

Review Article



Indoor Bacterial Exposure in Sick Buildings and Associated Inflammatory Pathways in Humans: A Mini-Review

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Abstract

Indoor air quality (IAQ) and sick building syndrome (SBS) have long been public health concerns, which were further exacerbated by the COVID-19 pandemic. SBS is associated with inflammatory responses, and immune-related reactions play important roles in its pathogenesis. Bacteria play a significant role in deteriorating IAQ, especially in indoor environments. While bacteria in indoor environments are known stressors, their contribution to low-grade systemic inflammation and its impact on mental and physical well-being, including central nervous system effects, is a crucial aspect of SBS. This inflammatory response involves key cytokines like IL-1, IL-6, IFN- γ , and TNF- α , potentially leading to neuroendocrine changes, acute phase responses, and altered neural activity impacting behavior. This review provides a comprehensive overview of current research from an environmental health perspective and sheds light on the importance of bacterial concentration in line with inflammatory pathways in understanding SBS and highlights the need for effective strategies to mitigate bacterial contamination in indoor environments.

Keywords: Indoor air quality, Bacterial load, SBS, Inflammation, Immune response, Cytokines

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Introduction

One of the major changes in human lifestyle since the beginning of industrialization has been a remarkable increase in the amount of time spent indoors. It has been revealed that the majority of the population across different age groups spends up to 90% of their time in indoor environments.¹ Following the outbreak of coronavirus disease 2019 (COVID-19), this trend became even more prevalent in daily life.² Of note, this condition results in a great rise in exposure to indoor air contaminants.^{3,4} Although one of the key considerations in modern building architecture is the provision of appropriate ventilation systems, many existing buildings are too old to accommodate modern ventilation technologies, which may contribute to the development of sick building syndrome (SBS).⁵ The term SBS has been used since 1980 by Theodor

D. Sterling, a tobacco consultant, and after the occurrence of Legionnaires' disease (a type of pneumonia that spread among participants at a conference through the ventilation system of a hotel in Philadelphia), it became a widely recognized concept.⁶ SBS-induced symptoms, including allergic and flu-like symptoms, usually resolve after individuals leave or change the affected environment.^{6,7,8} The factors that affect SBS are usually the factors that have impact on indoor air quality (IAQ) and can be divided into two major categories: environmental and individual factors. Bacteria are an important environmental component of biologically derived airborne contaminants.⁹ Bacteria can thrive and multiply in indoor environments, including ventilation systems, surfaces, and dust. High concentrations of airborne bacteria can interact with the human immune system through inhalation, skin contact, and ingestion,



potentially leading to irritation and inflammation in the respiratory tract and other organs.¹⁰ Inflammation, as a natural bodily response to harmful stimuli, can play a crucial role in the development and exacerbation of various diseases, including respiratory illnesses, allergies, and even cardiovascular diseases, if it persists and becomes chronic.¹¹ Therefore, investigating the association between bacterial concentrations in indoor environments, the occurrence of SBS, and the activation of inflammatory pathways in the body is of paramount importance.

Accordingly, evaluating airborne bacterial concentrations, their association with SBS occurrence, and their potential to activate inflammatory pathways represents an important public, environmental, and occupational health priority that requires coordinated efforts for effective prevention and control. This review synthesizes current knowledge regarding SBS, indoor bacterial species and concentrations, associated inflammatory pathways, and their combined impact on IAQ, while highlighting recent advances and identifying key research gaps that warrant further investigation.

Building Design and SBS

Based on different studies, myriad factors must be considered during the construction of buildings. Wemedo et al have evaluated the impact of building design and microbial concentration in different zones of Nigeria and reported that interior and exterior factors can define a building as healthy or sick structure. The exterior factors were claimed to be the location and basic concepts of building architecture; on the other hand, proper ventilation systems and inner space layout were identified as main interior factors. The number of windows and doors, along with their appropriate placement, and the height of the roofs are prerequisites for healthy building design. The function of each room within a building, which may be influenced by the number of occupants and the rate of human traffic, should also be considered during the building design process.^{12,13} In this regard, it seems that one of the neglected dimensions in building architecture is the response to this question: to what extent is each building appropriate not only for its intended function but also for providing a healthy environment for its inhabitants?

