

## TINJAUAN PUSTAKA

### The Hygiene Hypothesis And Covid-19: A Look At The Evidence And New Perspectives

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**Abstract:** The hygiene hypothesis postulates that early-life exposure to infectious agents and microbes has a significant impact on the maturation of the immune system, providing protection against allergies and autoimmune diseases. Recent studies have challenged the hypothesis's universality, suggesting that it might only be relevant in developed countries. New perspectives on the hygiene hypothesis propose a multifaceted theory that considers not only microbial exposure but also factors such as diet, stress, and the environment. The role of specific immune cells in the development of allergies and autoimmune diseases has been emphasized, and innovative therapies based on manipulation of immune cells have been proposed. The importance of reconciling the hygiene hypothesis with recent insights into the human microbiome and the importance of maintaining a balance between hygiene and microbial exposure is also emphasized. Lastly, the article delves into the hygiene hypothesis, investigates the connection between gut microbiota dysbiosis and the development of allergies and autoimmune diseases, and examines the influence of COVID-19 on both gut microbiota and immune function.

**Keywords:** allergies and autoimmune diseases, gut microbiome dysbiosis;

### Hipotesis Kebersihan Dan Covid-19: Melihat Bukti Dan Perspektif Baru

**Abstrak:** Hipotesis kebersihan (higienitas) mendalilkan bahwa paparan awal kehidupan terhadap agen infeksi dan mikroba memiliki dampak yang signifikan terhadap pematangan sistem kekebalan tubuh, memberikan perlindungan terhadap alergi dan penyakit autoimun. Sejumlah penelitian terbaru telah menantang universalitas hipotesis tersebut, menunjukkan bahwa hipotesis tersebut mungkin hanya relevan di negara maju.

*Perspektif baru tentang hipotesis kebersihan mengusulkan teori multifaset yang tidak hanya mempertimbangkan paparan mikroba tetapi juga faktor-faktor seperti pola makan, stres, dan lingkungan. Peran sel imun spesifik dalam perkembangan alergi dan penyakit autoimun telah ditekankan, dan terapi inovatif berdasarkan manipulasi sel imun telah diusulkan. Pentingnya menyelaraskan hipotesis kebersihan dengan wawasan terbaru tentang mikrobiota manusia dan pentingnya menjaga keseimbangan antara kebersihan dan paparan mikroba juga ditekankan. Terakhir, artikel ini membahas hipotesis kebersihan, menyelidiki hubungan antara disbiosis mikrobiota usus dan perkembangan alergi dan penyakit autoimun, serta meneliti pengaruh COVID-19 pada mikrobiota usus dan fungsi kekebalan tubuh.*

**Kata kunci:** *Alergi dan penyakit autoimun; Disbiosis mikrobiota usus; Hipotesis kebersihan; Perkembangan sistem kekebalan; Paparan mikroba*

### **Highlights of this study:**

Key findings of this study:

1. The significance of reconciling the hygiene hypothesis with contemporary knowledge regarding the human microbiome, emphasizing the importance of striking a balance between cleanliness and microbial exposure. We reference several studies that highlight the potential risk of disrupting the equilibrium of normal gut flora in individuals with a history of COVID-19 infection.
2. The association between the hygiene hypothesis, dysbiosis of the gut microbiome, and the potential impact of COVID-19 on an individual's future susceptibility to autoimmune and allergic diseases. Our findings include studies that indicate an increased likelihood of developing inflammatory bowel disease in individuals exposed to COVID-19, particularly those with limited exposure to diverse microorganisms during early life.

### **Sorotan dari penelitian ini:**

*Temuan-temuan utama dari penelitian ini:*

1. *Pentingnya merekonsiliasi hipotesis kebersihan dengan pengetahuan kontemporer mengenai mikrobiota manusia, yang menekankan pentingnya mencapai keseimbangan antara kebersihan (perilaku menjaga kebersihan) dan paparan mikroba. Kami merujuk pada beberapa penelitian yang menyoroti potensi risiko terganggunya keseimbangan flora usus normal pada individu dengan riwayat infeksi COVID-19.*
2. *Hubungan antara hipotesis kebersihan, disbiosis mikrobiota usus, dan potensi dampak COVID-19 terhadap kerentanan seseorang di masa depan terhadap penyakit autoimun dan alergi. Temuan kami mencakup penelitian yang menunjukkan peningkatan kemungkinan pengembangan penyakit radang usus pada individu yang terpapar COVID-19, terutama mereka dengan riwayat paparan mikroorganisme yang terbatas selama masa awal kehidupannya.*

