A Report on "Prophylactic Antibiotics in the Prevention of Infection After Operative Vaginal Delivery (ANODE): A Multicentre Randomised Controlled Trial" by Knight et al. (2019)

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: Knight, M., Chiocchia, V., Partlett, C., Rivero-Arias, O., Hua, X., Hinshaw, K., Tuffnell, D., Linsell, L., and Juszczak, E. (2019). Prophylactic Antibiotics in the Prevention of Infection After Operative Vaginal Delivery (ANODE): A Multicentre Randomised Controlled Trial. *Lancet*, Vol. 393, No. 10189, pp. 2395-2403.

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Abstract Summary: This multicentre randomised controlled trial investigated whether antibiotic prophylaxis prevented maternal infection after operative vaginal birth. The study found that significantly fewer women who received amoxicillin and clavulanic acid had a confirmed or suspected infection compared to those who received a placebo.

Key Methodology: Multicentre, randomised, blinded, placebo-controlled trial.

Research Question: Does antibiotic prophylaxis prevent maternal infection after operative vaginal birth?

Summary

Is It Credible?

Knight et al. present the results of the ANODE trial, a multicenter randomized controlled trial investigating whether a single intravenous dose of amoxicillin and clavulanic acid reduces maternal infection after operative vaginal delivery. The authors claim that this prophylactic intervention significantly reduces confirmed or suspected maternal infection within six weeks from 19% in the placebo group to 11% in the intervention group (p. 2395). They also report significant reductions in secondary morbidities, such as perineal wound infection and pain, and demonstrate that the intervention reduces healthcare resource use. Based on these findings, the authors advocate for a change in global guidelines to recommend routine antibiotic prophylaxis for operative vaginal births.

The headline claim of reduced infection is supported by a large sample size and a pragmatic design. However, the primary outcome of confirmed or suspected maternal infection is heavily driven by a subjective clinical decision, specifically a new prescription of antibiotics. While relying on a prescription as a proxy for infection can be problematic, the trial's findings are bolstered by statistically significant reductions in more objective secondary measures, including confirmed systemic infection on culture and deep incisional infections (p. 2400, Table 2). This alignment suggests that the clinical decisions to prescribe antibiotics were generally tracking genuine infectious complications.

The timing of the intervention complicates the interpretation of its prophylactic nature. The antibiotic was administered a median of 3.2 hours after delivery, with the protocol allowing administration up to six hours post-birth (pp. 2397, 2400). This delay, chosen pragmatically to minimize infant exposure, blurs the line between prophylaxis and early treatment of an incubating infection. Furthermore, supple-

mentary data reveal substantial heterogeneity in the treatment effect across the 27 participating hospitals, with some centers showing strong benefits and others showing none (p. S68, Table S10). While the authors report that a sensitivity analysis accounting for center effects did not alter the main conclusion, the clinical reasons for this variation remain unexplored in the main text (p. 2400).

The trial's methodological execution introduces notable uncertainties. Most significantly, the definition of the primary outcome was narrowed mid-trial to improve specificity. Supplementary materials indicate this change occurred after the Data Monitoring Committee reviewed interim data showing a null treatment effect under the original, broader definition (p. S67, Table A2). The authors state this change was made to focus only on infections preventable by the intervention (e.g., excluding prescriptions for unrelated chest infections) and that the core trial team remained blinded (p. 2397). While this rationale is logical for reducing noise, altering a primary endpoint after an unblinded committee reviews interim results inevitably introduces a risk of bias and weakens the confirmatory power of the trial. Additionally, the secondary outcomes, which rely on a six-week questionnaire, suffer from a 24% attrition rate (p. 2402). This loss to follow-up, combined with the authors' observation that respondents were more likely to be primiparous, limits the reliability of claims regarding perineal pain, wound breakdown, and outpatient visits.

The authors' secondary claims regarding cost-effectiveness and severe sepsis also require careful qualification. The trial was framed around the life-threatening risk of maternal sepsis, yet it was not powered to detect differences in this rare outcome, and the results showed no statistically significant reduction in systemic sepsis (p. 2400, Table 2). Similarly, while the authors highlight a reduction in healthcare resource use, the 99% confidence interval for the mean monetary cost difference crosses zero (-£115.10 to £9.90), meaning the total cost savings are not statistically significant according to the study's own pre-specified criteria (p. 2401; p. S63, Table S8). Finally, the recommendation for universal prophylaxis is made without a comprehensive as-

sessment of long-term harms. The trial did not routinely record non-serious adverse events and collected no specific data on the potential consequences of increased antibiotic use, such as antimicrobial resistance or disruptions to the infant microbiome, though the post-delivery timing was chosen specifically to mitigate direct infant exposure.