SBS Health Effects

It has been shown that IAQ can affect individuals in various angles, including their health status, well-being, and working efficiency.¹⁴ It has been revealed that bacterial concentration that were suspended in the air flow, usually uptake through inhalation and ultimately, caused respiratory system infections and airway allergic ailments.¹⁵ A broad spectrum of signs has been connected to SBS, such as eyes and nose itching, headaches and mental dizziness, acute respiratory syndrome, fever and chest pain.^{9,16} It is needed to be aware that the symptoms are not just limited to the mentioned signs and a list of flu-like, allergic/autoimmunity-like symptoms can fall in to this category.^{17,18,19} This may cause a high cost for health

care system providers. SBS can become an even greater challenge in hospitals, especially in intensive care units (ICUs) and operating rooms, which we will discuss in detail in the next section (Figure1).

Indoor Bacterial Species

Bacteria, as common microorganisms, can invade buildings through multiple routes (doors, windows, wall cracks, clothing of building occupants, and, surprisingly, heating and air-conditioning systems).¹³ Of note, dryness, high temperature and airflow have been reported as parameters of an increase in the count of air-borne microorganisms. Interestingly, the time of sampling like seasons and time of the day can affect the microbial concentration. In general, dry seasons and higher temperatures are considered as favorable conditions for better bacterial growth.

Before taking an in-depth look at the connection between SBS and bacterial concentration, a brief re-evaluation of different studies has shown that the bacterial types mainly responsible for SBS can be divided into normal flora and pathogenic species. In addition to live bacteria, bacterial-derived substances (toxins, antigens, glucans, and microbial volatile organic compounds [MVOCs]) can also be considered hazardous materials. Among bacteria and their derivatives, particle size is a particularly important characteristic.²⁰ There is an inverse correlation between the size of bacterial particulates and their suspension rate within the air. In addition, the acid/base strength of the environment and easy access to nutritional factors are highly valuable for optimum bacterial growth.²¹

Among pathogenic bacteria, particularly airborne species, the most well-known examples are *Yersinia pestis*, the causative agent of plague; *Klebsiella pneumoniae*, a leading cause of community-acquired pneumonia; and *Mycobacterium tuberculosis*, which causes tuberculosis.^{22,23,24}

Bacterial toxins can be classified as endotoxins and exotoxins. Exotoxins derived from *Staphylococcus aureus* and *Streptococcus pyogenes* can induce toxic shock syndrome.²⁵ Similarly, endotoxins which are a substructure of bacterial cell-wall can cause unwanted health effects. According to the standard measurements, an accepted range for endotoxin level is less than 100 endotoxin units (EU)/m³ of total exposure and is an accepted value for occupational safety requirements.²⁶ An important issue in analyzing bacterial species in SBS is the method of bacterial analysis. Replacing conventional culture-based techniques with advanced sequencing-based methods for indoor air assessment is of considerable importance.

SBS and Bacterial Concentration

There is a large body of evidence that emphasizes the relationship between total bacteria count (TBC), the severity of SBS, and IAQ factors. For instance, Wemedo et al proved that *Staphylococcus spp.*, *Bacillus spp.*, and *Enterobacter spp.* were the prevalent bacterial types in the airflow of different indoor spaces in Nigeria.¹³ In a recent publication by Mohammed et al, it has been proved that a significant decline was observable in bacterial and fungal

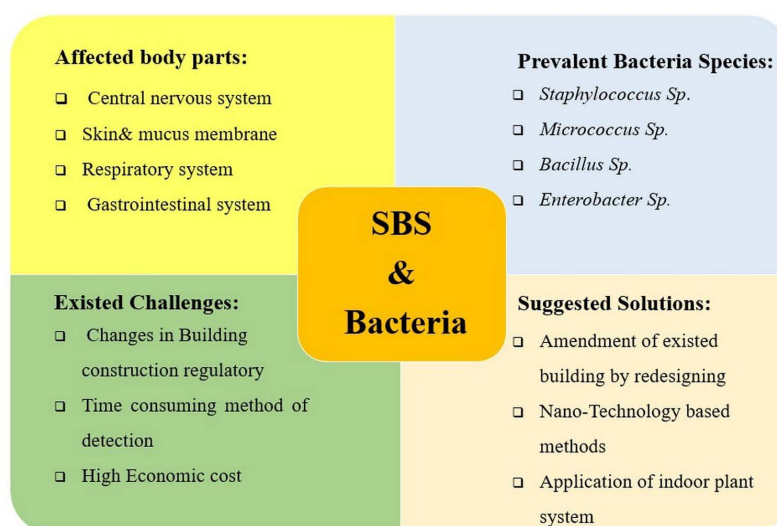


Figure 1. An Overview of the Relationship between Bacteria and SBS, Including Affected Body Systems, Common Bacterial Species, Challenges, and Suggested Solutions

concentrations of indoor air and surfaces after application of regular cleaning methods.²⁷ Moreover, Sudchoo et al revealed that a proper cleaning program can effectively down regulate the SBS related symptoms.²⁸

