META-ANALYSIS

Effects of Prophylactic Antibiotics on Intestinal Microflora Diversity in Preterm Infants: A Meta-analysis

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ABSTRACT

Objective • This meta-analysis aims to investigate the effects of prenatal prophylactic antibiotics on the diversity of intestinal flora in premature infants, with a focus on elucidating the rationale behind this investigation and the potential impact of altered intestinal flora on the health of preterm infants, such as increased susceptibility to infections, impaired nutrient absorption, and compromised immune function.

Methods • Relevant literature consistent with the effects of prenatal prophylactic antibiotics on intestinal flora diversity in preterm infants was systematically searched and screened from both domestic and foreign databases, including Wanfang Medical Center, CNKNET, VIpp, and PubMed. Meta-analysis was performed using RevMan 5.2 software. Inclusion criteria for the study were: (1) comparison of prophylactic antibiotic use versus non-use, (2) no restrictions on subjects' characteristics, (3) follow-up loss < 20%, (4) institutional approval, (5) publication within the time frame from January 2017 to December 2022, (6) minimal missing data or suppliable by author contact, and (7) no major errors in sequencing or detection. Outcome measures included intestinal flora composition, phylum flora content, abundance index, and Shannon index, comparing antibiotic-treated and non-treated groups. RevMan 5.2 software was used for statistical analysis. Counting data was expressed as risk ratio (RR), and weighted mean difference (WMD) or standard mean difference (SMD) was selected as analysis statistics.

Results • The study encompassed five Chinese literature sources, with one deemed low quality and four high quality. No significant publication bias was observed. Among the included studies, a significant reduction in the intestinal flora abundance index ACE was noted in the treated group compared to the non-treated group (RR: -8.10, 95% CI: -8.81 to -7.40, $P < .00001$). ACE estimates species richness in a microbial community by considering both abundant and rare species. Higher ACE values indicate greater diversity. Similarly, the Shannon diversity index was lower in the medication group compared to the non-medication group (RR: 0.73, 95% CI: 0.64 to 0.82, $P < .00001$). Shannon Diversity Index measures species diversity and evenness within a community. Higher values indicate higher diversity, considering both the number of species and their relative abundance. Analysis of Firmicutes content revealed a higher level in the treated group (RR: -6.44, 95% CI: -7.26 to -5.63, $P < .00001$). Additionally, lower Proteus (RR: 10.96, 95% CI: 9.47 to 12.45, $P < .00001$) and Klebsiella (RR: 15.96, 95% CI: 15.31 to 16.62, $P < .00001$) content was observed in the treated group. Conversely, Enterococcus content was higher in the treated group (RR: 2.18, 95% CI: 1.84 to 2.52, $P < .00001$), along with a higher proportion of Enterococcus (RR: 0.45, 95% CI: 0.27 to 0.76, $P = .003$). These findings collectively suggest that prophylactic antibiotic use in preterm infants significantly alters the composition of intestinal flora.

Conclusion • Our findings suggest that prophylactic antibiotic use in preterm infants leads to a notable reduction in intestinal flora diversity, potentially impacting their health outcomes. Decreased microbial diversity has been linked to gastrointestinal issues, infections, and weakened immune function. These results highlight the importance of cautious antibiotic use in this vulnerable population and the need for further research to better understand and mitigate the potential health implications. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

The intestinal tract plays a crucial role in the human digestive system, as it harbors a large number of bacteria that form an intestinal microecosystem. This microecosystem can influence immune function, growth, and metabolism.[1] The intestinal flora is partially established before birth but continues to change due to factors such as gestational age, feeding method, exposure to antibacterial drugs, birth weight, environmental factors, and genetic factors.[2,3] The neonatal period is a critical time for the establishment of a stable microenvironment for the intestinal flora. The intestinal flora regulates exposure to internal and external environmental factors, and an imbalance in the intestinal flora increases the risk of allergic diseases, inflammatory diseases, diabetes, and other conditions in the late neonatal period. Imbalances in intestinal flora increase the risk of allergic diseases, inflammatory conditions, diabetes, and other ailments later in infancy. Antibacterial drugs, often administered prophylactically to pregnant women undergoing cesarean sections, are a significant disruptor of neonatal intestinal flora.[2] Antibacterial drugs are a significant factor contributing to the disruption and imbalance of intestinal flora in neonates.[3]

