and non-randomized studies including adult patients with reported penicillin allergies where the primary outcome was patients with PAL

Databases searched: PubMed, Cochrane Database of Systematic Reviews, International Pharmaceutical Abstracts, Ovid MEDLINE, Ovid EMBASE, ClinicalTrials.gov, and medRxiv inception to October 2023 and updated in February 2024

PROGRESS[11] (place of residence, race/ethnicity/culture, language, occupation, gender/sex, religion, education, socioeconomic status, and social capital) to identify factors that may impact health equity

The Effective Public Health Practice Project (EPHPP) Quality Assessment Tool[12] for Quantitative Studies

Data Synthesis

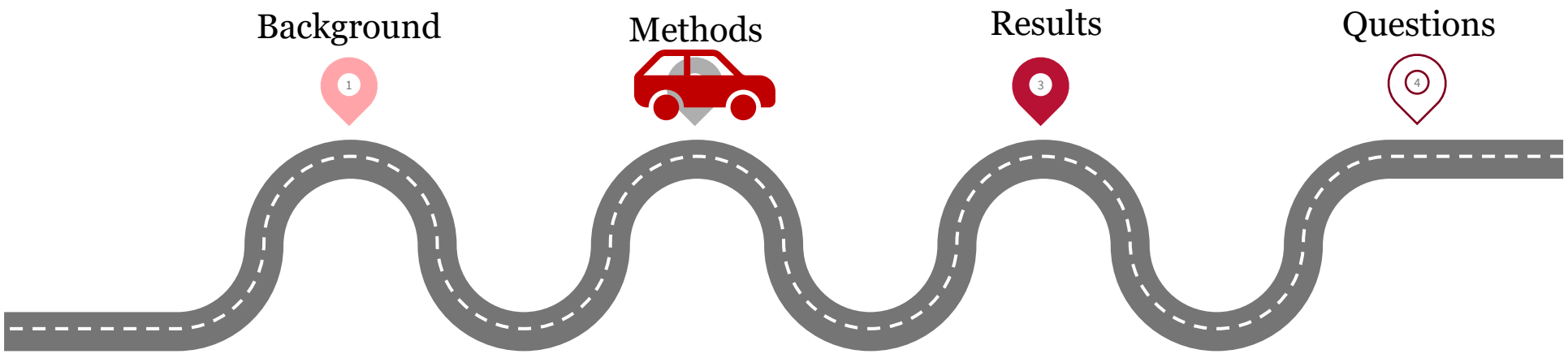
For randomized controlled trials (RCTs) intervention effect is expressed using relative risks (RR) and risk difference (RD)

For quasi-experimental studies, a random-effects proportional meta-analysis was conducted

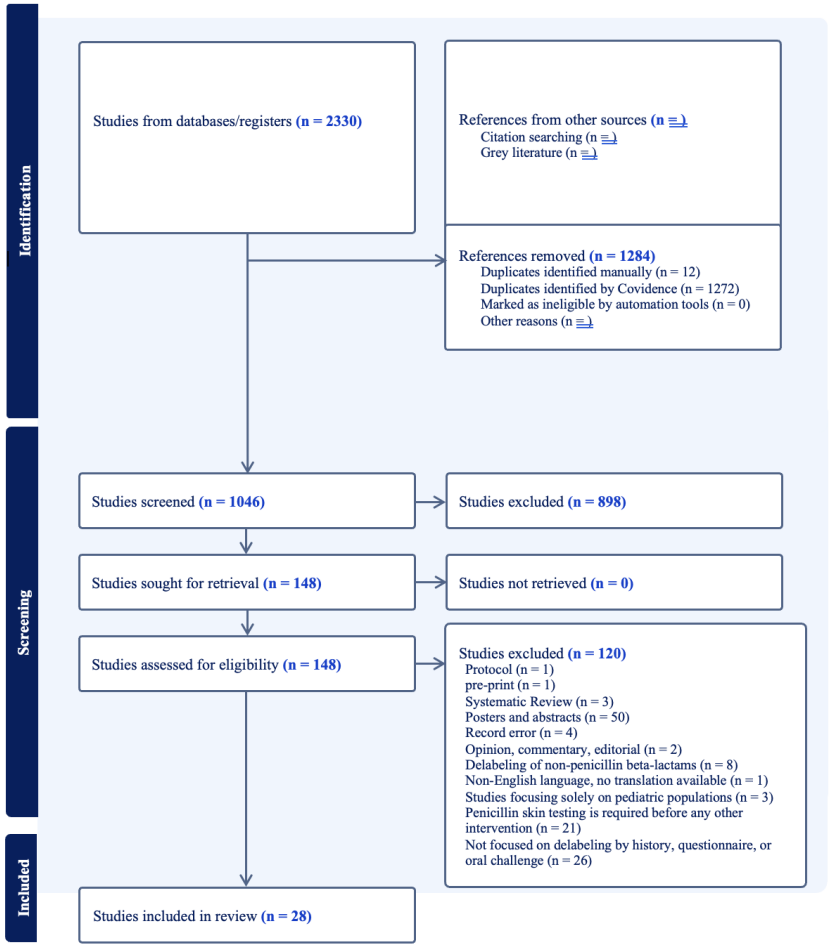
Heterogeneity was quantified using the I^2 statistic