Ultimately, the ANODE trial provides compelling evidence that a post-delivery dose of antibiotics reduces short-term infectious complications and related morbidities. However, the mid-trial alteration of the primary outcome, the attrition rate for survey-based secondary endpoints, and the lack of data on long-term public health risks suggest that the findings, while clinically important, should be interpreted with a degree of methodological caution.

The Bottom Line

The ANODE trial offers robust evidence that administering amoxicillin and clavulanic acid after operative vaginal delivery substantially reduces short-term maternal infections and related perineal morbidities. However, the certainty of these findings is tempered by a mid-trial change to the primary outcome definition and attrition rates for secondary questionnaire data. Furthermore, while the short-term clinical benefits are clear, the authors' recommendation for universal prophylaxis does not fully account for unmeasured long-term risks, such as antimicrobial resistance.

Potential Issues

Primary outcome changed mid-trial: A significant methodological issue arises from the modification of the primary outcome definition during the trial. The article states the definition was refined on November 30, 2017, at the request of the Data Monitoring Committee (DMC) to improve specificity by including only antibiotic prescriptions for infections potentially preventable by the intervention (p. 2397). Supplementary materials show this change occurred after the DMC's first meeting on February 7, 2017, which reviewed interim data from approximately 11% of the final sample (p. S67, Table A2). This initial analysis, based on the original, broader outcome definition (any antibiotic use), showed no treatment effect (risk ratio 1.00, 95% CI 0.73–1.37) (p. S67). The authors argue this change was necessary to remove "noise" from unrelated prescriptions (e.g., for urinary or chest infections) that were masking the signal. While the core trial team reportedly remained blinded and the refinement is logically sound, altering a primary outcome after an unblinded committee has reviewed data showing a null result introduces a risk of bias (p. 2397).

Reliance on a subjective primary outcome: The study's primary outcome, "confirmed or suspected maternal infection," is a composite measure whose event count is identical to that of a surrogate endpoint: "a new prescription of antibiotics" (180 events in the intervention group, 306 in the placebo group) (p. 2400, Table 2). A prescription is a clinical decision rather than a direct measure of a biological state. The authors acknowledge that using this clinical definition "could be regarded as a limitation" (p. 2402). However, the validity of this endpoint is supported by other findings. The study also found statistically significant reductions in more objective measures that are components of an infection diagnosis, including "confirmed systemic infection on culture" (11 vs. 25 events), "superficial incisional infection" (75 vs. 141 events), and "deep incisional infection" (36 vs. 77 events) (p. 2400, Table 2). This suggests the clinical decision to prescribe antibiotics was associated with

observable signs of infection.

High attrition rate for secondary outcomes: The reliability of the findings for secondary outcomes is weakened by loss to follow-up. The authors report achieving a 76% follow-up rate for most secondary outcomes, which were collected via a 6-week questionnaire, and identify this as "the main limitation of this trial" (p. 2402). This 24% attrition rate is substantially higher than the 5% anticipated in the trial's design (p. 2398). The risk of bias is increased by the authors' finding of a systematic difference between participants, noting that "A greater proportion of women who returned the 6-week questionnaire were primiparous" (p. 2402). While the primary outcome analysis was based on an intention-to-treat population with only 6% missing data, the higher attrition for secondary outcomes weakens conclusions regarding perineal pain, wound breakdown, and the economic analysis.

Inadequate assessment of long-term harms and antimicrobial resistance: The study's design does not permit a comprehensive assessment of the intervention's potential harms, particularly regarding antimicrobial resistance and infant health. The article recommends a policy of universal prophylaxis that would substantially increase antibiotic use, but it does not address the public health concern that this could drive antimicrobial resistance. Regarding infant health, the authors cite concerns about the infant microbiome as a reason for their post-delivery administration protocol but collected no specific follow-up data on infant outcomes to confirm safety (p. 2397). While the study collected 6-week maternal follow-up data, by focusing only on short-term maternal benefits, it provides an incomplete benefit-harm assessment for a policy with potentially significant long-term public health consequences.

