Antibiotics' Impact on Childhood Immunities

By

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Abstract

Even though antibiotics have critical health benefits in preventing or treating bacterial infection, they have adverse effects, primarily on host-microbiota homeostasis. This results in a crucial challenge to public health globally. Over the last couple of years, it has been revealed that children are frequently exposed to antibiotics because they are vulnerable to infections and have a high susceptibility to various diseases in their later life and other conditions. Their effect is that they cause an imbalance in the digestive system's microbial community that is closely associated with the disease, popularly known as dysbiosis. The disturbance changes the immune responses of the host against disease-causing microorganisms. They have more little effects on infants than on adults. This occurs since an infant's microbiota represents an evolving system that is immature and unstable for infants until they reach the age of between 2 and 3 years. The information on how antibiotics impact a child's and community's microbiota is scanty. Still, this paper focuses on how antibiotics affect a child's adaptive and innate immunity to pathogens using human and animal replicas that cause the host to be susceptible to pathogens in their future life. Therefore, it is critical to understand antibiotics' impacts on children's immunity since they may effectively affect the development of their therapeutics and prophylactics against pathogens in childhood and adulthood.

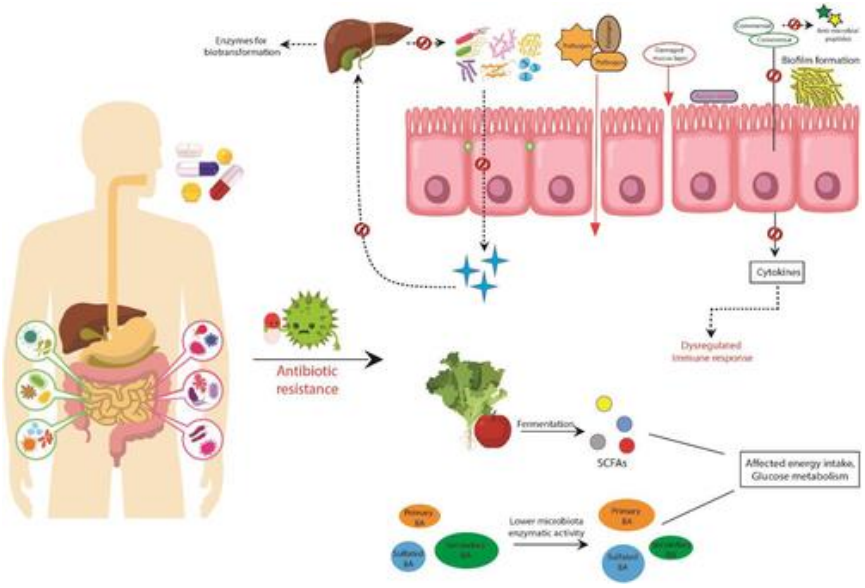
Keywords: Microbiota, pathogens, dysbiosis, infants, childhood, adulthood

Introduction

For an extended period, antibiotics have been used in the whole world to save human life and relieve caused by infections. Even though they benefit human life, they also have negative impacts, such as leading to human and mouse impairments to host immunity to vaccines and diseases. They also cause system deviation in the microbiota. The consequences are adverse to children since their microbiota is immature, and their immune system has not fully developed for functionality (Patangia et al., 2022). This makes their microbiota affected severely and longer in infants than in adults. Even though this difference exists, there is a scarcity of information on the mechanism and role of antibiotics in regulating children's functionality and their immune phenotype. In the whole world, preterm and underweight infants are more susceptible to bacterial infections leading to global morbidity and death rate and more so in third-world countries (Patangia et al., 2022). It is common practice for healthcare personnel to use antibiotics in neonatal ICUs to protect them from bacterial infections, especially in therapeutic or prophylactic treatments using the medicines.

Moreover, mothers are treated using antibiotics to reduce postpartum infection risks among newborns, especially during prepartum treatment. In the whole world, approximately 38 % of expectant mothers and infants are treated using antibiotics for infection control and prevention. (Patangia et al., 2022). Unfortunately, antibiotics are being used inappropriately and inadequately among infants, particularly in third-world countries. As a result, infants' immune systems and microbiota are affected, making them vulnerable to pathogens and other diseases in the future.