## INTRODUCTION

Early exposure to microbes and infectious agents, according to the hygiene hypothesis, aids in the immune system's development and guards against autoimmune disorders and allergies. While the hypothesis has gained widespread attention, recent studies have challenged its universality across the world.<sup>1</sup>

Suggest that the hygiene hypothesis might only be relevant in developed countries, where the incidence of autoimmune diseases and allergies is higher<sup>2</sup> and present novel perspectives on the hygiene hypothesis<sup>3</sup>, proposing a multifaceted theory that considers not only microbial exposure but also factors such as diet, stress, and the environment.<sup>4</sup> Highlight the critical function of certain immune cells in the onset of allergies and autoimmune disorders and propose novel immunotherapy approaches.<sup>5</sup> Advocate for reconciling the hygiene hypothesis with recent insights into the human microbiome and the importance of maintaining a balance between hygiene and microbial exposure.

The COVID-19 pandemic has brought to the forefront the critical role of the immune system in protecting our health. It has also shed light on the potential impact of modern hygiene practices on our immune function. According to the hygiene hypothesis, modern hygiene practices have reduced exposure to infectious organisms, which has resulted in a rise in allergy, autoimmune, and inflammatory illnesses. This article explores the relationship between the hygiene hypothesis, dysbiosis of the gut microbiota, and the origin of these diseases. It will also discuss the impact of COVID-19 on the gut microbiome and immune function, and highlight the need for interventions that promote a healthy and diverse gut microbiome while maintaining proper hygiene.

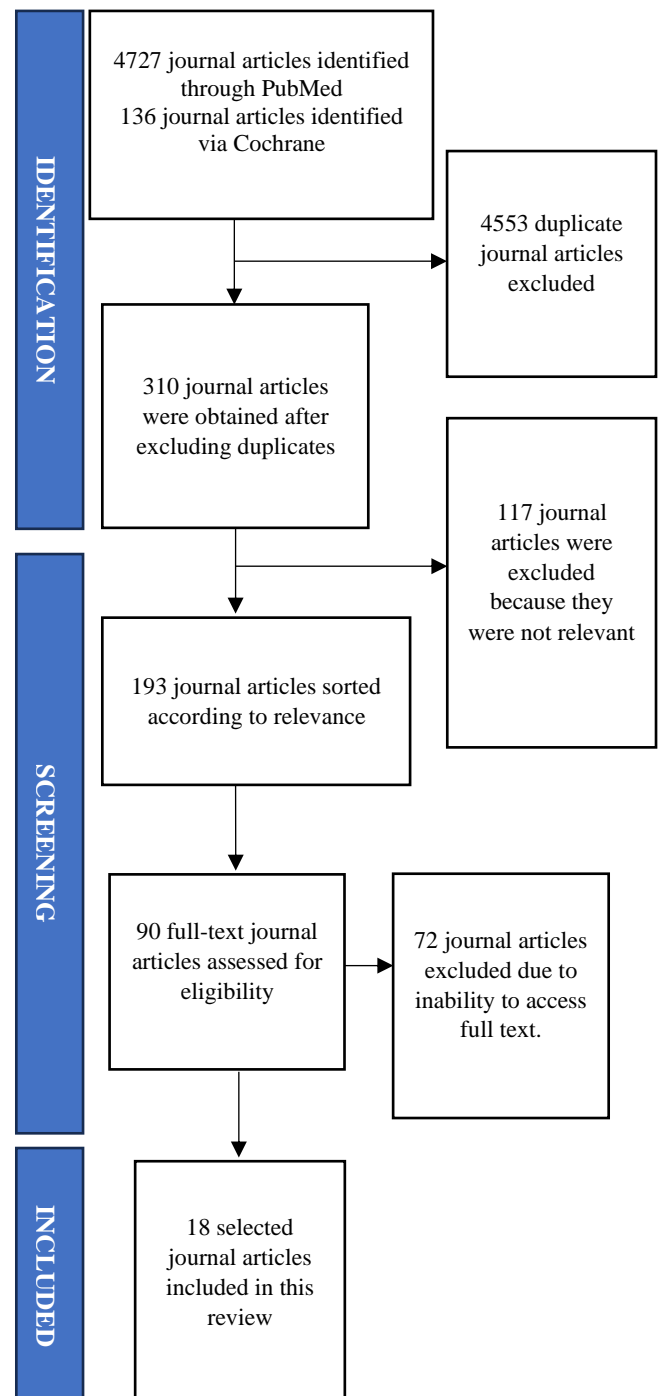
## METHOD

We conduct a search from databases such as PubMed, Cochrane Library, Web of Science and Scopus using these keywords: Hygiene hypothesis, Microbial exposure,