Mismatch between sepsis framing and results: The article's introduction frames the research by emphasizing the danger of maternal sepsis, a life-threatening condition (p. 2395). This suggests the trial addresses a problem of high clinical severity. However, the trial was not powered to detect a difference in this rare outcome, and

its results showed no statistically significant effect on "Systemic sepsis according to modified SIRS criteria for pregnancy" (6 vs. 10 events; p=0.307) (p. 2400, Table 2). While preventing infection is a valid strategy for reducing sepsis risk, and framing a study around the severe consequences of the condition is standard practice, readers should note that the study's positive finding rests on the much broader composite primary outcome of suspected or confirmed infection, rather than the severe outcome used to motivate the research.

Unexplained heterogeneity in treatment effect across sites: Supplementary data reveal substantial variation in the treatment effect across the 27 participating hospitals. A forest plot shows that while the overall effect was positive, the incidence rate ratios at individual centers ranged widely, with some showing a strong benefit, others showing no effect, and at least one suggesting potential harm (p. S68, Table S10). The authors report that a sensitivity analysis including center as a random effect did not alter the overall conclusion (p. 2400). However, the main text does not discuss the clinical reasons for this significant heterogeneity (e.g., differences in local hygiene practices or baseline infection rates), which raises questions about whether local factors modify the intervention's efficacy.

Cost-effectiveness claim requires nuance: The article suggests the intervention reduces resource use, but the monetary cost reduction is not statistically significant according to the study's own pre-specified criteria. The methods state that a more stringent 99% confidence interval (equivalent to $p<0.01$) would be used for secondary outcomes, which includes the economic analysis (p. 2398). The result for the difference in total mean costs was -£52.60, but the 99% confidence interval was -£115.10 to £9.90 (p. 2401; p. S63, Table S8). Because this interval contains zero, the result is not statistically significant at the pre-specified level. The authors transparently report this interval and focus their claims on the significant reduction in *resource use* (e.g., fewer GP visits), but care must be taken not to conflate resource use reduction with statistically significant monetary savings.

Delayed administration of the intervention: The intervention was administered a median of 3.2 hours after delivery, with the protocol allowing for administration up to 6 hours post-delivery (pp. 2397, 2400). This delay complicates the interpretation of the intervention's mechanism, as it could be functioning as a very early treatment for an incubating infection rather than as a true prophylactic. The authors explicitly justify this timing as a pragmatic choice to mitigate "concerns about the effects of prenatal exposure to antibiotics on the infant microbiome" (p. 2397). They also acknowledge in the discussion that the delay could have made the intervention "less effective" but do not fully explore the alternative interpretation that its effect is due to early treatment rather than prevention (p. 2402).

Reporting and data collection limitations: The study contains several reporting and data collection issues. First, formal screening logs were not kept, meaning the article does not report the number of patients assessed for eligibility or the reasons for exclusion before randomization. The authors transparently disclose this in the trial profile figure legend, but this lack of information limits a full assessment of the sample's representativeness (p. 2398). Second, the method for safety monitoring carries a risk of underreporting harms. The authors state that "Non-serious adverse events were not routinely recorded because the intervention is a licensed product being given at a standard dose" (p. 2397). While this is a common choice in pragmatic trials involving drugs with well-known safety profiles, it weakens the conclusion of "few observed adverse events" and provides an incomplete basis for a full benefit-harm assessment (p. 2401).

Future Research

Long-term antimicrobial resistance tracking: Future studies should investigate the population-level impact of universal prophylaxis after operative vaginal delivery on antimicrobial resistance and the infant microbiome, providing the necessary data to balance short-term maternal benefits against long-term public health risks.

Optimizing administration timing: Future trials could compare immediate post-delivery administration versus the delayed administration (up to six hours) used in this trial to determine whether the observed effect is primarily prophylactic or acts as early treatment for incubating infections.

Standardized objective infection criteria: Future work should utilize strictly objective, biomarker-driven, or culture-based primary endpoints to avoid the subjectivity inherent in using antibiotic prescriptions as a proxy for infection, while also employing strategies to maximize retention for patient-reported secondary outcomes.

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