In current obstetric practice, pregnant women undergoing cesarean section often receive prophylactic antibiotic treatment to prevent infection. Premature infants and those with low birth weight have relatively weak immune systems, making them more susceptible to infections during the perinatal period. The prophylactic use of antibiotics in these cases increases antibiotic

exposure, which can adversely affect the healthy growth and development of premature infants.[4] Antibiotics exert their effects on intestinal flora through various mechanisms, particularly concerning neonatal development. Firstly, antibiotics exert selective pressure on microbial communities, targeting specific bacterial species while sparing others. This selective pressure can lead to a decrease in overall microbial diversity as susceptible species are eliminated, allowing for the overgrowth of resistant strains. Additionally, antibiotics can disrupt the balance of beneficial bacteria in the gut, such as Lactobacillus and Bifidobacterium, which play essential roles in maintaining intestinal health and immune function. This disruption can compromise the integrity of the intestinal barrier, leading to increased permeability and inflammation.[5]

However, despite existing studies on the impact of prophylactic antibiotics on intestinal flora diversity in premature infants, consensus remains elusive in the medical community. These studies have reported conflicting findings, with some suggesting a reduction in microbial diversity and others finding no significant changes. Furthermore, the methodologies and outcomes assessed in these studies vary, contributing to the lack of consensus and uncertainty regarding the effects of prophylactic antibiotics on intestinal flora diversity in premature infants.

Ethical considerations surround the administration of prophylactic antibiotics to pregnant women, particularly concerning potential risks to neonatal health. While antibiotics are essential for preventing infections in cesarean deliveries, their indiscriminate use may disrupt the delicate balance of the neonatal microbiome, potentially predisposing infants to adverse health outcomes. Therefore, evidence-based guidelines are needed to ensure the judicious use of antibiotics in obstetric practice, minimizing the potential risks to neonatal health while effectively preventing maternal and neonatal infections.

Therefore, our study aims to address this gap in current research by conducting a comprehensive meta-analysis of existing literature. Given the complexity and variability of existing studies, a meta-analysis is the appropriate approach to synthesizing the available evidence on this topic. Meta-analysis allows for the quantitative synthesis of data from multiple studies, providing a more comprehensive and robust assessment of the effects of prophylactic antibiotics on intestinal flora diversity in premature infants. By pooling data from individual studies, meta-analysis can help identify patterns, trends, and sources of heterogeneity, providing valuable insights for clinical practice and future research efforts. Therefore, our study employs a meta-analysis approach to address the existing gaps and inconsistencies in the literature and provide evidence-based recommendations for optimizing maternal and neonatal health outcomes.

DATA AND METHODS

Literature Retrieval

The literature search focused on clinical controlled trials published from January 2017 to December 2022. Databases were searched, including Wanfang Medical Science, CNKI, VIP, and foreign PubMed. The primary objective was to explore the effect of prophylactic antibiotic use in premature infants. The keywords used for the literature search included "intestinal flora diversity index," "antibiotics," "premature infants," "Klebsiella," "enterococcus," "Firmicutes," and others. The search language was restricted to Chinese and English. Selected literature was then subjected to meta-analysis.

Literature Screening Criteria

The following inclusion criteria were applied: (1) the study protocol compared the prophylactic use of antibiotics with the non-use of antibiotics; (2) no additional restrictions were placed on the characteristics of the research subjects, such as gender, age, nationality, or race; (3) the follow-up loss of contact ratio was less than 20%; (4) the study had obtained approval from the relevant institution; (5) the publication date was within the last 6 years; (6) there were no significant missing data, or any missing data could be supplemented by contacting the author; (7) there were no major errors in high-throughput sequencing or other detection procedures. The outcome measures of interest included the composition of intestinal flora, content of phylum flora, abundance index, and Shannon index, with comparisons made between the prophylactic antibiotic treatment group and the non-antibiotic treatment group. (8) Only random controlled trials were included. The following exclusion criteria were applied: (1) repetitive or illogical literature content, significant missing data with no possibility of contacting the original author for completion, or lack of rigor in the methodology; (2) basic experiments; (3) studies in other research areas; (4) other types of literature.

One criterion, "the follow-up loss of contact ratio was less than 20%," was chosen to address potential biases and limitations in the included studies. This criterion is crucial because a high loss-to-follow-up ratio can introduce significant biases and compromise the validity of study findings.