Allergies, Autoimmune diseases, COVID-19, Gut microbiome, Immune function. We applied filters and inclusion/exclusion criteria to narrow down the search results to relevant studies. Search inclusion criteria were limited to publications from 2019 to 2023 to ensure the latest articles used. Papers used have been published in national and international journals. Additionally, searches are restricted based on language, only returning results for articles written in English and Indonesian.

Based on their quality and applicability to the review subject, questions, and objectives of the literature review, all pertinent publications were examined and analyzed before being included or excluded. Each article's title and abstract are in alignment with the research question at the same time. If there is a match between the title and abstract, we proceed to verify the availability of the complete article. Finally, researchers read the entire paper to determine if it is relevant. Exclusion criteria for research searches are limited to paid articles,

articles using languages other than English and Indonesian. The flow of sorting journal articles included in this study is shown in Figure 1.



**Figure 1.** The flow of sorting journal articles included in the study.

**RESULTS AND DISCUSSIONS**

No.	Authors	Title	Journal	Year	Origin	Purpose	Type of Source	Study Design	Focus of The Study	Main Findings
	Leong RW, Mitrev N, Ko Y.	Hygiene Hypothesis: Is the Evidence the Same All Over the World?	Dig Dis	2016	Australia	Investigate global evidence of hygiene hypothesis	Review	Literature Review	Variations in hygiene practices and disease patterns worldwide, highlighting the need to consider diverse environmental factors in assessing the hygiene hypothesis.	Diverse environmental factors play a crucial role in assessing hygiene hypothesis
	Pfefferle PI, Keber CU, Cohen RM, Garn H.	The Hygiene Hypothesis - Learning From but Not Living in the Past.	Front Immunol	2021	Germany	Understand hygiene hypothesis without advocating unsanitary conditions	Article	Literature Review	Emphasizes the importance of understanding the hygiene hypothesis without advocating unsanitary conditions, highlighting the need for new research approaches.	New research approaches needed for a comprehensive view
	Garn H, Potaczek DP, Pfefferle PI.	The Hygiene Hypothesis and New Perspectives- Current Challenges Meeting an Old Postulate.	Front Immunol	2021	Germany	Address current challenges in hygiene hypothesis field	Article	Literature Review	Discusses current challenges in the hygiene hypothesis field and proposes new perspectives for better understanding immune regulation.	Updated perspectives required for enhanced immune regulation

No.	Authors	Title	Journal	Year	Origin	Purpose	Type of Source	Study Design	Focus of The Study	Main Findings
	Alexandre-Silva GM, Brito-Souza PA, Oliveira ACS, Cerni FA, Zottich U, Pucca MB.	The hygiene hypothesis at a glance: Early exposures, immune mechanism and novel therapies.	Acta Trop	2018	Brazil	Summarize hygiene hypothesis; focus on early exposures, immune mechanisms, therapies	Review	Literature Review	Provides a concise overview of the hygiene hypothesis, focusing on early exposures, immune mechanisms, and potential novel therapeutic approaches.	Potential therapeutic approaches for hygiene-related diseases
	Gupta V, Kumar R, Sood U, Singhvi N.	Reconciling Hygiene and Cleanliness: A New Perspective from Human Microbiome.	Indian J Microbiol	2020	India	Balance hygiene and microbial exposure using insights from human microbiome	Article	Opinion	Discusses the importance of balancing hygiene and microbial exposure, considering insights from the human microbiome and advocating for a holistic health approach.	Holistic health approach recommended for overall well-being
	Shi N, Li N, Duan X, Niu H.	Interaction between the gut microbiome and mucosal	Mil Med Res	2017	China	Explore gut microbiome-mucosal immune	Review	Literature Review	Emphasizes the vital connection between the gut microbiome and mucosal immune	Gut microbiome essential for maintaining