Pre-defined subgroup analyses were conducted

Overview and Plan



Results: PRISMA Diagram



- 1046 citations screened
  - 28 studies included
- 2 (7%) were RCTs
  - OC vs. PST
- 26 (93%) were quasi-experimental
  - 2 included only DD
  - 16 included OC only
  - 8 included both DD and OC

Population Characteristics

Appendix B: Proportion of Female Participants in Included Studies

First Author	Year	Number of Females	% Females	Mean (SD) age
Tucker	2017	NR	NR	NR
Trubiano	2018	25	54%	56 (32)[T]
duPlessis	2019	156	62%	65 (30)[T]
Iammatteo	2019	120	77%	52 (NR)
Mustafa	2019	246	68%	35 (25)
Savic	2019	NR	NR	NR
Devchand	2019	65	61%	68 (22)[T]
Kuruvilla	2019	40	80%	59 (63)[TT]
Ramsey	2020	34	71%	65 (16)
Stevenson	2020	93	56%	42 (76)[T]
Chau	2021	738	60%	66 (26)[T]
Gateman	2021	72	73%	43 (16)
Sneddon	2021	68	61%	61 (18)
Zhang	2021	28	100%	35 (5)
Song	2021	NR	NR	NR
Ham	2021	34	68%	58 (66)[TT]
Steenvoorden	2021	33	58%	68 (19)
Livirya	2022	115	71%	73 (NR)
Koo	2022	93	45%	58 (21)[T]
Fanizza	2022	34	49%	70 (75)[T]
Trubiano	2022	767	57%	66 (NR)
Mak	2022	216	100%	34 (4)
Fransson	2022	134	66%	50 (24)[T]
Copaescu	2023	116	62%	52 (28)[T]
Rozario	2023	44	54%	64 (NR)
Wade	2023	NR	NR	NR
Stollings	2023	9	38%	62 (14)[T]
Alnaes	2023	92	62%	48 (74)[T T]

Legend:
IQR: Interquartile Range; NR: Not Reported; SD: Standard Deviation
[T] Median (IQR), [TT] Median (range)

- Mean age: 56 years, range: 34 to 73 years
  - 24 studies (85%)
- 61% female proportion in 22 studies; 2 studies included exclusively pregnant people
  - Sex reported in 24 studies (86%)
- Five studies (18%) included male and female participant demographic variables at baseline
- Ten studies (36%) reported ethnicities of participants
  - 88% were Caucasian, 2% Hispanic, 2% Black, 2% Pacific Islander, 1% Asian, 4% other ethnicity not defined, and <1% multiracial

