Microbiology of the built environment

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Abstract | The built environment comprises all structures built by humans, including our homes, workplaces, schools and vehicles. As in any ecosystem on Earth, microorganisms have been found in every part of the built environment that has been studied. They exist in the air, on surfaces and on building materials, usually dispersed by humans, animals and outdoor sources. Those microbial communities and their metabolites have been implied to cause (or exacerbate) and prevent (or mitigate) human disease. In this Review, we outline the history of the field of microbiology of the built environment and discuss recent insights that have been gained into microbial ecology, adaptation and evolution of this ecosystem. Finally, we consider the implications of this research, specifically, how it is changing the types of materials we use in buildings and how our built environments affect human health.

The built environment encompasses all manufactured structures, including buildings, transportation systems and other physical surroundings constructed by humans[1]. These are the spaces where we spend most of our time[2], and they harbour unique microbial assemblages that are unlike most microbial communities found in other environments on Earth. For the most part, we design, build and operate our buildings to be inhospitable for microbial life, which often results in selective pressures that enable only a minority of dispersed microorganisms to survive[3]. We have continually manipulated our living and working spaces to reduce and remove aspects that are uncomfortable, unsightly, disease-promoting or inconvenient, thereby inadvertently shaping the ecology and evolution of the microorganisms that colonize those spaces. We can find many types of microorganism in built spaces, but many aspects of the composition of those complex microbial communities, their ecological role or their impact on human health remain unknown. Are they biologically active and alive? Can they promote disease, or do they have a role in protecting us from illness? Are they actively adapting to our attempts to control them? Can we harness beneficial microbial organisms while simultaneously eradicating harmful ones? How can we further optimize our built environments by taking into consideration the existing microbial communities?

In this Review, we discuss the history of the field of microbiology of the built environment and explore our current understanding of the ecology and evolution of this microbiome. The surprisingly long history of research in this field dates back hundreds of years and includes visual observations, microscopy and application of culture-based techniques (BOX 1) and more recent advances enabled by rapid growth in the application of culture-independent techniques that have addressed new fundamental evolutionary and ecological questions (BOX 2). We review what these studies have taught us about the factors that shape the metabolism, ecology and evolution of bacteria, viruses, fungi and archaea in our built environments. We also consider the implications of this research, specifically, how it is changing the types of materials we use in buildings, how we clean and manage our spaces and how we understand human health in relation to our built environments. Although many studies have contributed to cataloguing microbial species that can be found in built environments, there has been a recent shift towards investigating the translational potential, as well as creating more fundamental knowledge on how microorganisms biochemically adapt to the resources available in human-made spaces and the impact on their evolution.

Ecology of the built environment

Although ribosomal RNA (rRNA) amplicon sequencing of cultured isolates became common in the 1990s, it was not until 2004 that the first sequence-based bacterial community-wide survey of an indoor environment was performed[4]. This study comprised a 16S rRNA amplicon survey of the bacterial biofilms associated with the soap scum film on shower curtains. The complex communities that were identified included many alphaproteobacterial genera, such as *Sphingomonas* and *Methylobacterium*. Although these surveys were limited in terms of what could be inferred about the microbiome, the authors interpreted the presence of these bacteria as potentially contributing to the pink coloration of many of the biofilms. They also highlighted the potential pathogenicity of those

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Box 1 | **A microbial history of built environments**

Throughout our history, we have sought to control microbial growth and eradicate causative agents of disease from our buildings. Records of humanity's understanding that 'unclean' indoor environments can adversely affect human health date back to ancient times[118]. The prevailing knowledge then was that sterilization of building materials is sometimes warranted to stop the spread of 'leprous disease' in a contaminated home. This doctrine of sterilization has dominated human efforts to mitigate microbial contamination in buildings for centuries. By the early 1900s, research began to demonstrate how overcrowding, poor ventilation and contamination of buildings by microorganisms and organic matter can lead to infection and disease[119–124]. The associations between these factors and adverse health effects became apparent[77,125,126]. As our understanding that microorganisms could be causative agents of human health issues grew, techniques to sample and quantify the number of microorganisms from environmental samples emerged and have continued to grow with ever-increasing complexity. First, in the late 1800s and early 1900s came the ability to separately count bacteria and fungi via microscopy from samples collected on culture media[127–130], followed by an ability to identify specific bacterial or fungal species from a sample using selective culture media discovered in the 1950s (REFS[131,132]). Throughout the 1960s, researchers turned their focus to understand the sources[133–138], survival[139,140] and, eventually, means of controlling[141–144] microorganisms in the built environment. Associations between fungal spores in air and dust and allergy symptoms were established and quantified[145–147]. The rates and mechanisms of microbial emissions from human respiration[148–152] were investigated with the goal of revealing the dominant modes of transmission of communicable respiratory diseaeses[153,154]. Culture-based investigations dominated studies of bacteria and fungi in the built environment throughout the 2000s (REFS[155–159]) (and continues to dominate industrial hygiene sampling) until ribosomal RNA sequencing was discovered, which enabled the identification of previously unculturable microorganisms and a deeper understanding of the complexity of the microbial ecology of environmental samples[160–163].