No.	Authors	Title	Journal	Year	Origin	Purpose	Type of Source	Study Design	Focus of The Study	Main Findings
		immune system.				system interaction			system, highlighting their significant role in preserving gut balance and immune functionality.	immune and gut health
	Liu AH.	Revisiting the hygiene hypothesis for allergy and asthma.	J Allergy Clin Immunol	2015	USA	Reexamine hygiene hypothesis for allergies and asthma	Article	Literature Review	Reexamines the hygiene hypothesis, emphasizing the role of microbial exposure in immune tolerance and discussing its potential benefits in preventing allergies and asthma.	Microbial exposure important in preventing allergies and asthma
	Perkin MR, Strachan DP.	The hygiene hypothesis for allergy - conception and evolution.	Front Allergy	2022	UK	Analyze hygiene hypothesis evolution and its role in allergies	Review	Literature Review	Analyzes the conception and evolution of the hygiene hypothesis for allergies, exploring epidemiological evidence and underlying biological mechanisms supporting the hypothesis.	Biological mechanisms support evolving hygiene hypothesis

No.	Authors	Title	Journal	Year	Origin	Purpose	Type of Source	Study Design	Focus of The Study	Main Findings
	Xu H, Liu M, Cao J, Li X, Fan D, Xia Y, et al.	The Dynamic Interplay between the Gut Microbiota and Autoimmune Diseases.	J Immunol Res	2019	China	Investigate gut microbiota-autoimmune diseases interaction	Article	Literature Review	Explores the dynamic interplay between the gut microbiota and autoimmune diseases, emphasizing the possible therapeutic approaches by manipulating the gut microbiome.	Manipulating gut microbiome could be a potential therapeutic approach
	Bach JF.	Revisiting the Hygiene Hypothesis in the Context of Autoimmunity.	Front Immunol	2021	France	Reevaluate hygiene hypothesis in relation to autoimmunity	Article	Literature Review	Reevaluates the hygiene hypothesis in relation to autoimmunity and discusses the possible role of early childhood microbial exposure in the development of a balanced immune system.	Early childhood microbial exposure may contribute to a balanced immune system
	van Tilburg Bernardes E, Arrieta MC.	Hygiene Hypothesis in Asthma Development: Is Hygiene to Blame?	Arch Med Res	2017	Canada	Explore hygiene hypothesis in asthma development	Article	Literature Review	Explores the hygiene hypothesis in asthma development, suggesting that microbial exposure during early life may	Microbial exposure important in preventing asthma development



No.	Authors	Title	Journal	Year	Origin	Purpose	Type of Source	Study Design	Focus of The Study	Main Findings
									play a significant role in asthma prevention.	
	Sehrawat S, Rouse BT.	Does the hygiene hypothesis apply to COVID-19 susceptibility?	Microbes Infect	2020	USA	Examine hygiene hypothesis's relevance to COVID-19 susceptibility	Article	Literature Review	Examines the suitability of the hygiene hypothesis in relation to the susceptibility to COVID-19, discussing the potential influence of hygiene practices on immune responses to the virus.	Hygiene hypothesis implications for COVID-19 susceptibility
	Brett Finlay B, Amato KR, Azad M, Blaser MJ, Bosch TCG, Chu H, et al.	The hygiene hypothesis, the COVID pandemic, and consequences for the human microbiome.	Proc Natl Acad Sci U S A	2021	Canada	Explore hygiene hypothesis within COVID-19 pandemic framework	Article	Literature Review	Explores the hygiene hypothesis within the framework of the COVID-19 pandemic, delving into the potential effects of the pandemic on both the human microbiome and immune well-being.	Potential effects of pandemic on human microbiome and immune health
	Santo CE, Caseiro C, Martins MJ, Monteiro R, Brandão I.	Gut microbiota, in the halfway between	Nutrients	2021	Portugal	Investigate gut microbiota-nutrition-lung	Article	Literature Review	Investigates the connection between the gut microbiota, nutrition, and lung	Gut microbiota impacts nutrition and

No.	Authors	Title	Journal	Year	Origin	Purpose	Type of Source	Study Design	Focus of The Study	Main Findings
		nutrition and lung function.				function connection			function, emphasizing the potential influence of the gut microbiota on respiratory well-being.	respiratory well-being
	Ruigrok RAAA, Weersma RK, Vich Vila A.	The emerging role of the small intestinal microbiota in human health and disease.	Gut Microbes	2023	Netherlands	Explore small intestinal microbiota's significance for health	Article	Literature Review	Explores the growing significance of the small intestinal microbiota in relation to human health and disease, highlighting its potential consequences for immune function and overall wellness.	Implications for immune function and overall wellness
	Wiertsema SP, van Bergenhenegouwen J, Garssen J, Knippels LMJ.	The Interplay between the Gut Microbiome and the Immune System in the Context of Infectious Diseases throughout Life and the Role of Nutrition in	Nutrients	2021	Netherlands	Investigate gut microbiome-immune system interaction in infectious diseases context	Article	Literature Review	Explores the intricate interplay between the gut microbiome and the immune system, particularly in the context of infectious diseases, and discusses the role of nutrition in optimizing treatment strategies.	Nutrition could enhance treatment strategies for infectious diseases