Quality Assessment

Appendix C: Effective Public Health Practice Project Quality Assessment Tool

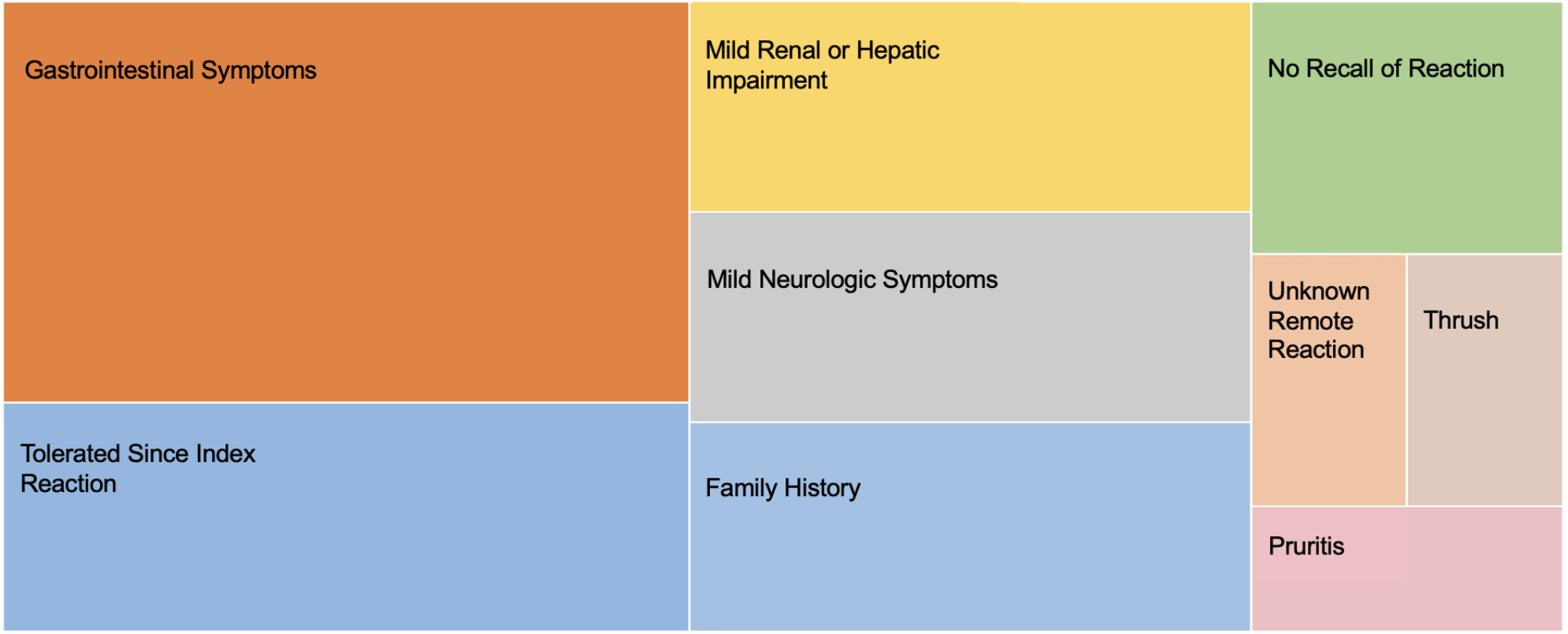
First Author	Year	Selection Bias	Study Design	Confounders	Blinding	Data Collection Method	Withdrawals and Dropouts	Overall
Alnæs MB	2023	🔴	🔴	🔴	🔴	🔴	N/A	🔴
Chua, K	2021	🟡	🔴	🟢	🔴	🟡	N/A	🔴
Copaescu, A	2023	🟢	🟢	🔴	🟡	🟢	🟢	🟡
Devchand, M	2019	🟢	🔴	🔴	🔴	🟡	N/A	🔴
duPlessis, T	2019	🟡	🔴	🔴	🔴	🔴	🟢	🔴
Fanizza FA	2022	🟡	🔴	🔴	🟡	🔴	N/A	🔴
Fransson, S	2022	🟡	🔴	🔴	🟡	🔴	🔴	🔴
Gateman, DP	2021	🟢	🔴	🔴	🟡	🔴	N/A	🔴
Ham, Y	2021	🔴	🔴	🔴	🟡	🔴	N/A	🔴
Iammatteo, M	2019	🟡	🟢	🔴	🔴	🔴	🟢	🔴
Koo, G	2022	🟢	🔴	🔴	🟡	🔴	N/A	🔴
Kuruvilla, M	2019	🟡	🔴	🔴	🟡	🔴	N/A	🔴
Livirya, S	2022	🔴	🔴	🔴	🔴	🔴	N/A	🔴
Mak, R	2022	🔴	🔴	🔴	🟡	🟢	N/A	🔴
Mustafa, S	2019	🔴	🟢	🔴	🔴	🔴	🟡	🔴
Ramsey, A	2020	🔴	🔴	🔴	🔴	🔴	N/A	🔴
Rozario, C	2023	🟡	🔴	🔴	🟡	🔴	N/A	🔴
Savic, L	2019	🔴	🔴	🔴	🔴	🔴	🟡	🔴
Sneddon, J	2021	🟡	🔴	🔴	🔴	🔴	🔴	🔴
Song, YC	2021	🔴	🔴	🔴	🔴	🔴	🔴	🔴
Steenvoorden, L	2021	🟡	🔴	🔴	🔴	🔴	N/A	🔴
Stevenson, B	2020	🟡	🔴	🟡	🔴	🔴	N/A	🔴
Stollings, J	2023	🟡	🔴	🔴	🟡	🟡	N/A	🔴
Trubiano, J	2022	🟡	🔴	🔴	🔴	🟡	N/A	🔴
Trubiano, JA	2018	🟡	🔴	🔴	🟡	🔴	N/A	🔴
Tucker, MH	2017	🔴	🔴	🔴	🔴	🔴	N/A	🔴
Wade, S	2023	🔴	🔴	🔴	🔴	🟡	🔴	🔴
Zhang, BY	2021	🔴	🔴	🔴	🟡	🔴	🔴	🔴