Figure 337: Negative effects to host due to overuse or misuse of antibiotics

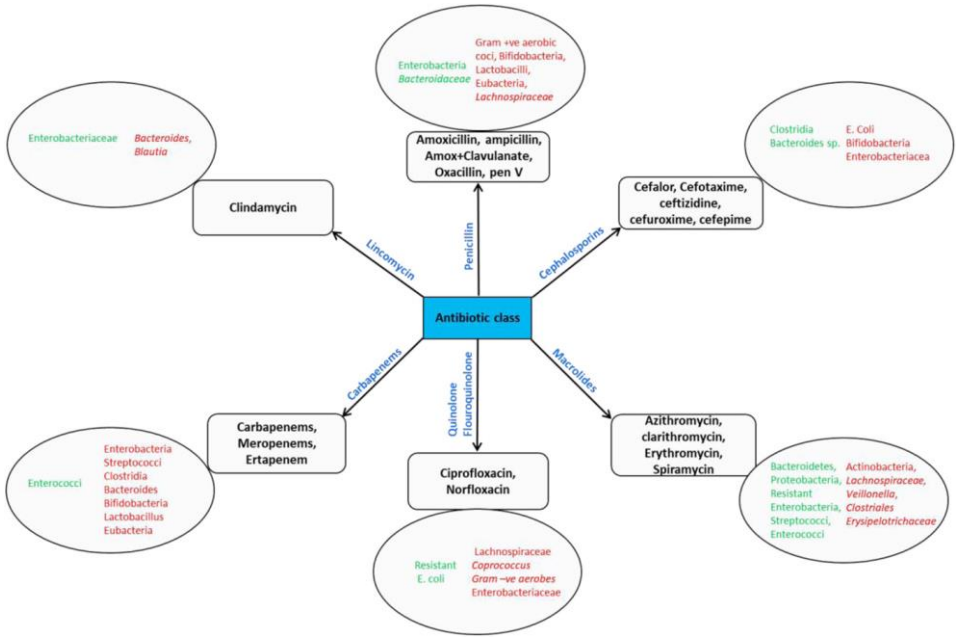


Source: (Patangia et al., 2022).

As a result, policymakers, physicians, and scientists must dig into the issue promptly.

This paper discusses the current findings stretching from animal and human studies on the issue of antibiotics' impact on the adaptive and innate immune systems of infants to infection responses. Early-life infants' exposure to antibiotics, making them vulnerable to infections later, is also focused on (Patangia et al., 2022). Thus, it is critical to understand the effects of antibiotics on the immune systems of infants so that a rational strategy for the development of the management and control of disease in both adults and infants.

Figure 2: Effects of different antibiotics on gut human gut bacteria



Source: (Patangia et al., 2022).

Proposal

Research Overview

Antibiotics are critical in treating patients, whether they are children or adults. They are used by health professionals in their daily life while helping patients. They reduce pain in patients and treat them. Children are used primarily in intensive care units. However, these antibiotics have been linked to having adverse effects on children later in life if they start using them while young. This paper will dig deeper to know when they are suitable for use and when they are not.

Background Information

Antibiotics are used in hospitals to reduce the risks of prepartum infections among infants as they are being treated. About 38 % of pregnant mothers and their children are globally treated using these antibiotics for

infection control. However, they have been misused in treating infants and, more so, in developing countries. Consequently, they affect their microbiota and their innate immune system, making them susceptible to pathogens in their later life.

Statement of the problem

This research aims to examine how the use of antibiotics affects children's immunity. It will also examine how their use in early life impacts the children's later life by examining how the drugs are being misused. The examination will focus on the negative side of antibiotics and their positives on children's immunity.

Significance of the study

This study is critical since it brings to light how antibiotics are used among the young population, which is essential since it holds the world's future. The study on antibiotics will help in their improvement if need be, maintained, or discarded if they threaten the children's life. Through that, the future generation will be protected.

Research Objectives.

The research aims to examine how antibiotics have been used in the past to either improve the lives of children or ruin their immunity, determine the advantages and the disadvantages of using antibiotics for children's immunity, and examine the alternative methods of treatment that can be used instead of antibiotics or combined with them to achieve better results.

The specific objective of the paper is to examine how the use of antibiotics affects children's immunity.

Research Question

Has antibiotics in the past helped children and their mothers improve their immunity? In what ways has that been? How does their use affect their immunity in their later life?