When a study has a high loss-to-follow-up ratio, particularly exceeding 20%, there is a risk that the characteristics of the participants lost to follow-up may differ systematically from those who remained in the study. This discrepancy can lead to biased estimates of treatment effects and compromise the internal validity of the study findings. By setting a threshold of less than 20% for loss to follow-up, we aimed to minimize this risk and ensure that the included studies maintained sufficient participant retention to yield reliable and robust results.

Quality Evaluation

The selected literature underwent quality assessment using a modified Jadad score scale, with scores ranging from 1 to 7. Studies with a score of ≤3 were considered to be of low quality, while those with a score of ≥4 were considered to be of high quality. The modified Jadad score scale utilized for quality assessment encompasses several essential components to evaluate the rigor and reliability of the included studies. These components include randomization, blinding, withdrawals and dropouts, allocation concealment, intention-to-treat analysis, and description of withdrawals and dropouts. By

systematically assessing these aspects, the scale ensures thorough scrutiny of the methodological quality of each study, enhancing the overall validity and credibility of the findings synthesized in the meta-analysis. This comprehensive evaluation allows readers to confidently assess the robustness of the evidence and its applicability to clinical practice.

Statistical methods

RevMan5.2 statistical software was used to analyze the study data, and the counting data was expressed as risk ratio (*RR*). Weighted mean difference was selected as analysis statistics. WMD)or standard mean difference (SMD). Both weighted mean difference (WMD) and standard mean difference (SMD) were selected as analysis statistics to accommodate the different scales and units of measurement used across the included studies. WMD was chosen when the outcome measure was expressed in a common unit of measurement across all studies, allowing for a straightforward comparison of treatment effects. On the other hand, SMD was employed when the outcome measure varied across studies, requiring standardization to facilitate meaningful comparisons. By utilizing both WMD and SMD, we ensured a comprehensive analysis that accounted for the heterogeneity in outcome measures across the included studies. All effect sizes were expressed with 95%confidence interval (*CI*). The heterogeneity between the results of each study was tested by the Chi-square test. Heterogeneity between the results of each study was assessed using the Chi-square test and I^2 statistic. High heterogeneity, indicated by I^2 values of 50% or higher, suggests substantial variability among the study results beyond what would be expected by chance alone. In such cases, subgroup or sensitivity analysis was performed to explore potential sources of heterogeneity and assess the robustness of the findings. When heterogeneity was statistically significant ($P < .1$ and $I^2 \geq 50\%$), subgroup or sensitivity analysis was conducted to investigate the impact of various study characteristics on the results. Conversely, when heterogeneity was not statistically significant ($P > .1$ and $I^2 < 50\%$), indicating low variability among the study results, a fixed-effect model was employed for meta-analysis. Publication bias assessment was conducted to evaluate the potential impact of selective reporting or publication of studies with positive results. Funnel plots and Egger's test were utilized to visually inspect and statistically test for asymmetry in the distribution of study effect sizes. This assessment helped to determine the robustness of the meta-analysis findings and provided insights into the potential presence of publication bias.

RESULTS

Basic features of literature

A total of 5 Chinese pieces of literature were included in the Chinese and English donation database according to keywords and research directions. One of the included pieces of literature was of low quality, and four were of high quality. The basic characteristics and quality evaluation results of the included literature are shown in Table 1. There was no significant publication bias in the 5 included articles, as shown in Figure 1-4.

Table 1. Basic characteristics of literature

Author	The year of publication	Outcome index	Quality score
Zhu WW[6]	2018	①②③④⑤	6
Ying WY[7]	2020	①②⑦	4
Zhu DP[8]	2016	①②⑦	4
Guo KP[9]	2020	⑥⑦	3
QanYY[10]	2020	①②③④⑤⑥	7

Note: ① Intestinal flora abundance index ACE; ② Shannon diversity index; ③ Firmicutes; ④ Proteus; ⑤ Klebsiella; ⑥ Enterococcus; ⑦ Composition and composition ratio of enterococcus.