Legend	Colour
Strong	🟢
Moderate	🟡
Weak	🔴

Themes with Definitions of Low-Risk: 11 DD Studies

- 11 studies included DD and 9 themes emerged

Appendix E: Direct Delabel Themes within Definitions of Low-Risk Across 11 Studies



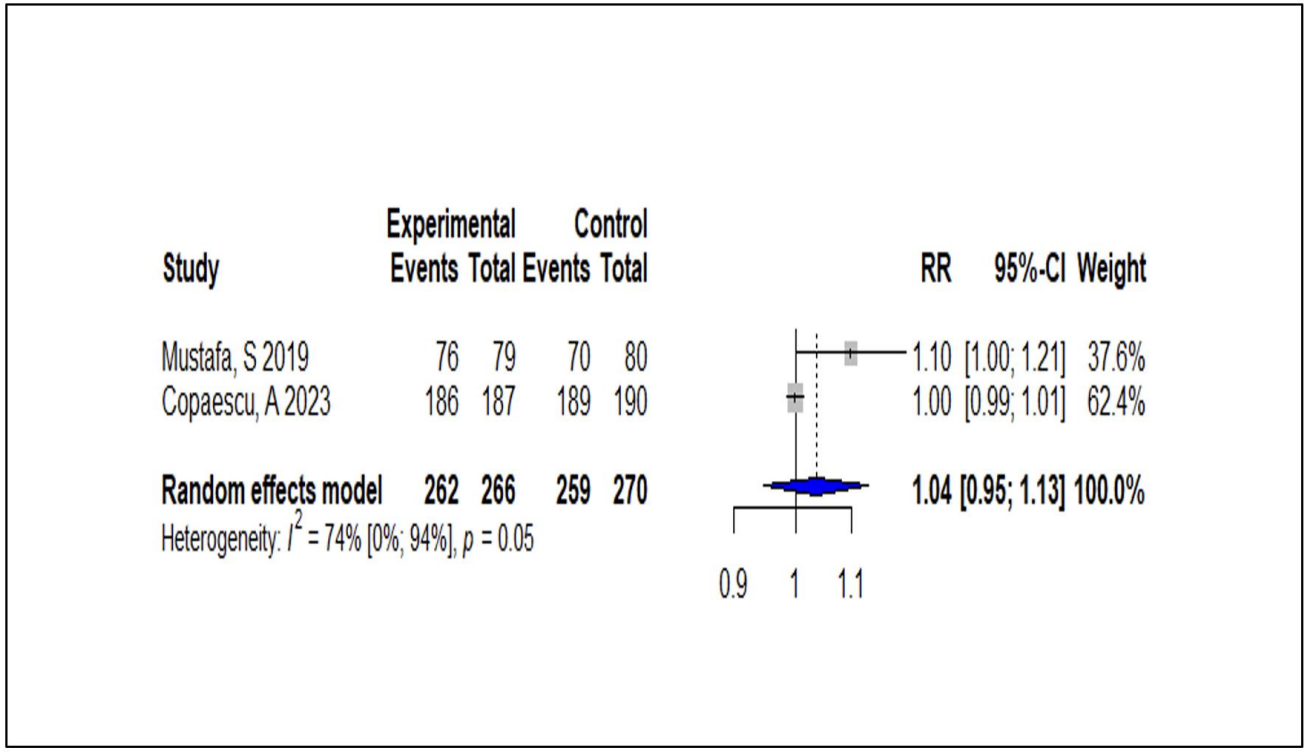
Themes with Definitions of Low-Risk: 26 OC Studies

- 26 studies that included OC and 7 major themes were identified

Appendix F: Oral Challenge Themes within Definitions of Low-Risk Across 26 Studies