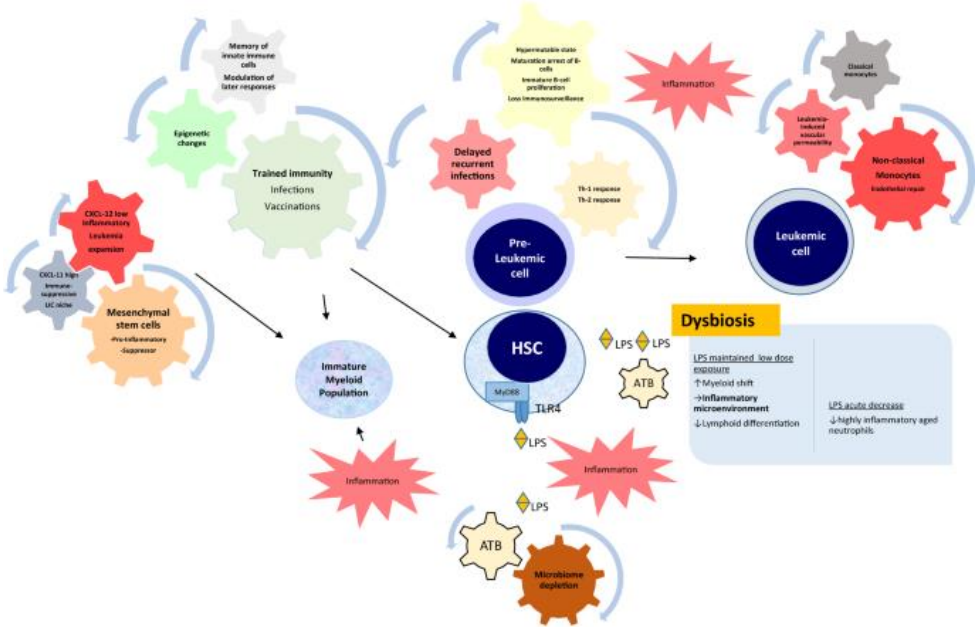
Literature Review

Dysbiosis of the Microbiota

Dysbiosis is a term in biology that describes the imbalance in the digestive system's microbiota associated with extra-intestinal and intestinal pathogenesis [process for an infection to result in a disease]. There are microbes in the microbiota of human beings, which may include viruses, bacteria, and fungi. Among the microbes, one more research has been done on id bacterial (Patangia et al., 2022). These affect the body's functionality and phenotype by targeting metabolites, nutrient absorption, and synthesis. As a result, they promote the immunity of pathogens and eventually regulate a person's behavior and brain functionality.

There are probabilities that infants encounter microbiota through substances that are passed through the placenta of the fetus as nutrients are being transferred from the mother to it while in the uterus. However, recent research on the topic has focused on the contamination of the equipment used in the laboratories and reagents as well as tissue samples through the use of bacterial DNA, leading to the conclusion that there exists sterility of the tissues originating from the placenta and the fetus (Zhu et al., 2017). The studies say that intergenerational transfer of the microbiota occurs between childbirth and labor, leading to colonization that extends to the child's age of 3 years.

Figure 3: Antibiotics in childhood



Source: (Cardesa et al., 2022).

Immunological printing then follows. This is the education and development of the immune system of neonates that prepares them to respond to signals of danger in their future life. At this stage, dysbiosis, which entails both functional and compositional system deviation of the microbiota, has unreasonable results. Dysbiosis can be characterized in function, composition, and diversity through microbiological approaches like biology systems and metagenomics. The leading causes of dysbiosis include antibiotics, stress, the mode in which the child was born, and dietary habits (Zhu et al., 2017). The one caused by antibiotics is the one that has significance to clinicians and is correlated to various other diseases. It results in a decrease in microbial diversity in adults and children. However, multiple factors affect its effects, such as dosage and types of antibiotics. There may be long-lasting effects of antibiotics on infants and lead to health and disease consequences in the long run.

Effects of Host's Immunity Against Infections

Much attention has been attracted to antibiotics as one of the key causal factors of microbial dysbiosis in infants. They have been linked with higher risks of affecting the immunity of infants in their later life. It makes them more vulnerable to diseases, including infectious diseases. An individual's prolonged exposure to antibiotic therapy through retrospective studies in case-control was associated with a rise in enterocolitis necrotization, late-onset sepsis, and death for infants born with low weights. Zhu et al., while analyzing infants' preterm metabolites and stool microbiota with treatment with empirical antibiotics for seven days, showed a bacterial diversity reduction and pathogens enrichment like Pseudomonas and Streptococcus.