Figure 1. Overall literature publication bias

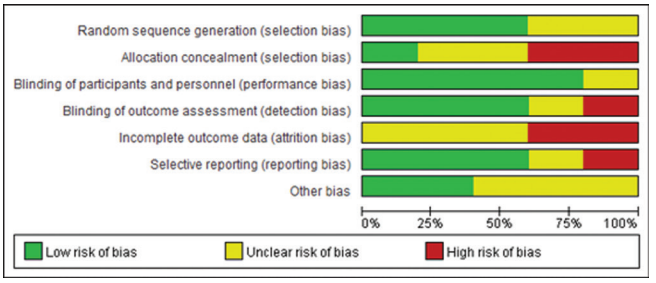


Figure2. Publication bias of single literature

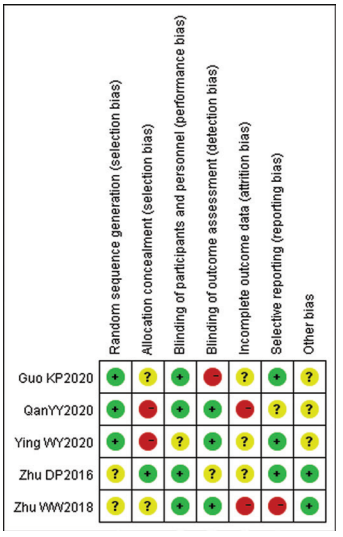


Figure 3. Literature screening process

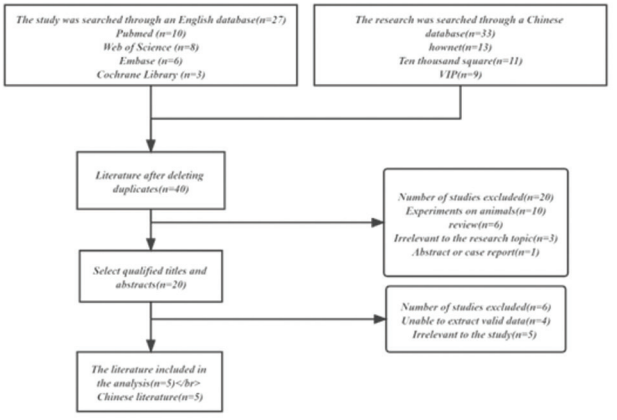


Figure 4. Time point of literature observation

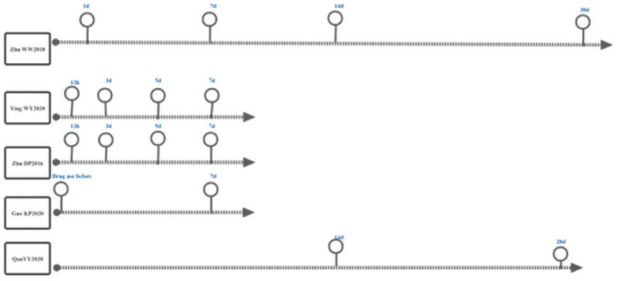


Figure 5. Forest plot of intestinal flora abundance index

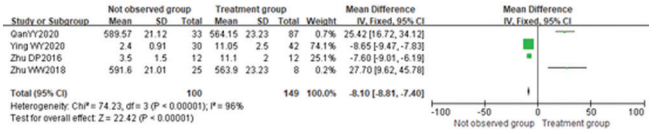


Figure 6. Forest map of intestinal flora Shannon diversity index

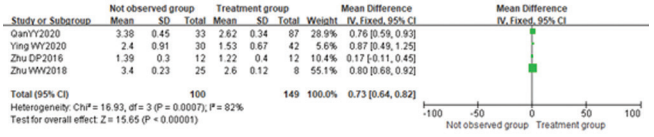


Figure 7. Forest map of Firmicutes content

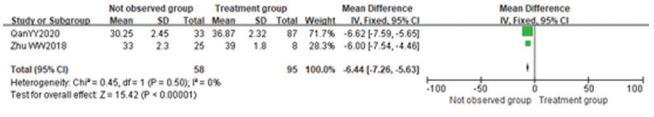


Figure 8. Forest map of Proteus content

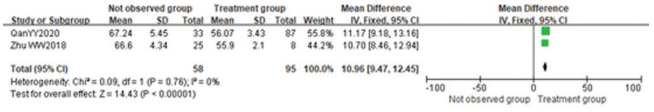


Figure 9. Forest map of Klebsiella content

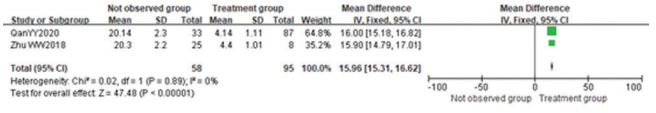
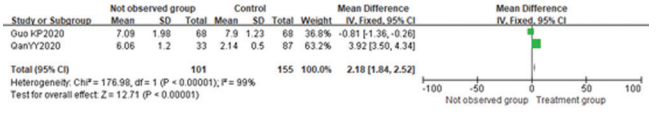