Effectiveness of Interventions: RCTs

Figure 1: *Random Effects Meta-Analysis of Randomized Controlled Trials*



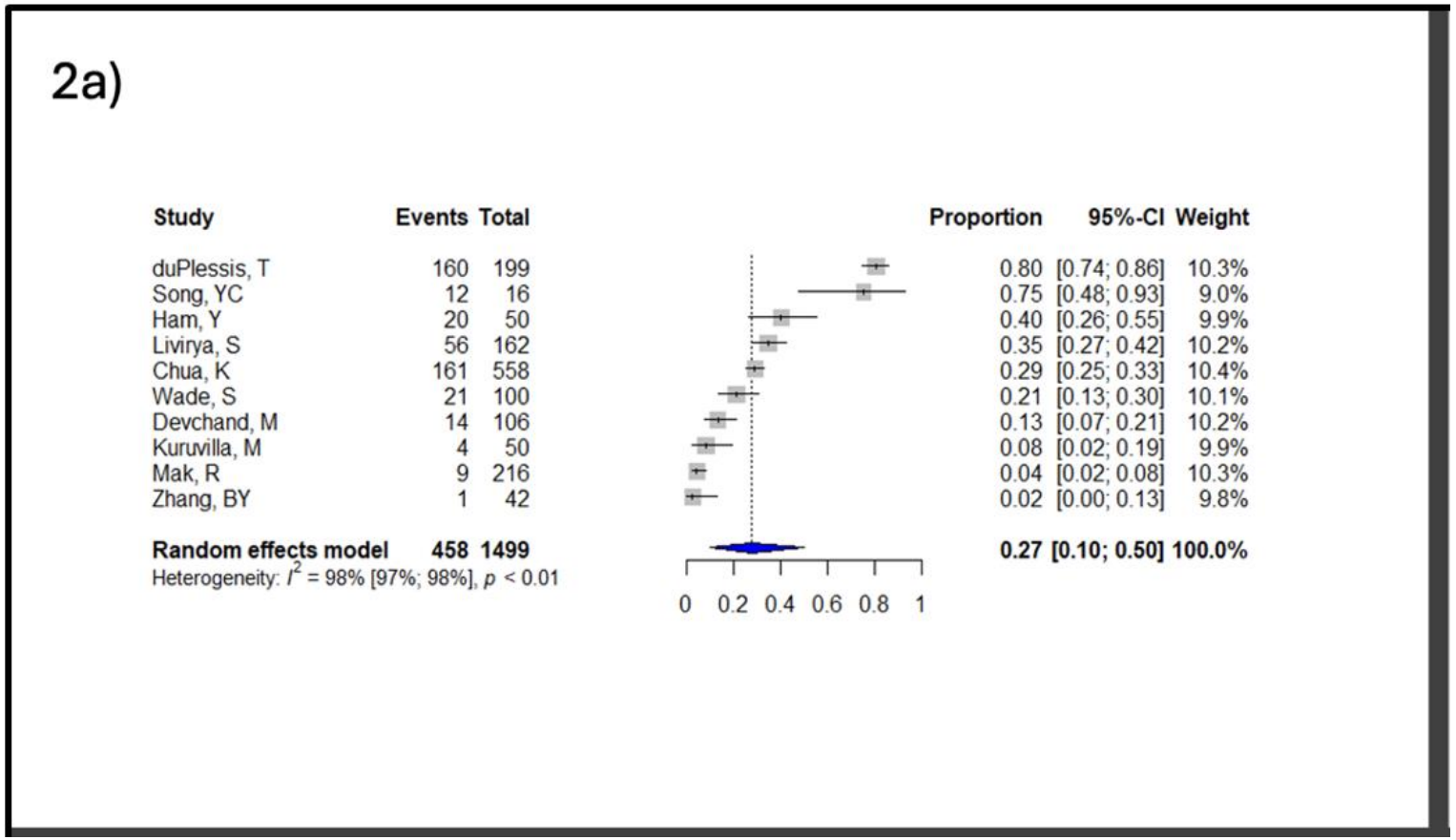
Oral Challenge (OC)

OC showed no difference from PST

2 studies, RR 1.04;
(95% CI 0.95, 1.13), I^2=74%

The pooled RD was 0.03
(95% CI 0.05, 0.12)