A study by Danish Cohort showed that the use of antibiotics in mothers, either prescribed before or during expectancy, has a high risk of hospitalization related to infant infection. Epidemiological studies shed more on how human infants are predisposed to respiratory tract infections and diarrhea susceptibility by using antibiotics. Even though the discussed studies demonstrate an increase in the vulnerability to conditions due to antibiotics, a direct and more convincing can only come from studies that use animal models.

Gonzalez-Perez et al. studied antibiotic's role in the regulation of immune defense and causing dysbiosis through the use of a mouse model. The model was used against a virus infection of systemic vaccinia, while the mouse model was exposed to perinatal antibiotics. Dam antibiotic treatment resulted in a critical change in the composition of the infant's gastrointestinal system microbiota, where there was **Enterococcus faecalis** ascendancy (Shekhar & Petersen, 2020). Consequently, there was the death of infant mice that had not been treated with sham but with an antibiotic. It died after being injected intraperitoneally with a high percentage of vaccinia virus inoculum. This implied that dysbiosis driven by an antibiotic reduces infection resistance. The control mice also exhibited a decrease in viral titers, even at low levels of viral inoculum. This was after being compared to mice exposed to an antibiotic.

For the infant mice not exposed to an antibiotic but under environmental conditions related to hygiene, it was shown that there was a high susceptibility to infection driven by the vaccinia virus (Cardesa-Salzmann et al., 2022). The revelation underscored the relationship between immunity development against infection and hygiene conditions where the infants had been raised.

Recent studies have been done to assess the effects of mediated antibiotics on the susceptibility of a host to infections containing a-negative bacteria and Gam-positive ones. Using the bacterial infections mouse model, antibiotics in drinking water were used to treat nursing dams (Shekhar & Petersen, 2020). Afterward, their infants were exposed to t days later and challenged with their mothers' milk. When the exposed infants were compared with naïve controls, and then 80 days later, "Citrobacter rodentium," the results were loss of body weight, bacterial burden, and enhanced technology. These demonstrated the inauspicious impacts of using antibiotics in an individual's early life on the defense against pathogens in their future life.

In addition, transferring microbiota perturbed with antibiotics to germ-free mice resulted in worse disease pathologies. The suggested microbiota driven by antibiotic dysbiosis was the one that led to the development of the disease phenotype. On the same note, the microbial homeostasis in the newborn mice's gut was visited by antibiotic exposure, which increased vulnerability to Streptococcus pneumonia infection (Shekhar & Petersen, 2020).

Reduced survivability was demonstrated through the exposure of neonatal mice to antibiotics. This was done against an infection challenge containing Klebsiella pneumoniae compared to mice. All these studies conclude that antibiotics perturb the microbiota composition, resulting in the host's long-run susceptibility to bacterial and viral infections. It stresses the critical role played by the commensal microbiota in the promotion of resistance of infants to infections.

Methodology

Use of Animal Models in Exploring Infant Immunity Mediated by Antibiotics

These models are critical in establishing causal relationships that cannot be tested directly in settings controlled by humans. There have been some shortcomings in findings extrapolation from these models. However, the design of experiments in close resemblance to the antibiotics used in humans may have the potential to offer better information. This includes the administration route, combination of antibiotics, and doses (Shekhar & Petersen, 2020).

There is a need to use better approaches like allometric scaling, involving dose normalization to the body surface area, to calibrate a dose for a drug. The mice are the animal models preferred for conducting neonates studies related to antibodies. However, for two main reasons, a better alternative may be provided by using large animals like pigs or cows. One, Easy therapeutic manipulations are allowed when large neonates are used. The manipulations may include intravenous injections and intramuscular injections. Secondly, large animals have physiological and anatomical similarities with human beings.

Modulating Immune Systems Response to Disease-Causing Microorganisms

This can be discussed by focusing on innate and innate immunity.

