A Report on "Antibiotic prophylaxis for childbirth-related perineal trauma: A systematic review and meta-analysis" by Armstrong et al. (2025)

Reviewer 2

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> I am wiser than this person; for it is likely that neither of us knows anything fine and good, but he thinks he knows something when he does not know it, whereas I, just as I do not know, do not think I know, either. I seem, then, to be wiser than him in this small way, at least: that what I do not know, I do not think I know, either.
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> Plato, *The Apology of Socrates*, 21d

> To err is human. All human knowledge is fallible and therefore uncertain. It follows that we must distinguish sharply between truth and certainty. That to err is human means not only that we must constantly struggle against error, but also that, even when we have taken the greatest care, we cannot be completely certain that we have not made a mistake.
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> Karl Popper, 'Knowledge and the Shaping of Reality'

Overview

Citation: Armstrong, H., Whitehurst, J., Morris, R. K., Hodgetts Morton, V., & Man, R. (2025). Antibiotic Prophylaxis for Childbirth-Related Perineal Trauma: A Systematic Review and Meta-Analysis. *PLoS One*, 20(5), e0323267.

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Abstract Summary: This systematic review and meta-analysis evaluated the effectiveness of prophylactic antibiotics in preventing complications from perineal trauma across all types of childbirth-related perineal trauma. The study found that prophylactic antibiotics are associated with a reduced risk of perineal wound infection.

Key Methodology: Systematic review and meta-analysis of 14 studies (8 RCTs, 6 observational) involving 8,878 women, using a random effects model to combine results.

Research Question: What is the effectiveness of prophylactic antibiotics for preventing complications from perineal trauma across all types of childbirth-related perineal trauma?

Summary

Is It Credible?

Armstrong et al. present a systematic review and meta-analysis evaluating the effectiveness of prophylactic antibiotics for preventing complications following childbirth-related perineal trauma. The authors conclude that prophylactic antibiotics are associated with a reduced risk of perineal wound infection across all types of tears, reporting a relative risk of 0.57 when combining observational and randomized data, and 0.51 when restricting the analysis to randomized controlled trials (pp. 10–12). While the review successfully highlights critical gaps in the current evidence base, its headline quantitative claims are compromised by significant methodological limitations and clinical heterogeneity.

A pressing issue is the review's heavy reliance on a single, non-representative study for its primary aggregate estimates. In the rigorous randomized controlled trial sensitivity analysis for perineal infection, a secondary analysis of the ANODE trial accounts for 84.6% of the statistical weight (p. 12). Because the ANODE trial exclusively enrolled women who underwent operative (assisted) vaginal deliveries, the pooled estimate is heavily skewed toward a specific, high-risk population. However, it is important to note that the authors did perform a subgroup analysis by tear type which demonstrated a statistically significant reduction in infection even for first and second-degree tears (RR 0.50), a subgroup that excludes the high-risk ANODE data (p. 14). Thus, while the *magnitude* of the overall pooled effect is driven by the high-risk study, the *existence* of a benefit appears to persist across risk strata, a nuance that the top-line summary does not fully highlight.

Furthermore, the meta-analysis pools data from studies with profound clinical heterogeneity. The definition of perineal wound infection varied drastically across the included literature, ranging from strict microbiological criteria to subjective clini-

cal signs. One influential study relied on a proxy measure—clinician prescribing behavior—rather than direct diagnosis (p. 7). The interventions were equally disparate, encompassing various antibiotic classes, administration routes, and durations (pp. 6–9). Aggregating such conceptually and pharmacologically distinct variables into a single summary effect estimate produces a clinically ambiguous result that does not map onto any specific treatment protocol. The inclusion of a trial conducted exclusively in a cohort of HIV-infected women further introduces immunological heterogeneity, though the authors appropriately flag this as a limitation to generalizability (p. 15).

The authors' decision to include observational studies in their primary analysis also weakens the top-line findings. All six observational studies were judged to be at critical or serious risk of bias (p. 10). While the authors responsibly provide an analysis restricted to randomized trials to mitigate this, leading with a pooled analysis of confounded observational data and randomized trials risks presenting a statistically precise but potentially misleading primary result. Additionally, the review's finding regarding wound dehiscence requires careful interpretation. While a pooled analysis of all studies showed a significant reduction (RR 0.60), the more rigorous RCT-only analysis found no significant benefit (RR 0.77), with a very wide confidence interval of 0.37 to 1.58 (p. 12). This suggests the RCT finding is likely underpowered and inconclusive rather than definitive evidence of no effect.