No.	Authors	Title	Journal	Year	Origin	Purpose	Type of Source	Study Design	Focus of The Study	Main Findings
		Optimizing Treatment Strategies.								
	Bacorn M, Romero-Soto HN, Levy S, Chen Q, Hourigan SK.	The Gut Microbiome of Children during the COVID-19 Pandemic.	Microorganisms	2022	USA	Study gut microbiome of children during COVID-19 pandemic	Article	Observation	Examines the gut microbiome of children during the COVID-19 pandemic, exploring potential changes and their implications for children's health.	Potential changes and implications for children's health
	Shahrbaf MA, Hassan M, Vosough M.	COVID-19 and hygiene hypothesis: increment of the inflammatory bowel diseases in next generation?	Expert Rev Gastroenterol Hepatol	2022	Iran	Investigate hygiene hypothesis's influence on Inflammatory Bowel Diseases (IBD) in future generations due to COVID-19	Article	Literature Review	Explores the potential impact of the hygiene hypothesis on the development of Inflammatory Bowel Diseases (IBD) in future generations due to the influence of COVID-19.	Consideration of future generation's susceptibility to IBD due to hygiene hypothesis and COVID-19

### **Hygiene Hypothesis: Link to Allergy and Autoimmune Diseases**

The Hygiene Hypothesis suggests that decreased exposure to microbes during early life may elevate the likelihood of developing allergies and autoimmune diseases. The immune system requires early exposure to microbes to develop properly, and lack of exposure to microbes can result in an imbalanced immune system. This theory is supported various studies that demonstrate an association between lower levels of microbial exposure and higher incidence of allergies and autoimmune diseases.

### **Hygiene Hypothesis and Allergy**

The hygiene hypothesis proposes that it is crucial for early childhood to be exposed to a diverse range of microbes in order to foster the development of a well-balanced immune system capable of tolerating harmless allergens. According to the hypothesis, an increase in allergic diseases such as asthma, atopic dermatitis, and food allergies has been contributed to by reduced exposure to microorganisms due to

improved hygiene practices and living conditions in developed countries.

Research investigations have supplied proof that the gut microbiome has a fundamental role in the development of the immune system, specifically in the modulation of immune responses to allergens. The article authored explores the discussions regarding the interactions between the gut microbiome and the mucosal immune system.<sup>6</sup> The mucosal immune system refers to the immune system that is present in mucosal tissues such as the gastrointestinal tract, respiratory tract, and genitourinary tract. The research study emphasizes the significance of the gut microbiota in preserving gut balance and supporting immune functionality. It is noted that the gut microbiome helps to promote immune tolerance, which is the ability of the immune system to tolerate harmless substances such as food proteins and commensal bacteria.

The role of microbial exposure in immune tolerance is summarized who revisits the Hygiene Hypothesis for allergy and asthma

and discusses the potential benefits of microbial exposure for allergy prevention.<sup>7</sup>

The Hygiene Hypothesis suggests that insufficient exposure to microbes during early childhood may raise the likelihood of developing allergies and asthma. Liu summarizes the importance of microbial exposure in immune tolerance and discusses the potential benefits of microbial exposure for preventing allergies. She notes that exposure to a diverse range of microbial species, particularly during early childhood, may promote immune tolerance and reduce the risk of developing allergies and asthma .

The conception and evolution of the Hygiene Hypothesis for allergy are reviewed, and the epidemiological evidence and underlying biological mechanisms that support the hypothesis are analyzed.<sup>8</sup> They propose that early life exposure to microbial diversity is essential for the establishment of immunological tolerance and the avoidance of allergy disorders.

### **Hygiene Hypothesis and Autoimmune Diseases**

The development of autoimmune diseases has also been linked to the Hygiene Hypothesis. According to the hypothesis, dysregulation of the immune system and an increased risk of autoimmune diseases can result from reduced exposure to microorganisms during early childhood.