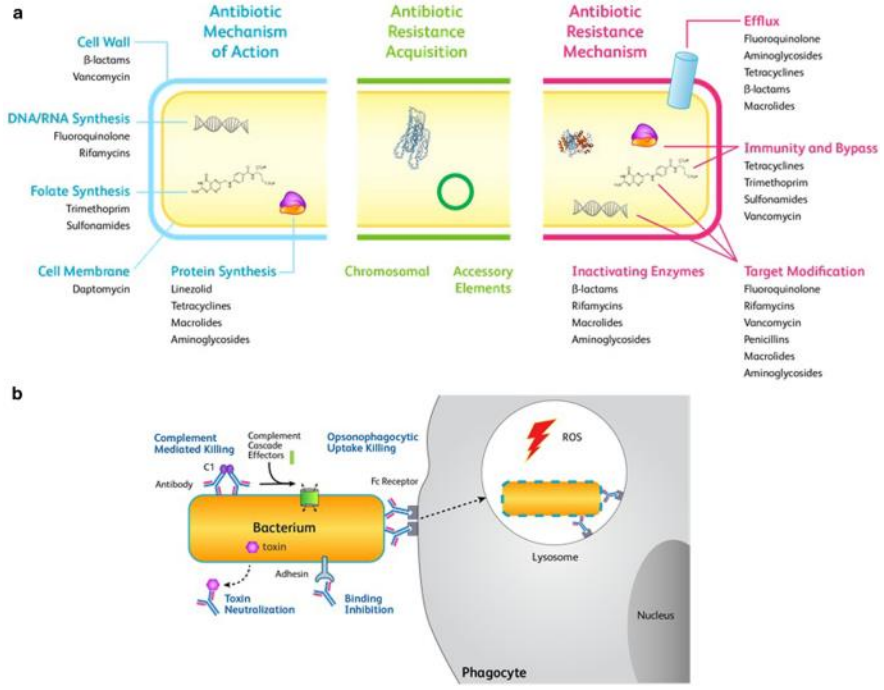
a] Innate Immunity

In innate immunity, dysbiosis driven by antibiotics bestows an intense effect on the infants' generation's adaptive and innate immune responses to vaccines and pathogens. Innate immune cells are influenced by exposure to antibodies during infancy. Natural killer [NK] cells are also critical (Jansen et al., 2021). The cells may include innate lymphoid cells or dendritic cells [DCs]. The latter tends to be the most powerful cells that join adaptive and innate immunity.

Regarding the infections due to the vaccinia virus, reduced frequency, and a total splenic DCs number were associated with the infant mice from the dams treated with antibiotics. Compared with the control

mice, the DCS had CD11c^{hi}MHC-II^{hi} as a unique feature (Hagan et al., 2019). The main subsets of DCs include CD8α-, DCs, and CD8α+. It was found that mice exposed to antibiotics had high frequencies of CD11b-CD103+ DCs. The latter and CD8α+ are sometimes called type 1 DCs.

Figure 345: Effects of human vaccines on the bacterial resistance



Source: (Jansen et al., 2021).

Cross-presenting CD8+ T cells with exogenous antigens are critical since they provide antiviral immunity due to epigenetic changes; antibiotic treatment lowers IFN-γ responsive genes' expression in the periphery of DCs and blood monocytes. NK cells in infants exposed to antibiotics showed significant changes phenotypically and in frequency (Jansen et al., 2021). After an infection, the NK cells were reduced with CD62L, activation markers expression, NKG2D, and CD11b compared to the control (Shekhar & Petersen, 2020).

It is also shown in the mouse model that antibiotic treatment reduces the circulation of peptidoglycan, depletes microbiota, and results in the

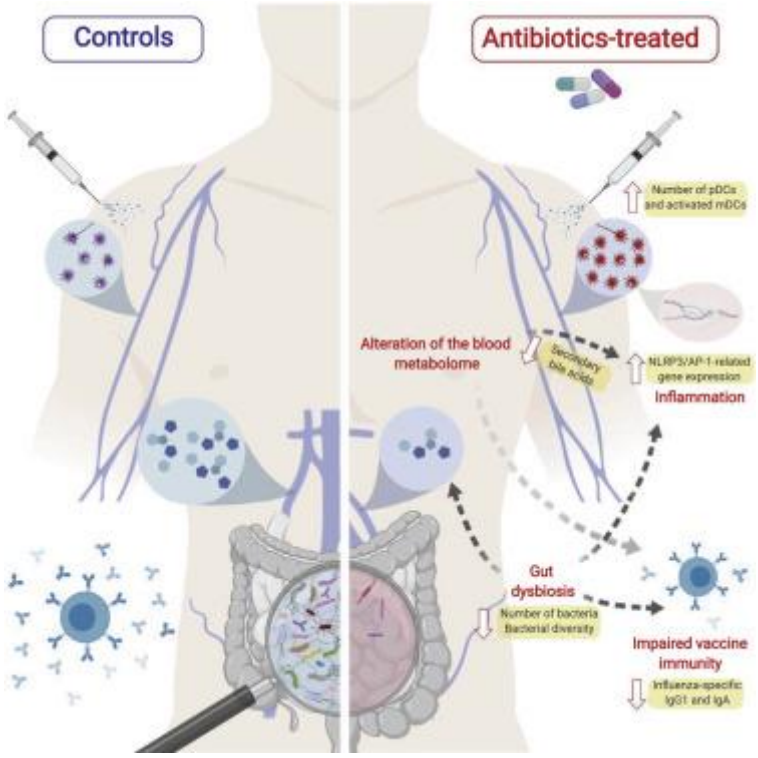
killing of **Staphylococcus aureus** and **streptococcus aureus**. As per the data, early-life antibiotics' microbial colonization hindrance results in innate immune cells' inefficiency in generating optimal immunity.