Finally, the clinical utility of the review is constrained by a lack of context regarding baseline risk and potential harms. A relative risk reduction translates to vastly different absolute benefits depending on a patient's underlying risk of infection, which varied widely across the included studies. Moreover, the review acknowledges a near-total absence of data on adverse events, such as allergic reactions or antimicrobial resistance (p. 15). Without an accounting of these harms, it is impossible to assess the true net benefit of widespread prophylactic antibiotic use. Ultimately, while the review makes a valuable contribution by systematically mapping the poor

state of the literature and identifying the urgent need for better research, its specific quantitative estimates should not be viewed as a definitive guide for clinical practice.

The Bottom Line

The review provides a comprehensive overview of the literature, but its headline claim that prophylactic antibiotics reduce perineal infection across all types of childbirth-related trauma requires nuance. The aggregate quantitative findings are heavily influenced by a single trial focused exclusively on high-risk, assisted deliveries, though subgroup analyses suggest the benefit may extend to lower-risk spontaneous births. Coupled with high clinical heterogeneity and a lack of data on potential harms, the meta-analysis highlights the urgent need for better research rather than offering a reliable estimate of clinical benefit.

Potential Issues

Over-reliance on a single, non-representative study: The review's main conclusions are heavily influenced by a single study, Humphreys et al., which is a secondary analysis of the ANODE trial. This single study accounts for 55.9% of the weight in the primary meta-analysis for perineal infection and a dominant 84.6% in the more rigorous RCT-only analysis (pp. 10, 12). This means the review's aggregate quantitative findings are less a synthesis of a broad evidence base and more a reflection of this one trial. This is a significant issue because the ANODE trial exclusively studied women who had an operative (assisted) vaginal delivery, a specific high-risk population. However, it is crucial to note that the authors did conduct a subgroup analysis for "1st/2nd degree tear or episiotomy" (excluding ANODE) which still showed a significant reduction in infection (RR 0.50) (p. 14). Therefore, while the *weight* of the evidence is skewed, the *conclusion* that antibiotics reduce infection appears to hold across tear types, a distinction that clarifies the generalizability of the findings.

Failure to contextualize findings by baseline risk: The review reports a single relative risk (RR) of 0.57 for infection and a single Number Needed to Treat (NNT) of 15, but does not adequately discuss how the clinical meaning of these figures changes with baseline risk (pp. 12–13). The included studies show a more than tenfold variation in the baseline risk of infection in the control groups, ranging from approximately 2% to over 36%, as calculated from the data presented in the forest plots (pp. 10, 12). A relative risk reduction is not a constant measure of clinical impact; a 43% reduction in risk has vastly different absolute benefit when the starting risk is 2% versus 36%. While the authors do provide a single Absolute Risk Reduction of 6.6% based on the RCT data (p. 13) and acknowledge the difference between their population and the ANODE trial, the lack of a structured discussion on how the NNT would vary across different risk strata is a significant omission in interpretation.

Heterogeneity of outcome definitions and interventions: The meta-analysis pools data from studies with profound clinical heterogeneity, which makes the summary effect estimate difficult to interpret. The primary outcome, "perineal wound infection," was defined in widely disparate ways across studies, including strict microbiological criteria and various combinations of clinical signs (pp. 7–9, 15). One major study (Humphreys et al.) used a proxy measure—"new prescription of antibiotics"—rather than a direct clinical diagnosis (p. 7). Similarly, the intervention, "prophylactic antibiotics," encompassed a wide variety of drugs, routes (intravenous, oral, topical), and durations (from a single dose to seven days) (pp. 6–9). The authors acknowledge these as limitations (p. 15), but pooling such conceptually different outcomes and pharmacologically distinct interventions into a single effect estimate produces an uninterpretable average that does not correspond to a specific clinical scenario.

Inclusion of observational studies in the primary analysis: The review's primary analyses for both perineal infection and wound dehiscence combine data from randomized controlled trials (RCTs) with data from observational studies (pp. 10–11). The authors justify this by noting the scarcity of RCT evidence for certain populations (p. 3). However, this methodological choice is debatable for a review assessing the effectiveness of an intervention. The authors' own risk of bias assessment found that all six included observational studies were at "critical or serious risk of bias" (p. 10). By leading with a pooled analysis that includes this lower-quality evidence, the review risks presenting a statistically precise but potentially misleading result that gives undue weight to confounded data. While the authors mitigate this by providing a more appropriate RCT-only sensitivity analysis (pp. 11–12) and using it for GRADE assessments, the prominence given to the mixed-design analysis remains a structural weakness.