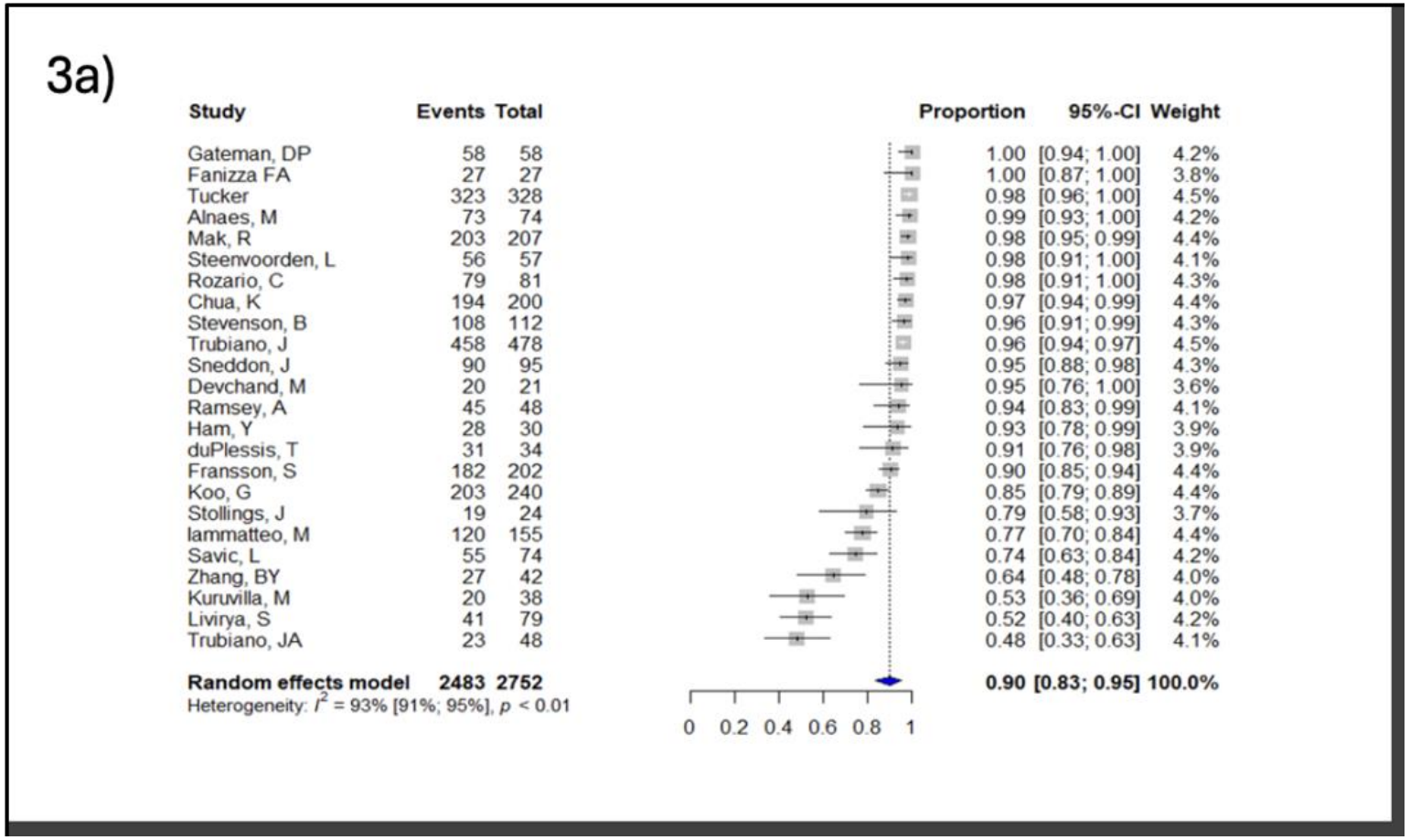
Effectiveness of Interventions



Direct Delabel (DD)

- 1,499 participants
- 27% (95%CI 10%, 50%) of participants had the allergy label removed
- High degree of between study heterogeneity (I^2= 96%)