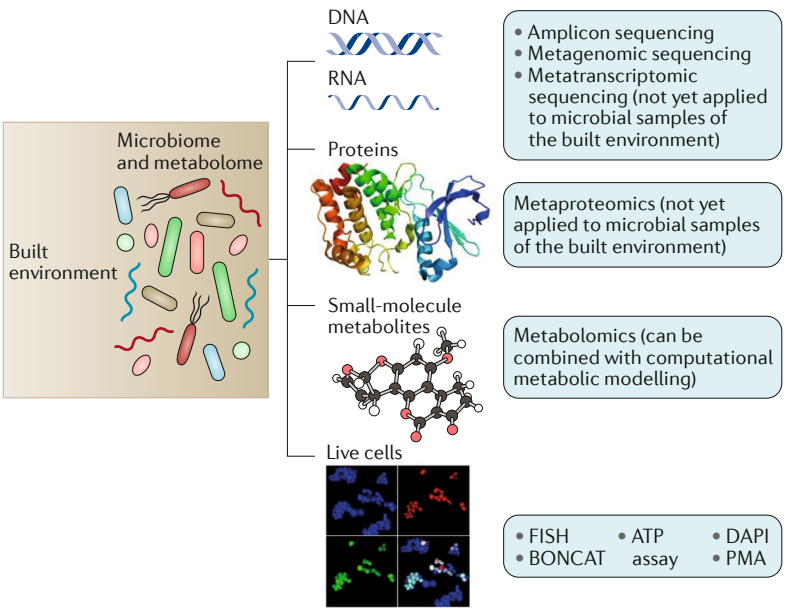
bacteria, as closely related strains have been shown to be opportunistic pathogens. Dozens of studies over the following decade continued to characterize patterns, associations and drivers of microbial community structures in various built environments, elucidating the most abundant taxa and investigating the similarities and differences of the microbial communities between spaces. Many of these studies have demonstrated that the majority of bacterial microorganisms found on surfaces seem to originate from human skin and oral sites. By contrast, built environments that are situated in more biodiverse environments (for example, farms or rural sites) have a greater number of organisms that originate from that environment, such as animal-associated microorganisms[5–29] (FIG. 1). A number of studies have quantified the absolute biomass of bacteria and fungi in built environment samples using molecular methods[30–33] and chemical surrogates, including ergosterol[34], glucans, hydroxy fatty acids and muramic acid[35]. Using DNA-based methods and leveraging a mass-balance modelling approach, one study estimated the average human emission rates of total particles to be 31 mg per hour, with approximately 37 million bacterial genome copies and approximately 7 million fungal genome copies per hour being dispersed from a human[30]. There have also been recent promising attempts to merge relative taxonomic abundance data with absolute abundance data from quantitative PCR[36–38]. Much less attention has been paid to viruses that may be present in built environment samples, in large part owing to the methodological challenges associated with analysing samples with extremely low viral biomass[39,40].

To advance beyond characterizing microbial taxonomic affiliation, it was necessary to sequence the genetic information for each microbiome (that is, metagenomics). In 2008, a study that applied shotgun metagenomic sequencing to indoor air sampled from two shopping centres in Singapore[41] found that the microbiota in the air comprised primarily bacteria that originate from indoor sources, such as occupants, and included potential opportunistic pathogens, including species of *Brucella*, *Bordetella* and *Mycobacterium*. A few years later, another study applied shotgun metagenomics sequencing to indoor and outdoor air samples from a modern high-rise building in New York City, as well as a hospital medical centre, a family home and a pier in San Diego[42]. The study described the bacterial and fungal taxonomic composition and functional gene diversity in these samples, revealing that indoor air often contained human and fungal associated DNA, whereas external air samples contained a more diverse mix of DNA fragments, including DNA fragments from mice, fish, plants and insects. The indoor air was dominated by genera such as *Pseudomonas*, which are commonly associated with human skin. Interestingly, although the functional gene abundances were mostly consistent across all environments (both indoor and outdoor), outdoor air in New York City was enriched for β-lactamases and tetracycline resistance genes.