Inadequate analysis of harms: The review concludes that prophylactic antibiotics reduce infection risk but cannot provide a corresponding analysis of harms, which is

essential for assessing the net benefit of an intervention. The authors state that there was "scarce reporting of any potential harms in the included studies" (p. 15). This absence of data on adverse events—such as allergic reactions, antimicrobial resistance, or effects on the maternal and infant microbiomes—is a critical evidence gap. While the authors acknowledge this limitation and call for future trials to collect this data (p. 16), the lack of a structured discussion on how this void impacts any potential clinical recommendation leaves the assessment of the intervention's overall value incomplete.

Conclusion for wound dehiscence may be inconclusive due to low power: The review notes that for wound dehiscence, "prophylactic antibiotics were not found to be superior to placebo or control in our RCT only analysis" (p. 13). This conclusion is based on a non-significant result (RR 0.77) with a very wide 95% confidence interval of 0.37 to 1.58. This wide interval suggests the analysis, which included only five studies and 920 women, was likely underpowered to detect a clinically meaningful difference. The authors' phrasing risks being misinterpreted as evidence of no effect, when a more accurate interpretation is that the analysis is inconclusive due to insufficient statistical power.

Inclusion of a distinct HIV-positive cohort: The meta-analyses for infection include the Sebitloane et al. study, which was conducted exclusively in a cohort of HIV-infected women (p. 8). Women with HIV have an altered immune status, which may affect both their baseline risk of infection and their response to antibiotics. The authors acknowledge that including this trial may limit generalizability (p. 15). While excluding this study might actually strengthen the effect size (as its RR was 0.76, higher than the pooled estimate), the decision to pool this immunologically distinct population with the general obstetric population introduces significant clinical heterogeneity.

Lack of analysis by timing of antibiotic administration: The review notes that the timing of antibiotic administration varied across studies, with some given before re-

pair and some after, while for two studies the timing was unreported (pp. 4, 6–9). The timing of prophylaxis is a critical determinant of its efficacy. While the authors did perform subgroup analyses on the *route* of administration (p. 12), they did not perform any analysis based on timing. This limits the practical utility of the findings, as it provides no guidance on *when* antibiotics should be administered for optimal effect.

Overstated confidence in the absence of publication bias: The authors conclude that "Funnel plots suggest an absence of significant publication bias" (p. 13). However, funnel plot analysis and associated statistical tests like Egger's test have low statistical power to detect bias when the number of included studies is small, as it is here (12 for infection, 9 for dehiscence). Given this well-known limitation, concluding an "absence" of bias may be an overstatement; a more cautious interpretation would be that the analyses were underpowered to detect it.

Minor presentation and transparency issues: Several minor issues affect the clarity and replicability of the article. First, there are multiple inconsistencies in the cited publication years for studies between the text, tables, and reference list; for example, Cox is cited as both 2021 and 2022 (pp. 6, 10, 19). Second, the data for the influential Humphreys et al. study was derived by combining the numerator and denominator from two separate publications (p. 4). While the authors are transparent about this method, explicitly stating the exact numbers extracted from each source in the text, rather than only in the forest plot, would have improved ease of verification.

Future Research

Adequately powered trials for spontaneous vaginal births: Future research should prioritize large, randomized controlled trials specifically evaluating prophylactic antibiotics in women sustaining first- and second-degree tears or episiotomies during spontaneous vaginal births. This would ensure that efficacy estimates are not confounded by the higher baseline risks associated with operative deliveries.

Standardization of outcome measures: Future work must utilize validated, standardized tools for defining and measuring perineal wound infection and dehiscence. Moving away from highly variable clinical signs or proxy measures, such as subsequent antibiotic prescriptions, will ensure comparability across clinical settings and improve the reliability of future meta-analyses.

Comprehensive assessment of harms and baseline risk: Subsequent trials should rigorously track and report adverse maternal and neonatal outcomes, such as allergic reactions, antimicrobial resistance, and impacts on the microbiome. Additionally, researchers should stratify results by baseline infection risk and the timing of antibiotic administration to determine the true net clinical benefit of prophylaxis.

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