Another group of cells that have been shown to play a significant role in the immunity of an infant against **Streptococcus pneumonia is the** innate lymphoid cells, shortened as (ILC3). These cells produce a cytokine called IL-22 (IL-22+ILC3), used for pathogen protection and repairing lung epithelial. From the study, there was a decrease in the ability of cytokine originating from the newborn mice exposed to antibiotics to migrate to the lungs. This was after it was compared with the cells separated from control mice. However, they could move to other body parts like the intestines, liver, and others (Shekhar & Petersen, 2020). Chemokine receptor (CCR) 4's lower expression caused the decrease in migration of the cells. The CRR is significant in the T cells' homeostasis traffic to the lungs. IL-22+ILC3's migration capabilities were restored by the reversion of dysbiosis from the mediation of antibiotics brought about by the reconstitution of the microbiota.

It was also demonstrated that CD103+CD11b+ DCs originating from the infants exposed to antibiotics in terms of efficiency compared with the CD103+CD11b+ DCs from mice that had not been exposed; the former were less efficient. The lack of exposure happened on IL-22+ILC3. It was established through the co-culture system of the cells in the intestines (Hagan et al., 2019). CD103-CD11b+ DCs, on the other hand, did not induce such kind of effects but instead suggested a difference in the functional abilities of the DC subsets (Cardesa-Salzmann et al., 2022). To sum up, the data revealed how antibiotics' early life exposure impacts the ILC3 [in the lungs] migration patterns resulting in protective immunity against the pneumococcal infection of the lungs.

Adaptive Immunity

Figure 5: How antibiotics affect child immunity to vaccines



(Hagan et al., 2019).

A deep study on how dysbiosis driven by antibiotics influences the immune responses of vaccines in mice was conducted by Lynn et al. First, the mice infants were exposed to antibiotics. They were immunized with various vaccines that were clinically relevant such as Hexa, BCG, PCV 13, Men C, or B. These vaccines protect children from Tuberculosis, pneumococcal disease, meningitis, polio, diphtheria, hepatitis B, tetanus, **Haemophilus influenzae** type b infection, and pertussis. (Shekhar & Petersen, 2020). It was observed that three months after immunization, the mice's IgG antibody responses specific to antigens were impaired. The responses were conducted in comparison to sham-treated mice. It was also shown that antibody specific to antigens had an unsustainable and transient impact. However, the titer specificity of antibodies was boosted by the

vaccine boosters for the various types of vaccines above. In addition, no variation between the antibodies of the IgG total antibodies and the mice treated with Sham. It can be deduced that impairments in the antibodies' responses with vaccination specifications did not occur because of B cell functionality defects. Also, the immunization of murine infants exposed to antibiotics aged around seven days using complete Freund's adjuvant and ovalbumin resulted in a decrease in the antibody titers for the antibody specific to the antigen (Shekhar & Petersen, 2020). From the discussion, it could be concluded that exposure of individuals to antibodies in early life impairs their humoral responses that play a bigger role in protecting immunity to the highest percentage of vaccines.

Also, the T cell community to infections for the infant mice is altered by antibiotics for treatment. Whenever infected with the vaccinia virus, the splenic T cell's profile of functionality from the mice exposed to antibiotics differed from the control mice's. The flow cytometric analysis discovered that all CD8+ T cells expressing IFN-γ were fewer in the mice treated with antibiotics (Shekhar & Petersen, 2020). After ex-vivo and in vitro CD8+ T cells stimulation with CD28 agonists and T cell receptor (TCR), the results were similar to the one above. The better side of the story was that the CD8+ T cells resulted in anti-apoptotic down-regulation (Bcl-2) and exhaustion up-regulation (PD-1).