Maleki et al²⁹ recently published a report on the IAQ of Imam Hossein Hospital in Iran, showing that *Pseudomonas*, *Klebsiella*, and *Enterococcus* species were the major bacterial types, with higher concentrations detected during peak occupancy periods. However, no significant changes were recorded with respect to the humidity and temperature of the hospital's indoor environment, which was in contrast to the findings of Wemedo et al.¹³ In another study by Naddafi et al conducted in a children's hospital in Tehran, Iran, the total bacterial count was below the international standard limit (500 colony-forming units [CFU]/m³).³⁰ In this study, it was reported that although the bacterial concentration was below the recommended limit, 14% of the evaluated samples exceeded the cutoff value, and, unfortunately, 11% of these samples originated from the oncology ward. This finding represents an important warning sign, as patients in this ward are immunocompromised and highly susceptible to infections associated with SBS-related bacteria.³⁰ In a recent survey by Mirhoseini et al a spectrum from 19 to 356 CFU/m³ of bacteria was detected in different wards of evaluated hospital mainly filled with gram-positive bacteria species (approximately 75%) with an emphasis on *Staphylococcus* and *Micrococcus*.³¹ For hospitals, IAQ is far more important, since it can affect the health of staff, patients and visitors by having the capability of inducing nosocomial infections that are highly resistant to common antibiotics. Referring to the World Health Organization (WHO), up to 15% of patients that stay in hospitals were infected with nosocomial infections and the statistics are even worse for developing countries in proportion to developed countries (three times higher).^{32,33} The scientific evidence proves that *methicillin-resistant Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Mycobacterium tuberculosis* are capable of spreading via the aerosol route. According to Mirhoseini

et al, the most concerning finding among the bacterial concentrations measured in different hospital wards was observed in the operating rooms, where bacterial levels substantially exceeded the Iranian standard limits (180 CFU/m³).³¹ In a study conducted by Ahmednur et al in a prison in Ethiopia, an excessive burden of *Staphylococcus aureus* (891–15,439 CFU/m³) was detected in almost every room. The authors suggested that factors such as high temperature, dampness, overcrowding, poor hygiene practices, particularly inadequate floor cleanliness, and insufficient ventilation were responsible for these elevated concentrations. Increasing the available space per inmate was proposed as one of the most practical mitigation measures.¹² One of the buildings with high population flow is airport complexes in almost all countries. In an attempt by Veronika et al the bacterial load of different terminals, bus services and waiting rooms at Soekarno Hatta International Airport as the largest airport in Indonesia was evaluated. They reported that based on the literature the highest bacterial load was related to *S. aureus* type, although the number of evaluated bacteria in their study was lower than the standard defined limit by Indonesia ministry (700 CFU/m³).³⁴

Herein, we have presented examples of different building types that are generally regarded as highly crowded environments. A summary of bacterial loads, climatic conditions, sampling methods, and building characteristics reported in recent studies is presented in Table 1.

SBS and Bacterial Concentration Reduction: Possible Approaches

There are a body of evidence and valuable research that has suggested noticeable methods and procedures for decreasing bacterial concentration.⁴⁶ To provide a simple method for reducing the bacterial count, using a proper cleaning system according to the specific features of each building could be considered first-in-line solution. Other alternatives include physical methods (ultraviolet (UV) light and appropriate filters), chemical agents (disinfectants)

Table 1. A Summary of Bacterial Load in Different Building Types from Recent Studies