Summarizes the research that suggests a link between gut dysbiosis and disorders such multiple sclerosis, rheumatoid arthritis, and type 1 diabetes in their explanation of the complicated association between the gut microbiota and autoimmune diseases. They propose that manipulating the gut microbiome could be a promising therapeutic approach for autoimmune diseases.<sup>9</sup>

Within the context of autoimmunity, examines the evidence that supports the Hygiene Hypothesis, proposing that early childhood exposure to microbes may play a crucial role in the development of an immune system capable of distinguishing between self and non-self-antigens.<sup>10</sup> Emphasizes the potential involvement of the gut microbiome in the development of

asthma, highlighting its role in the pathogenesis of the condition. The discussion of the Hygiene Hypothesis in relation to asthma development suggests that early-life microbial exposure might hold significance for preventing asthma.<sup>11</sup>

Overall, the Hygiene Hypothesis suggests that Early-life exposure to a wide range of microorganisms is crucial for the maturation of an immune system that is well-balanced, capable of tolerating harmless allergens, and effectively distinguishing between self and non-self-antigens. This exposure has the potential to lower the risk of both allergic and autoimmune diseases.

### **The Hygiene Hypothesis, Gut Microbiome, and COVID-19: Exploring the Interplay and Potential Consequences for Human Health**

The Hygiene Hypothesis suggests that early-life exposure to a broad variety of microorganisms is essential for the formation of an immune system that is well-regulated, capable of distinguishing between

self and non-self-antigens, and potentially lowering the risk of allergic and autoimmune diseases. In recent times, there has been notable interest in this hypothesis within the context of the COVID-19 pandemic, as researchers raise inquiries regarding whether increased adherence to hygiene measures, leading to reduced exposure to microbes, might be a contributing factor to the heightened vulnerability to COVID-19. Some studies suggest that the human gut microbiota may play an important role in determining a person's susceptibility to COVID-19.

According to a study conducted,<sup>12</sup> there is evidence indicating that the hygiene hypothesis might be relevant to the susceptibility of individuals to COVID-19., as reduced exposure to microbes due to hygiene measures may lead to dysregulation of the immune system, which may make individuals more susceptible to the virus. According to a separate study conducted<sup>13</sup>, there are indications that the COVID-19 pandemic and the subsequent rise in hygiene practices could have

enduring effects on the human microbiome. They put forward the suggestion that limited exposure to microbes could potentially result in dysbiosis, which in turn may elevate the risk of developing autoimmune diseases later on.

The human gut microbiome has also been linked to COVID-19 susceptibility. It is proposed that the gut-lung axis could have a significant impact on an individual's vulnerability to COVID-19.<sup>14</sup> They suggest that the gut microbiome may have the ability to modulate the immune response to respiratory infections, including COVID-19. Study has argue that the small intestine microbiota, long considered an overlooked microbiome in human health and disease, is a crucial ecosystem that regulates both local and systemic immune responses.<sup>15</sup> The microbiome has the capability to directly regulate the physiological and metabolic functions of the host by producing various metabolites such as short-chain fatty acids, bile acids, and vitamins. The authors suggest that the small intestine microbiota is also capable of influencing host responses

to infectious agents, such as viruses and bacteria, and can protect against the development of chronic inflammatory disorders.

Furthermore, one study has propose that disturbances in the microbiota of the small intestine, such as dysbiosis, could potentially contribute to the onset of various gastrointestinal disorders, including inflammatory bowel disease, celiac disease, and small intestinal bacterial overgrowth.<sup>15</sup> Inflammatory bowel diseases (IBD) are chronic inflammatory disorders of the gastrointestinal tract that include Crohn's disease (CD) and ulcerative colitis (UC). Recent research has demonstrated that COVID-19 can heighten the likelihood of developing inflammatory bowel disease (IBD).

The gut microbiota has important roles in modulating host immune responses and maintaining intestinal homeostasis. They emphasize the necessity for additional research to comprehend the exact mechanisms through which the small intestine microbiota influences human health and disease. Additionally, there is a need to

identify potential therapeutic approaches for addressing small intestine dysbiosis.