It was demonstrated that CD8+ T cells from infant mice born to dams treated with antibiotics showed T cell receptor signaling alterations. As a result, there is a partial restoration of IFN-γ's production due to in vitro and LPS in vivo TLR4 stimulation. It also reduced the number of deaths arising from infections from the vaccinia virus (Shekhar & Petersen, 2020).
On the same note, when mice with antibiotics were treated b for one month, the function of CD8+ T cells and CD4+ specific to an antigen resulted in decreased functionality. However, local and distal injections of TLR ligands restored immune impairment.

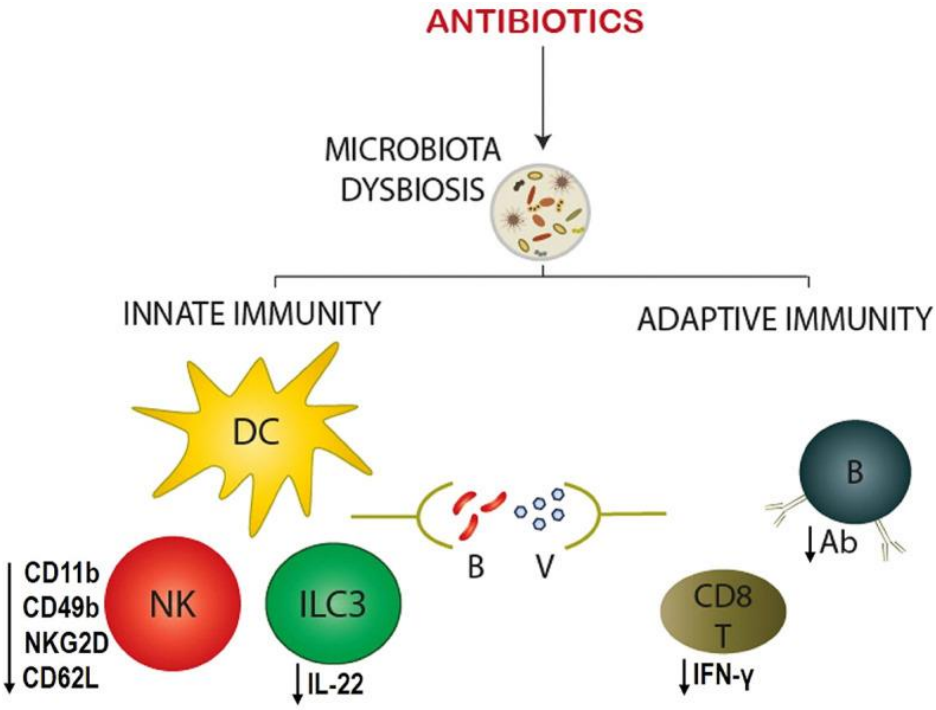
On the side of dysbiosis, it alters T cells' function, but people tend to misunderstand this for several reasons. One, it produces altered metabolites

like commensal bacteria and fatty acids that are involved in the generation of the T cell.

On the other hand, higher levels of cytokines like IFN-γ were separated from mice treated with Sham due to CD4+ T cells isolated from mice treated with antibodies and had been immunized with PCV 13,

On top of that, there was an increase in IFN-γ after the isolation of splenocytes from the mice exposed to antibiotics and the stimulation of immunizations through the Hexa vaccine. There was an enhancement in the secretion of IFN-γ c by the peripheral mononuclear blood cells originating from the piglets exposed to antibiotics compared with unexposed mice. This was after in vitro polyclonal stimulation using the phytohaemagglutinin (Shekhar & Petersen, 2020). There was a significant upregulation of expressions of blood genes such as IL, -2 IFN-γ, and IL-6 in piglets exposed to antibiotics after killing **almonella** Typhimurium by heat. The changes in the findings could be due to factors such as experimental design, various animal models, vaccine challenges, a combination of antibiotics, and infection challenges. As a whole, the data demonstrate critical implications for children's programs vaccination since the whole world they are being exposed to antibiotics.