Building Type	Bacteria Concentration (CFU/m ³)	Climate type	Building Type	Sampling method	Reference
Jimma Town Prison Administration	891-15439	Ethiopia (Adisababa, Forested region)	Old and crowded	Settle plate method	12
Dormitory Jimma Universty	511-4010	Ethiopia (Adisababa, Forested region)	Old and crowded	Passive air sampling petri dish	35
Jimma University Library	367-2595	Ethiopia (Adisababa, Forested region)	Highly crowded	Passive air sampling petri dish	36
Ghana Hospital	278-2022	Ghana (tropical climate)	Highly crowded	Passive air sampling petri dish	37
Euthopia Public Primary School	23504	Ethiopia (Gondar city) subtropical high land climate	Different rooms from different buildings	Passive air sampling petri dish	38
Jimma University medical center	3106-9733	Italy (standard demitarian climate)	Crowded	Passive air sampling petri dish	39
Italian Office Building	50-500	Korea (continental climate)	Partially old buildings	Impactor Sampler	40
Animal Research Room	<500	Malaysia (Equatorial)	Old and Crowded	Microbial Air Sampler	41
Day Care Facilities	540.25	Korea (continental climate)	Crowded	MAS100	42
Medical Facilities	245.49	Korea (continental climate)	Crowded		42
Elder Care Facilities	149.63	Korea (continental climate)	Crowded		42
Postnatal Care Centers	169.65	Korea (continental climate)	Crowded		42
Johor primary care Facility	>500	Malaysia (Equatorial, hot and humid all year)	Different crowded buildings	Buck bio culture sampling pump	43
Sari Imam Khomeini & Shahid Zare Hospital	66-3330 22-227	Iran (sari, humid subtropical climate)	Different crowded buildings	Sibata personal sampler pump	44
Jawaharlal Nehru University libraries -Delhi	911-1460	India (Delhi, continental air)	Old, crowded	Buck bio culture sampling pump	45
Burn Hospital-Yazd	294	Iran (Yazd, hot desert climate)	Old	Quick Take30 pump	46
Portuguese Hospital	12-170 240-736	Portugal (Mediterranean)	NA	MAS100	47
Pakistani Hospital	60-467	Pakistan (Islamabad, humid subtropical)	old	Gilian 5000	48
Hospital-Singapore	>500	Singapore (tropical climate)	Modern	Andersen particle impactor	49
Research Laboratory	234.34-270	Malaysia (Equatorial)	NA	Passive air sampling petri dish	50
University Dormitory-China	2847	China (Tianjin, continental)	NA	Passive air sampling petri dish	51

and the application of ions (ozone).⁵² In a recent attempt by Leow et al it was been shown that a far-UVC system (far-UVC 222 nm) as a cleaning approach removed 90% of pathogens within 30 min.⁵³ Another possible strategy is avoiding the repeated use of a single building or room, which results in a higher population flow rate.¹³

Nanotechnology has had a revolutionary effect in many fields, thus its application as a new method for preventing SBS effects should not be neglected. Bhardwaj et al have improved old-fashioned bacterial detection methods with novel nano-based procedures. In general, nano-diagnostic methods make the detection of air-borne bacteria more focused, less biased, easier, simpler and less time-consuming.⁵⁴ Hajipour et al have reported that different types of nanoparticles have been applied for bacterial detection within various studies and these methods provide benefits such as synchronized detection of different bacteria within a sample, reduced detection time, and increased sensitivity for even very low bacterial concentrations.⁵⁵ Another environmentally friendly alternative to traditional methods of bacterial removal is the use of indoor-safe plants that do not pose allergic hazards. Tkachenko et al evaluated the possible benefit of this novel green method, and their finding was that the concentration of microorganisms was 1.5 to 5 times lower than in non-vegetated areas. They

proposed that *Ficus benjamina*, *Ficus benjamina* Wiandi, *Zamioculcas zamiifolia*, *Dracaena marginata*, *Dracaena fragrans*, *Yucca elephantipes*, *Schefflera digitata*, *Aspidistra elatior*, *Crassula ovata*, and *Spathiphyllum wallisii* are the best options for this purpose.⁵⁶ From a comprehensive comparative perspective, we believe that the use of indoor-safe plants might be the most economical approach at first glance. On the other hand, from a public health point of view, the ideal approach might be the one with acceptable disinfecting power. Thus, finding an optimal method requires considering many factors, such as how crowded the building is and which bacterial species are prevalent. Moreover, the type of building facility for maintaining humidity and temperature should be taken into account. An ultimate decision for each building should be based on these considerations. Of note, a combination of different methods or the renovation of existing systems with new, updated types should not be neglected.