Effectiveness of Interventions



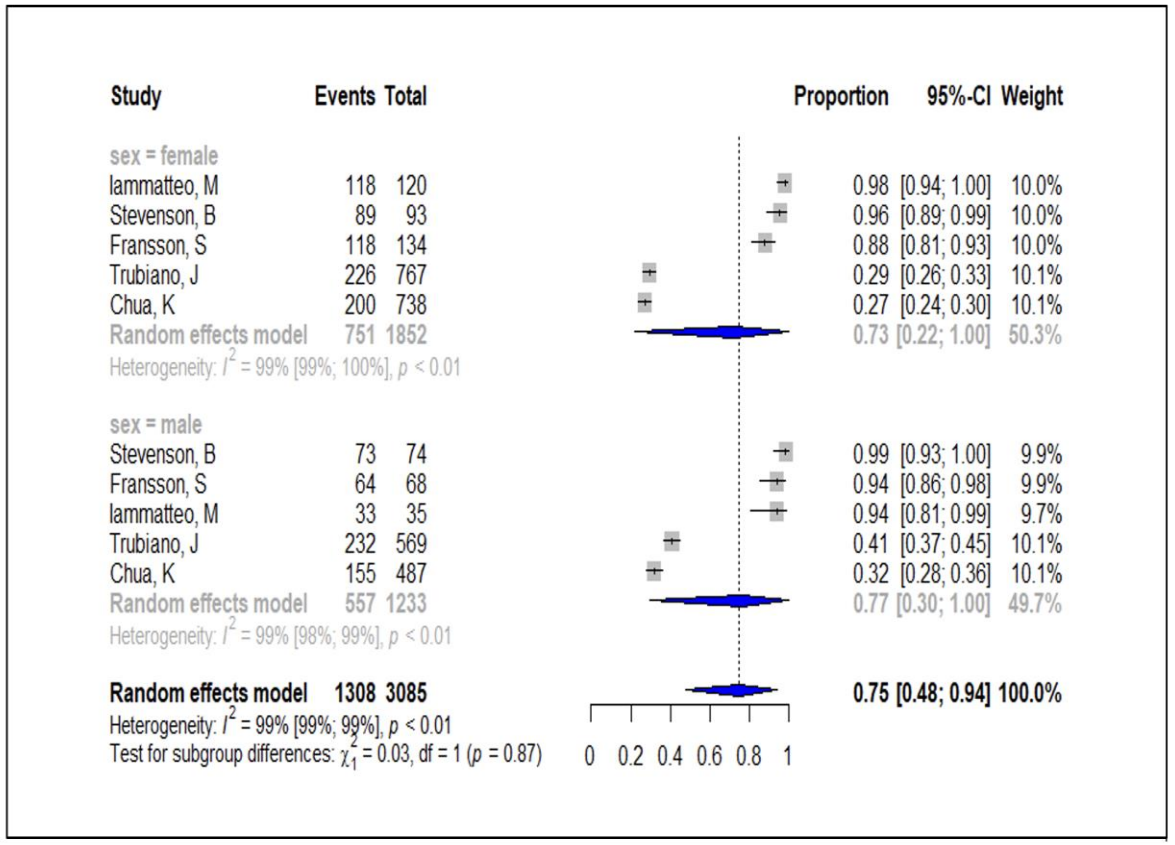
Oral Challenge (OC)

- 2,752 participants
- 24 quasi-experimental studies
- 90% (95%CI 83%, 95%) of participants had allergy label removed
- High degree of heterogeneity (I^2= 93%)

Sex Disaggregated Outcomes

- 5 studies sex disaggregated outcomes
  - 73% females delabeled
    - (22%; 100%), I^2=99%
  - 77% males delabeled
    - (48%; 94%), I^2=99%
  - No significant sex differences
    - (p = 0.87)
  - High degree of heterogeneity

Figure 4: *Random Effects Meta-Analysis for Sex Disaggregated Oral Challenge Efficacy Outcomes*



PROGRESS FACTORS

Race and ethnicity often used interchangeably and without definitions

None described lived gender of the participants, culture, language, occupation, religion, education, socioeconomic status, or social capital

None of the studies were conducted in middle- or lower-income countries

Safety of Oral Challenge

Appendix G: Reported Reactions to OC (26 Studies)