Figure 6: Summary of Innate and Adaptive Immunity



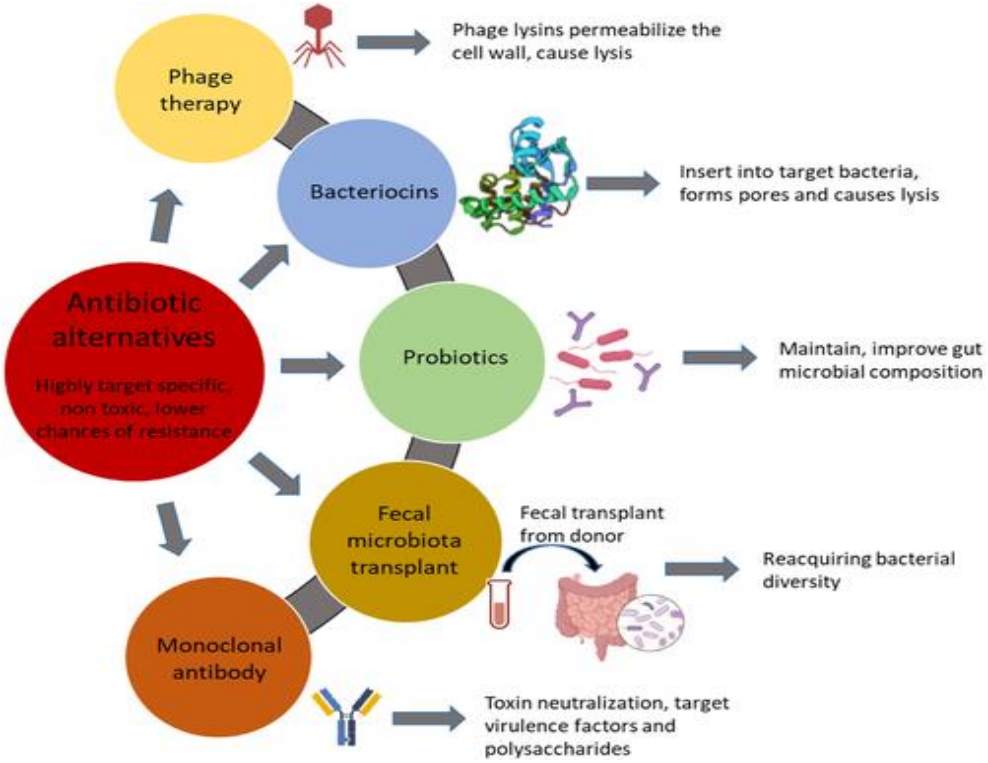
Source: (Shekhar & Petersen, 2020).

Many studies have tried to tackle the effects of dysbiosis or antibiotics on the immune system of human infants. The effects of neonatal treatment using antibiotics were one by Oosterloo et al. (2020). They studied the effects of 84 various markers on the immune cells in "infants" from an INCA study within one year. They evaluated whether the immune profile was associated with infantile colics and mental disorders such as wheezing and eczema. From their study, they found the existence of a vital association between the broad usage of antibodies.

With inflammatory markers of the immune system such as IL-1RII, HSP70, sCD14, sVEGF-R1, sVCAM-1, sCD19, IL-1RII, and sCD27. At one year of age, it resulted in an immune profile for the disorders, where some were not in any way associated with antibiotic treatment (Shekhar & Petersen, 2020). Another study showed microbiome dysbiosis for those aged

12, a life full of Gammaproteobacteria and Bacilli, with the highest T cell population. The cells include + TEMRA, CD8+ TEMRA cell CD4, CD4+ TEM, and

Figure 7: Alternatives to be used alone or with an antibiotic combination



Source: (Patangia et al., 2022).

Conclusion

For neonatal clinical care, antibiotics are drugs that cannot be avoided since they treat and prevent bacterial infections that may lead to a heavy socioeconomic societal burden. They are critical because of the issues associated with neonatal sepsis precise diagnosis. In addition, awareness of the effects of antibiotics on infants is increasing. These antibiotics encourage microbiological ecology changes. Changes in immune responses against vaccines and pathogens have been suggested, increasing infants' vulnerability to their future life.

It is essential to understand fully how the treatment of antibiotics in infancy affects their immunity and microbiota since it is critical in designing better, modern, and sophisticated therapeutic and prophylactic strategies. However, there is no clarity on the direct modulation of the functionality of the infants' immune system (Shekhar & Petersen, 2020). There are findings of interest in recent studies where adult mice with no germs have resulted in critical findings demonstrating how antibiotics can regulate host immunity. Unfortunately, those findings are yet to be confirmed in infants.

Future studies on this topic should address various issues, such as how better animal models can be developed to study the effect of antibiotics effects on immunity and microbiota. Also, it should try to answer questions such as the available underlying mechanisms in which dysbiosis driven by antibiotics in infants control how their immunity responds to infections and vaccines (Shekhar & Petersen, 2020). It should also focus on revealing whether antibiotics act directly on the immune system of infants where microbiota is not involved. Another critical area of research is how antibiotics' adverse effects can be neutralized in strengthening programs on antibiotic stewardship.

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