Moreover, suggest that the gut microbiome might have a vital part in the immune response against infectious diseases, including COVID-19.<sup>16</sup> They propose that nutrition could play a crucial role in optimizing treatment approaches for infectious diseases through the modulation of the gut microbiome. Carried out a study during the COVID-19 pandemic, focusing on the gut microbiome of children. The study aimed to examine how COVID-19 infection affects the composition of the gut microbiome in children.<sup>17</sup>

The study findings indicated notable distinctions in the gut microbiome composition between children with COVID-19 and those who were healthy. Particularly, COVID-19 infection was linked to a decrease in the presence of beneficial gut bacteria, including *Bifidobacterium*. This specific bacterium is associated with enhanced immune function and reduced inflammation. On the other hand, the study found an increase in

opportunistic pathogens in children with COVID-19, which could potentially lead to negative health outcomes. It is important to recognize that the gut microbiome has a vital role in the development and operation of the immune system, and alterations in its composition can have substantial consequences for overall well-being. These discoveries imply that COVID-19 infection could have wider health ramifications beyond its acute respiratory symptoms, especially for children who are still in the process of developing their immune systems. The study underscores the significance of monitoring the gut microbiome in children diagnosed with COVID-19, and it emphasizes the potential advantages of interventions aimed at fostering a healthy gut microbiome.

Nevertheless, there is also compelling evidence indicating that COVID-19 infection might elevate the likelihood of developing inflammatory bowel diseases and other autoimmune conditions later on. According to<sup>18</sup> it is proposed that COVID-19 infection has the potential to disrupt the immune system's



regulation, thereby increasing the future risk of developing inflammatory bowel diseases. They suggest that the Hygiene Hypothesis may have a crucial role in the development of these diseases following a COVID-19 infection.

In summary, the Hygiene Hypothesis posits that being exposed to a wide variety of microorganisms during early life is crucial for the establishment of a well-regulated immune system. The human gut microbiome has been linked to COVID-19 susceptibility, with some studies suggesting that reduced exposure to microbes due to hygiene measures may lead to dysregulation of the immune system, which may make individuals more susceptible to the virus. Nonetheless, there is also available evidence indicating that COVID-19 infection could raise the potential for developing inflammatory bowel diseases and other autoimmune conditions in the future. This increased risk may be attributed to the potential dysregulation of the immune system caused by COVID-19. To gain a comprehensive understanding of the

relationship between the Hygiene Hypothesis, the human gut microbiome, and COVID-19, further research is warranted.

## CONCLUSIONS

The hygiene hypothesis proposes that the rise of modern hygiene practices, resulting in reduced exposure to infectious agents, has contributed to a surge in allergic, autoimmune, and inflammatory diseases. Modifications in the gut microbiome, influenced by the implementation of hygiene practices, could potentially contribute to an increased susceptibility to developing these conditions.

The COVID-19 pandemic has emphasized the significance of maintaining a robust immune system and the involvement of the gut microbiome in immune function. COVID-19 infection has the potential to modify the composition of the gut microbiome, which can have implications for the severity of the disease and long-term health outcomes among individuals who have recovered. To address these concerns, maintaining a diverse gut

microbiome through dietary and lifestyle interventions is crucial. Practices that increase microbial exposure, like outdoor activities and pet ownership, can be beneficial. It is essential to improve hygiene practices without compromising microbial exposure for effective public health strategies. The hygiene hypothesis and gut microbiome dysbiosis play significant roles in allergic, autoimmune, and inflammatory diseases.

Further research is necessary to fully understand the implications of COVID-19 on microbial exposure and immune health. Promoting a healthy gut microbiome while maintaining adequate hygiene practices holds important implications for public health.

#### ACKNOWLEDGEMENT

The authors express their gratitude to the Faculty of Medicine Hang Tuah University for their support and for fostering an environment that encourages academic staff to produce scientific publications.

#### CONFLICT OF INTEREST

The authors state that they have no conflicts of interest to disclose in relation to this study.

#### REFERENCES

1. Leong RW, Mitrev N, Ko Y. Hygiene Hypothesis: Is the Evidence the Same All Over the World? *Dig Dis* [Internet]. 2016 Mar 1 [cited 2023 Apr 27];34(1–2):35–42. Available from: <https://pubmed.ncbi.nlm.nih.gov/26982573/>
2. Pfefferle PI, Keber CU, Cohen RM, Garn H. The Hygiene Hypothesis - Learning From but Not Living in the Past. *Front Immunol* [Internet]. 2021 Mar 16 [cited 2023 Apr 27];12. Available from: <https://pubmed.ncbi.nlm.nih.gov/33796103/>
3. Garn H, Potaczek DP, Pfefferle PI. The Hygiene Hypothesis and New Perspectives-Current Challenges Meeting an Old Postulate. *Front Immunol* [Internet]. 2021 Mar 18 [cited 2023 Apr 27];12. Available from: <https://pubmed.ncbi.nlm.nih.gov/33815389/>
4. Alexandre-Silva GM, Brito-