Figure 10. Forest map of enterococcus content



Changes in intestinal flora abundance index ACE

Four studies were included, and heterogeneity test showed that there was heterogeneity among the studies (I^2=96.0%, P < .00001)According to random effect model analysis, ACE in the treated group was lower than that in the non-treated group, and the difference was statistically significant after all studies were combined [*RR*: -8.10, 95%*CI*: (-8.81, -7.40), P < .00001]. These results suggest that prophylactic use of antibiotics can reduce the intestinal flora abundance index. As shown in figure 5.

Shannon diversity index

Five studies were included, and the heterogeneity test showed that there was heterogeneity among the studies (I^2=82.0%, P = .007). According to the random effect model analysis, the Shannon index of the medication group was lower than that of the non-medication group, and the difference was statistically significant after the combination of all studies [*RR*: 0.73, 95%*CI*: (0.64, 0.82), P < .00001]. These results suggest that prophylactic use of antibiotics can reduce intestinal flora Shannon index. As shown in figure 6.

Difference in firmicutes content

Two studies were included, and the heterogeneity test showed that there was heterogeneity among the studies (I^2=0.0%, P = .50). According to fixed-effect model analysis, firmicute content in the treated group was higher than that in the non-treated group, and the difference was statistically significant after all studies were combined[*RR*: -6.44, 95% *CI*: (-7.26,-5.63), P < .00001]. It is suggested that prophylactic use of antibiotics can increase intestinal firmicutes content. As shown in figure 7.

Difference in proteus content

Two studies were included, and the heterogeneity test showed that there was heterogeneity among the studies(I^2=0.0%, P = .76). According to fixed-effect model analysis, the content of Proteus in the treated group was lower than that in the non-treated group, and the difference was statistically significant after all studies were combined [*RR*: 10.96, 95%*CI*: (9.47, 12.45), P < .00001]. It is suggested that prophylactic use of antibiotics can reduce the intestinal proteus content. As shown in figure 8.

Differences in Klebsiella content

Two studies were included, and the heterogeneity test showed that there was heterogeneity among the studies (I^2=0.0%, P = .89). According to fixed-effect model analysis, the content of Klebsiella in the treated group was lower than that in the non-treated group, and the difference was statistically significant after all studies were combined [*RR*: 15.96, 95%*CI*: (15.31, 16.62), P < .00001]. It is suggested that prophylactic antibiotic use can reduce intestinal Klebsiella content. As shown in figure 9.

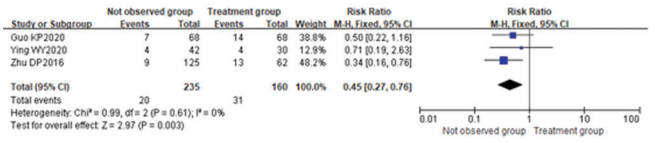
Differences in enterococcus content

Two studies were included, and the heterogeneity test showed that there was heterogeneity among the studies (I^2=99.0%, P < .00001). Random-effect model analysis showed that the enterococcus content in the treated group was higher than that in the non-treated group, and the difference was statistically significant after all studies were combined [*RR*: 2.18, 95%*CI*: (1.84,2.52), P < .00001]. It is suggested that prophylactic antibiotic use can increase enterococcus content. As shown in figure 10.

Proportion of enterococcus

Three studies were included, and the heterogeneity test showed heterogeneity among the studies (I^2=0.0%, P = .61). According to fixed-effect model analysis, the content of Klebsiella in the medication group was lower than that in the non-medication group, and the difference was statistically significant after all studies were combined [*RR*: 0.45, 95%*CI*: (0.27, 0.76), P = .003]. These results suggest that antibiotic prophylactic use will increase the enterococcus proportion. As shown in figure 11.