First author	Number (%) of reactions on oral challenge	Comments
Alnaes	1 (1%)	Non-severe rash
Chau	9 (5%)	Six patients had a positive oral challenge, and 3 patients reported a non-immune-mediated reaction to oral challenge (1 fever [38.1°C, concurrent urosepsis], 1 vomiting, and 1 pruritis without rash)
Copaescu	1 (1%)	1 immune mediated reaction in both the OC and PST arms
Devchand	NR	No follow up once delabeling completed
duPlessis	3 (9%)	Of those with a reaction on direct delabel, the reactions were nausea, vomiting or headache
Fanizza	0 (0%)	No reactions were described for patients in the oral challenge arm
Fransson	20 (10%)	19 cutaneous symptoms, 1 hyperventilation. 13 of 19 individuals with cutaneous reactions experienced symptoms 3 days after OC
Gateman	3 (3%)	3 pediatric patients had a reaction, none of the adult patients had a reaction
Ham	2 (7%)	Two patients retained their allergy label due to mild reactions in the two-step challenge
Iammatteo	19 (12%)	16 people experienced a reaction to placebo, not included in reaction to oral challenge. Of those with reaction to oral challenge, 4 were allergic and 15 were non-allergic reaction types but included in this table
Koo	NR	
Kuruvilla	3 (15%)	3 reactions reported: chest tightness, pruritis and dizziness. All resolved within minutes and no treatment required, not considered a positive reaction in this study
Livirya	4 (10%)	Description of reactions not reported. Relabeling on follow-up
Mak	4 (2%)	No immediate hypersensitivity, 4 delayed cutaneous reactions, 1 vomiting (unrelated to challenge)
Mustafa	3 (4%)	No reactions in PST arm, 3 cutaneous reactions (treated with antihistamines) in OC arm
Ramsey	3 (6%)	1 rash with amoxicillin/clavulanate on day 17 of therapy (10 days after discharge), 1 facial swelling and nausea/vomiting with amoxicillin/clavulanate on the day after the challenge, and 1 from the PST group experienced a rash with cefazolin on day 17 of cefazolin therapy
Rozario	2 (2%)	Of the 79 patients who were delabeled, allergy label was only removed from EMR for 64 (81%) and 2 cases of delayed reactions were noted
Savic	1 (2%)	One patient developed urticaria in her hands after the second dose and stopped taking the amoxicillin. On questioning, it was discovered that her index reaction had been of widespread urticaria, but she had chosen not to disclose this to the study team previously as she was keen to be tested
Sneddon	1 (1%)	1 patient did not have a documented success or failure rate and was therefore deemed non-successful, but no reaction was reported
Steenvoorden	2 (4%)	1 admitted patient had worsening of ongoing bronchial obstruction symptoms, resolved with ipratropium bromide-salbutamol inhalation. This patient could not be delabeled although likely not an IgE reaction. One other patient reported a mild maculopapular rash 2 days after oral challenge - no need for treatment and was delabeled
Stevenson	6 (4%)	Direct challenge was performed for both low and moderate risk and described in the supplementary material
Stollings	NR	No oral challenge completed
Trubiano	20 (4%)	10 immune mediated (9 delayed rash, 1 immediate rash, 1 decreased consciousness, 1 self-resolving throat tightness, 1 fever, and 1 unknown); none required epinephrine) and 10 non-immune mediated.
Trubiano	0 (0%)	All patients who received the oral challenge tolerated it
Tucker	5 (2%)	Description of reactions not reported.
Zhang	NR	No reactions reported

Legend
NR: None Reported; OC: Oral Challenge; PST: Penicillin Skin Test; EMR: Electronic Medical Record

- Average of 4% of participants who experienced non-severe reactions
- **None reported severe reactions** such as severe cutaneous delayed reactions, hepatic or renal impairment, neurological deficits, or anaphylaxis

CONCLUSION

Direct delabeling and oral challenge interventions are **effective for delabeling low-risk penicillin allergies**

Comprehensive data is **lacking on sex and gender differences**, indicating a need for further research.

Acknowledgements

- PhD Committee:
  - Dr. JM Gamble
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  - Ontario Graduate Scholarship (OGS)
  - President's Graduate Scholarship (PGS)
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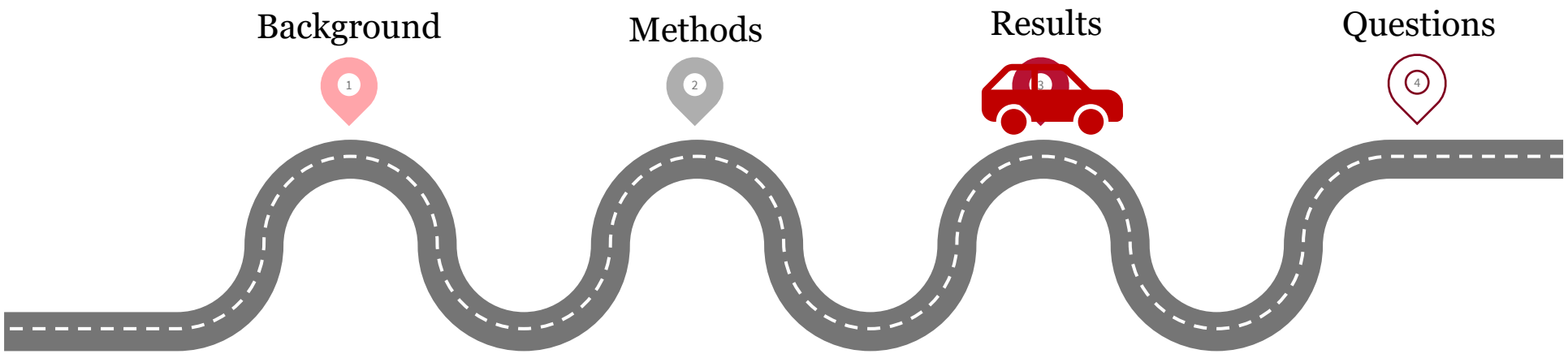
Overview and Plan



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