SBS Consequence: Inflammation and Bacteria Confrontation

The missing part in many studies that evaluate the features of different bacteria and SBS as an inevitable consequence is inflammation and the role of immune-related reactions in the ultimate status of SBS. The presence of previously

mentioned bacteria which affect IAQ represents one of the stressors capable of creating a low-grade systemic inflammatory response, which has been shown to have mental and physical side effects on workers, thereby reducing their productivity.⁵⁷ It is noteworthy that the central nervous system (CNS) is among the body regions significantly impacted by the inflammatory response triggered by environmental stressors, such as the bacterial species implicated in SBS. Specifically, a set of inflammatory cytokines including interleukin-1 (IL-1), IL-6, interferon-gamma (IFN- γ), and tumor necrosis factor-alpha (TNF- α) are usually responsible for triggering basic inflammation after any encounter with bacterial ligands. This activation eventually leads to changes in neuroendocrine signals, activation of acute phase response,⁵⁸ and the production of either stimulatory or inhibitory neural responses that may impact behavioral traits.^{59,60,61} Along with that, through inflammation, a slight difference in kynurenine metabolism in the hippocampal area may lead to the manifestation of depressive behaviors, which is not far from expectations.⁶² Saeki et al reported that ocular ailments, a common manifestation of SBS, could be considered an allergic response. A comparison of 12 SBS individuals with ocular irritation against patients with allergic conjunctivitis (AC) revealed a pattern of IL-4 and IgE increase in tear and serum samples, respectively. Inconsistent with these findings, the frequency of eosinophils and the number of clinically positive allergens were lower than in AC cases.⁶³ An important finding that fills a knowledge gap was supported by a recent publication by Izaki et al, which revealed that the frequency of IL-4-producing CD4⁺ T cells increased in cases with SBS manifestations compared to healthy subjects. They found a positive correlation between the frequency of IL-4-producing CD4⁺ T cells and atopic ocular disease, thus suggesting that SBS should be considered a form of allergic ailment.⁶⁴

A glance at the inflammatory pathways activated upon exposure to SBS-inducing bacterial species shows that nuclear factor-kappa B (NF- κ B) and inflammatory cytokines, in addition to inflammasome activation, play a pivotal role in creating an inflammatory response toward these potential pathogenic inducers of SBS.⁶⁵ A detailed evaluation of *Staphylococcus sp.* as an example of various immune-activating bacteria involved in SBS is depicted in Figure 2. Overall, activation of innate immune system cells, especially macrophages and dendritic cells, by different bacterial products can lead to the production of NF- κ B, which results in the production of inflammatory cytokines. Subsequently, adaptive immune responses, including different subtypes of T helpers,⁶⁶ become stimulated, resulting in cytokine-mediated inflammation or atopic inflammation as factors responsible for the clinical manifestations of SBS.

Conclusion

Redesigning old buildings based on modern architectural values and replacing outdated ventilation systems with high-tech alternatives in skyscrapers or buildings with

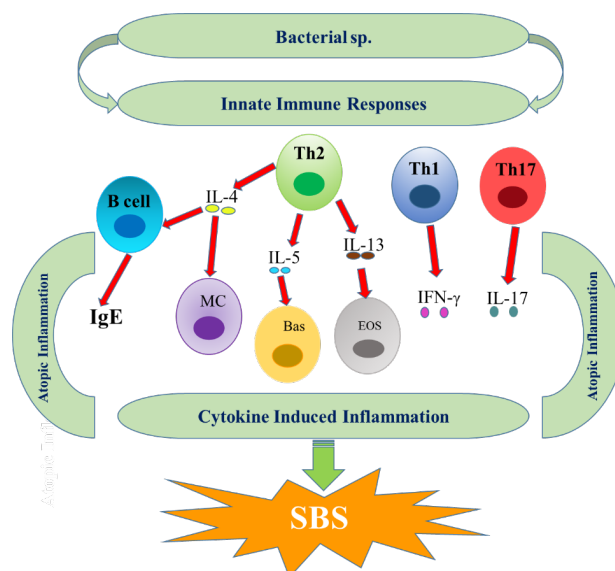


Figure 2. An in-detail Evaluation of *Staphylococcus sp.* as a Sample of Various Immune Activating Bacteria Involved in SBS

high population traffic are important factors in building correction efforts. Moreover, novel approaches such as plant-based or nanotechnology-derived air purification need to be considered as urgent prerequisites. These suggestions should be emphasized by both constructors and policymakers. A national plan for random intermittent inspections could reduce economic costs in the long term across different countries. One challenge affecting the results across studies is the sampling time during which the bacterial growth media is exposed to airflow. Additionally, the lack of similarity in building types across studies and the neglect of cultural differences between countries have been problematic. Therefore, accurate conclusions are difficult to draw, and these issues must be carefully considered. To overcome this variation, research in the field of SBS should be redirected toward optimizing a common sampling time; for example, sampling at times of highest and lowest population density in each building could be helpful. A meta-analysis based on different cultural zones should provide more clarifying evidence in the future.

Authors' Contribution

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Competing Interests

The authors of this article declare that they have no conflict of

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