Other recent advances in understanding the microbial ecology of the built environment include efforts to further characterize the microorganisms that were identified to colonize those spaces. One study[43] used 16S rDNA amplicon sequencing of reverse transcribed RNA, a technique that attempts to characterize the microbial organisms that are actively transcribing in the environment. However, there is substantial evidence that, unlike most RNA, the RNA transcript of the 16S rDNA gene is very stable in the environment, and as such, it is not a good indicator of viability and metabolic activity[44]. The viability of microorganisms that exist in indoor environments is an area of great interest, with decades of research suggesting extensive viability of bacteria and fungi (BOX 1). However, many studies indicate that most DNA detected using recent molecular tools does not represent viable microorganisms[3,5,45]. In contrast to these findings, a study reported that some of the organisms are alive, as bacterial and fungal growth were observed when water became available on household surfaces[43]. Most efforts to determine microbial viability have used axenic isolation on a limited range of substrates in vitro, limiting the detection of viable organisms as well as reflecting a bias towards organisms that may be able to grow in vitro but will not contribute actively in vivo. Advances in techniques to visualize microorganisms in situ, to determine their viability and activity, and to apply computational models of microbial metabolism are now being used to analyse samples from the built environment, and such approaches may soon lead to novel findings regarding the metabolic associations between organisms that support growth or competition on surfaces of those environments. Applying these tools to a biologically active event, such as material wetting, could be valuable in identifying

Box 2 | **New technologies and tools**

Rapid growth in the discovery and application of culture-independent techniques over the past few decades has greatly increased our understanding of the microbiology and ecology of built environments, revealing a vast and previously unknown diversity of microorganisms. The application of multi-omic technologies to examine the genomics, transcriptomics, metabolomics and proteomics of microbiomes has elucidated the phylogenetic and functional diversity of the indoor microbial world and helped us to understand some of the adaptive mechanisms microorganisms are using to survive (see the figure). Although amplicon sequencing of 16S, 18S and internal transcribed spacer ribosomal RNA (rRNA) genes has enabled a rich contextualization of thousands of samples from these environments (in part owing to the low cost, which is approximately US$25 a sample), metagenomic analysis is the preferred method for characterizing the taxonomic and functional potential of the community. Shotgun metagenomic surveys use either plasmid-based random environmental DNA sequencing from clone libraries or massively parallel direct sequencing platforms (for example, Illumina or 454-pyrosequencing) to survey the microbial genomic information from a sample. Metatranscriptomics leverages the same mechanism but using reverse transcribed messenger or total RNA to examine the genes that are actively transcribed in a sample. Metaproteomics is a valuable tool for examining the protein fragments that are actually produced, whereas metabolomics provides chemical dynamics associated with a surface or built substrate. However, to the best of our knowledge, only one study has applied metatranscriptomics to analyse samples from the built environment[47], whereas metaproteomics has yet to be applied to those samples. This is likely due to the low biomass preventing researchers from obtaining sufficient bacterial mRNA and protein.
In addition, new tools are allowing us to visualize microorganisms in situ, which enables us to interrogate their intimate associations using species or functional gene-specific probes and electron microscopy. Assays such as ATP detection are routinely used to detect microbial metabolic activity, but drawbacks of this approach are inaccuracy and the inability to specify which organisms are metabolically active. Techniques that test membrane integrity using chemicals that crosslink DNA (for example, propidium iodide and propidium monoazide) are useful for determining whether cells were alive or dead upon sampling, but again, are not always accurate owing to their differential impact on different microbial families[164]. Other approaches such as isotope probing or bioorthogonal noncanonical amino acid tagging (BONCAT)[165] rely on incorporating labelled chemicals into metabolically active organisms. These techniques are operationally difficult, and so are often used less but are possibly more accurate compared with the approaches discussed above[45]. Finally, the application of computational metabolic modelling of the biologically active organisms in a built environment has yet to be published but presents an exciting frontier for improving our understanding of the fundamental drivers of microbial ecology in buildings. Techniques such as genome-enabled metabolic flux balance models[166] enable the metabolic needs and products of each taxon to be captured in silico and can be extended to enable mapping of the metabolic relationships between microorganisms in the ecology community[167]. DAPI, 4′,6-diamidino-2-phenylindole; FISH, fluorescence in situ hybridization; PMA, propidium monoazide.



the mechanisms by which moisture facilitates mould growth; these fungi can produce microbial volatile organic compounds (MVOCs) that influence human health outcomes[46]. We expect that fungi will spontaneously grow when wetted; however, it is equally likely that their growth rate and metabolic activity are influenced by co-occurring species of fungi and bacteria, or even by archaea and viruses. Catalogues of indoor microbial genomic diversity can facilitate building these models, which will also benefit substantially from metatranscriptomic and metaproteomic data[47]. These data, in combination with metabolomics (which can be used to validate metabolite predictions), may help to identify the fundamental components that underlie the ecological characteristics of the built environment and also aid the identification of small molecules or elements that could be used to intervene in the microbial emergent properties that have negative health consequences.