- Souza PA, Oliveira ACS, Cerni FA, Zottich U, Pucca MB. The hygiene hypothesis at a glance: Early exposures, immune mechanism and novel therapies. *Acta Trop* [Internet]. 2018 Dec 1 [cited 2023 Apr 27];188:16–26. Available from: <https://pubmed.ncbi.nlm.nih.gov/30165069/>
5. Gupta V, Kumar R, Sood U, Singhvi N. Reconciling Hygiene and Cleanliness: A New Perspective from Human Microbiome. *Indian J Microbiol* [Internet]. 2020 Mar 1 [cited 2023 Apr 27];60(1):37–44. Available from: <https://pubmed.ncbi.nlm.nih.gov/32089572/>
  6. Shi N, Li N, Duan X, Niu H. Interaction between the gut microbiome and mucosal immune system. *Mil Med Res*. 2017 Apr 27;4(1).
  7. Liu AH. Revisiting the hygiene hypothesis for allergy and asthma. *J Allergy Clin Immunol*. 2015 Oct 1;136(4):860–5.
  8. Perkin MR, Strachan DP. The hygiene hypothesis for allergy - conception and evolution. *Front allergy* [Internet]. 2022 Nov 24 [cited 2023 Apr 27];3. Available from: <https://pubmed.ncbi.nlm.nih.gov/36506644/>
  9. Xu H, Liu M, Cao J, Li X, Fan D, Xia Y, et al. The Dynamic Interplay between the Gut Microbiota and Autoimmune Diseases. *J Immunol Res*. 2019;2019.
  10. Bach JF. Revisiting the Hygiene Hypothesis in the Context of Autoimmunity. *Front Immunol*. 2021 Jan 28;11.
  11. van Tilburg Bernardes E, Arrieta MC. Hygiene Hypothesis in Asthma Development: Is Hygiene to Blame? *Arch Med Res*. 2017 Nov 1;48(8):717–26.
  12. Sehrawat S, Rouse BT. Does the hygiene hypothesis apply to COVID-19 susceptibility? *Microbes Infect* [Internet]. 2020 Oct 1 [cited 2023 Apr 27];22(9):400–2. Available from: <https://pubmed.ncbi.nlm.nih.gov/32653475/>
  13. Brett Finlay B, Amato KR, Azad M, Blaser MJ, Bosch TCG, Chu H, et al. The hygiene hypothesis, the COVID pandemic, and consequences for the human microbiome. *Proc Natl Acad Sci U S A* [Internet]. 2021 Feb 9 [cited 2023 Apr 27];118(6).

- Available from:  
<https://pubmed.ncbi.nlm.nih.gov/33472859/>
14. Santo CE, Caseiro C, Martins MJ, Monteiro R, Brandão I. Gut microbiota, in the halfway between nutrition and lung function. *Nutrients*. 2021 May 1;13(5).
15. Ruigrok RAAA, Weersma RK, Vich Vila A. The emerging role of the small intestinal microbiota in human health and disease. *Gut Microbes* [Internet]. 2023 Dec 31 [cited 2023 Apr 27];15(1):2201155. Available from:<http://www.ncbi.nlm.nih.gov/pubmed/37074215>
16. Wiertsema SP, van Bergenhenegouwen J, Garssen J, Knippels LMJ. The Interplay between the Gut Microbiome and the Immune System in the Context of Infectious Diseases throughout Life and the Role of Nutrition in Optimizing Treatment Strategies. *Nutrients* [Internet]. 2021 Mar 1 [cited 2023 Apr 27];13(3):1–14. Available from:  
<https://pubmed.ncbi.nlm.nih.gov/33803407>
17. Bacorn M, Romero-Soto HN, Levy S, Chen Q, Hourigan SK. The Gut Microbiome of Children during the COVID-19 Pandemic. *Microorganisms* [Internet]. 2022 Dec 1 [cited 2023 Apr 27];10(12). Available from:  
<https://pubmed.ncbi.nlm.nih.gov/36557713>
18. Shahrabaf MA, Hassan M, Vosough M. COVID-19 and hygiene hypothesis: increment of the inflammatory bowel diseases in next generation? *Expert Rev Gastroenterol Hepatol* [Internet]. 2022 [cited 2023 Apr 27];16(1):1–3. Available from:  
<https://pubmed.ncbi.nlm.nih.gov/34919489/>