Figure 11. Forest diagram of enterococcus composition and proportion



Summary

The observed changes in intestinal flora composition, including reductions in ACE and Shannon index alongside increases in Firmicutes and Enterococcus content, carry significant clinical implications, particularly for premature infants. The reduction in microbial diversity, as indicated by the lower ACE and Shannon index, may compromise the resilience and functionality of the intestinal microbiota, potentially leading to dysbiosis-related health issues. Furthermore, the increase in Firmicutes and Enterococcus levels, known to be associated with opportunistic infections and immune dysregulation, could heighten the vulnerability of premature infants to infections and adversely impact immune development. These findings underscore the importance of judicious antibiotic use in this vulnerable population and highlight the need for further research to elucidate the long-term health consequences of alterations in intestinal flora composition.

The high heterogeneity observed above prompts consideration of potential sources. Variations in antibiotic types, dosages, durations of treatment, and patient populations could contribute to this heterogeneity. Further exploration of these factors is warranted to better understand their impact on the observed outcomes.

Subgroup analyses were not conducted in this study due to limitations in the available data. However, exploring the differential impacts of specific types of antibiotics or treatment durations on intestinal flora diversity through subgroup analyses would offer valuable insights into the nuanced effects of prophylactic antibiotic use in premature infants. Such analyses could elucidate whether certain antibiotics or treatment regimens are associated with more pronounced alterations in microbial composition, helping to inform clinical decision-making and antibiotic stewardship practices in neonatal care. Future studies with more comprehensive data may consider incorporating subgroup analyses to further elucidate the specific factors influencing the effects of prophylactic antibiotics on intestinal flora diversity.

DISCUSSION

The meta-analysis presented here offers a unique contribution to the existing literature by addressing the gap in understanding the effects of prenatal prophylactic antibiotics on the gut microbiota of premature infants. While previous studies have investigated the impact of antibiotic use on neonatal health outcomes, there has been a lack of consensus and verification in this area, particularly concerning the diversity and composition of the intestinal flora in preterm infants. Our study fills this gap by synthesizing the available evidence from recent clinical controlled trials, providing valuable insights into the consequences of prophylactic antibiotic use on the intestinal microecology of premature infants.

Clinical administration of prophylactic antibiotics in pregnant women undergoing cesarean section has been shown to reduce the risk of infection. Still, it is associated with an increased risk of perinatal infection in premature infants. However, the use of antibiotics directly impacts the exposure rate of antibiotics in preterm infants and disrupts the balanced and diverse structure of their intestinal flora. This disruption, in turn, raises the risk of nutritional intolerance in premature infants. Moreover, research reports have demonstrated a close relationship between intestinal disorders and the occurrence and progression of obesity, diabetes, and allergic diseases, all of which are significant risk factors for the growth, development, and overall health of premature infants.[11-13]

In a study conducted by Huang Qingmei et al.,[14] it was suggested that the preventive use of gentamicin and penicillin antibiotics in premature infants does not have a short-term impact on the diversity of their intestinal microbiota. However, the intestinal microbiota diversity in premature infants exhibits a significant decreasing trend between 8 and 21 days.[15,16] The study's findings indicate that the ACE and Shannon diversity indices of intestinal flora in preterm infants treated with antibiotics are lower than those in the non-treated group. This suggests that the use of prophylactic antibiotics affects the microenvironment of the intestinal flora in preterm infants, leading to a restricted homeostatic environment in the gut. This effect may be attributed to the initial colonization of certain bacteria, such as bifidobacteria, enterococcus, and enterobacter, in the intestinal tract through breastfeeding. Additionally, newborns may acquire bacteria from the mother's skin during breastfeeding. Antibiotics directly inhibit and kill these bacteria, resulting in changes to the intestinal environment, decreased diversity of the intestinal flora, and an imbalance in its composition.

Another study by Chen Lu et al.[17] demonstrated that using antibacterial drugs increases intestinal enterobacter, enterococcus, and streptococcus in premature infants, with small amounts of Veron coccus and Clostridium also being detected. The prophylactic use of antibiotics significantly increases the content of enterococcus and thick-walled bacteria in the intestinal flora of premature infants while

reducing the levels of Proteus and Klebsiella. The analysis suggests that antibiotic use delays the establishment and colonization of intestinal flora in newborns, inhibits the growth of anaerobic bacteria, and leads to changes in the composition of the intestinal flora.[18,19] Some scholars[20] have pointed out that thick-walled bacteria are advantageous in premature infants born after 34 weeks of gestation. Proteus bacteria exhibit an increasing trend within 10-14 days after birth and become dominant fungi. However, it is important to note that there may be variations in the study results due to differences in research subjects influenced by regional and genetic factors. Therefore, further expanding the scope and number of literature screening is necessary for in-depth analysis and validation studies.

Prophylactic antibiotics in premature infants primarily impact the gut microbiome through antimicrobial action, reducing overall bacterial diversity and favoring antibiotic-resistant strains. This disruption can affect immune system development, metabolic processes, and resistance to pathogens. Maintaining a diverse gut microbiota is crucial for optimal health outcomes in premature infants, emphasizing the need for targeted interventions to mitigate the effects of antibiotic use on gut flora diversity and function.[21] These mechanisms collectively contribute to the observed changes in intestinal flora composition and diversity.

It is important to acknowledge the potential biases introduced by the retrospective nature of the meta-analysis. Retrospective studies rely on previously published data, which may be subject to publication bias. This bias occurs when studies with positive or significant results are more likely to be published, leading to overestimating the treatment effect. To mitigate this bias, the researchers conducted a comprehensive literature search and included studies from both domestic and foreign databases. Additionally, statistical methods, such as funnel plots, can help assess publication bias.

The study findings emphasize the need for careful consideration of prophylactic antibiotic use in premature infants. While antibiotics are crucial for preventing infections, their impact on the gut microbiome diversity of premature infants cannot be overlooked. The observed reduction in intestinal flora diversity highlights potential risks for immune system development, metabolic processes, and pathogen resistance. Clinicians should weigh the benefits of infection prevention against the risks of disrupting the neonatal gut microbiome. Strategies such as probiotic supplementation or targeted antibiotic therapies may help mitigate negative effects. Individualized approaches that balance infection prevention with gut microbiome preservation are essential for optimizing the health outcomes of premature infants. Further research is needed to identify optimal antibiotic strategies that minimize harm to the gut microbiome while ensuring effective infection control. Furthermore, Patient-centered care requires a balanced approach, weighing the risks and benefits of antibiotic use in pregnant women and premature infants. Tailored risk assessments can guide antibiotic therapy, considering factors like gestational age, maternal health, and regional antibiotic resistance. Shared decision-making involving patients and providers ensures alignment with individual preferences and values. Regular monitoring allows for early detection of adverse effects, promoting optimal care for both mother and infant. Regional differences in antibiotic prescribing, cesarean section rates, and infant feeding practices can impact how premature infants' gut microbiota responds to prenatal prophylactic antibiotics. Higher cesarean section rates in certain regions may lead to more pronounced disruptions in gut microbiota diversity due to increased antibiotic exposure. Similarly, variations in breastfeeding rates can affect microbial composition and susceptibility to antibiotic-induced changes. Regional variances in antibiotic resistance patterns may also influence prophylactic antibiotic effectiveness and gut microbiota responses. Areas with higher resistance rates may experience distinct shifts in microbial composition post-antibiotic exposure compared to regions with lower resistance. Considering these regional nuances is crucial for interpreting study findings and guiding clinical decisions. Healthcare providers should consider local microbiome profiles and resistance patterns when prescribing prophylactic antibiotics. Tailoring antibiotic regimens based on regional microbiome characteristics could minimize disruptions while effectively preventing infections. Promoting evidence-based practices, like breastfeeding and prudent antibiotic use, can further optimize premature infants' gut microbiota health across diverse regions.

However, it is essential to consider the limitations of the study. One limitation is the heterogeneity among the included studies, as indicated by the significant heterogeneity test results. This heterogeneity could stem from differences in study design, participant characteristics, antibiotic regimens, and outcome measures. As a result, the generalizability of the findings may be limited to the specific populations and interventions included in the analysis. Future studies with larger sample sizes and standardized protocols must validate these findings and provide more robust evidence. Future research should prioritize longitudinal studies to elucidate the long-term health outcomes of premature infants exposed to prenatal prophylactic antibiotics. Moreover, investigations into alternative strategies for infection prevention, such as targeted antibiotic therapies or probiotic supplementation, are warranted. By addressing these limitations and exploring alternative approaches, future studies can provide more robust evidence to guide clinical practice and optimize the care of premature infants.

In conclusion, the meta-analysis suggests that prophylactic antibiotic use in preterm infants can reduce intestinal flora diversity. This disruption in the gut microbiota may have implications for the health and development of premature infants. However, further research is required to better understand the long-term consequences and to develop strategies to mitigate the potential negative effects of

prophylactic antibiotics on the intestinal microflora in this vulnerable population.

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