Interactions between microorganisms and hosts

Humans and other animal occupants of built spaces have extensive microbial interactions with the air and surfaces. These interactions have traditionally been examined only with regard to the transmission of potential pathogens. For example, bacterial pathogens such as *Bacillus anthracis*[48], *Legionella pneumophila*[49] and *Mycobacterium tuberculosis*[50]; fungal pathogens such as *Cryptococcus neoformans*[51], *Histoplasma capsulatum*[52] and *Aspergillus fumigatus*[53]; and pathogenic viruses such as rhinovirus[54–56] and influenza virus[57–59] can be transmitted by direct inhalation. Other pathogens, such as *Clostridium difficile*[60], *Staphylococcus aureus*[61], *Pseudomonas aeruginosa*[61], *Pseudomonas putida*[61] and *Enterococcus faecalis*[61], as well as norovirus[61,62] and influenza virus[57,63], can be transmitted through surface contact, whereby they are transferred to the mucous membranes by hand-to-face contact (FIG. 2). These same transmission routes also occur for usually benign microorganisms, although they have been investigated in much less mechanistic detail than possible human pathogens.

The first study to examine the correlative relationships between the human microbiome and the microbiome of the built environment focused on home environments and mapped the sharing of bacteria between occupants and their homes[12]. This investigation demonstrated that the majority of bacteria associated with the surfaces had a statistically significant probability of having originated from the occupants of that home. Also, owing to the longitudinal design of the study, it was possible to correlate the occurrence of bacteria between occupants and surfaces and thus predict the 'movement' of organisms. For example, genotypes reassembled from metagenomic data, including uncultivated taxa assigned to Enterobacteriaceae, *Acinetobacter* and bacteriophages, which often comprised genes associated with pathogenicity and antibiotic resistance, could be identified on the hand of one of the occupants, and subsequently on home surfaces, and then on the hand of another occupant[12].

Subsequent human and indoor surface co-sampling studies have demonstrated that these patterns are not always conserved. For example, although the airborne

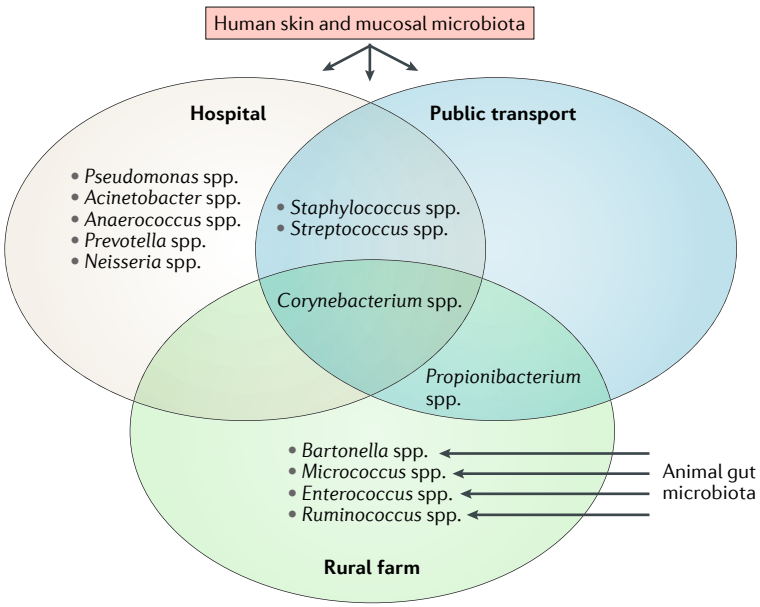


Fig. 1 | **Bacterial diversity of the built environment.** Cataloguing the bacterial diversity of hospitals, public transport and rural homes has revealed the abundance of bacteria associated with human skin and oral sites in built spaces, such as common potential human pathogens *Staphylococcus* spp. and *Streptococcus* spp., as well as commensals of the human microbiota, including *Corynebacterium* spp. and *Propionibacterium* spp. This suggests that humans are the major source of microorganisms found in the built environment. However, the microbial communities commonly associated with rural homes, for example, the homes of Amish farmers[72], also had an increased abundance of *Bartonella* spp., which have been associated with many animals and are potential opportunistic human pathogens. In addition, *Enterococcus* spp. and *Ruminococcus* spp., which are common gut-associated microorganisms in humans and animals, were also detected in rural homes. Hospital environments are associated with human-associated microorganisms, including common potential pathogens such as *Pseudomonas* spp., *Acinetobacter* spp., *Staphylococcus* spp. and *Streptococcus* spp., as well as common commensals such as *Anaerococcus* spp., *Prevotella* spp., *Corynebacterium* spp. and *Neisseria* spp.

microbiome inside homes was shown to be dominated by human-associated bacteria that were specific to each household, these microbiota did not resemble the microbiome of the occupants' skin any more than the skin microbiome from occupants of other households[64]. This confirms other studies that have demonstrated that, although occupant density influences the density of microbial particles in indoor air[6,13,65], outdoor air-associated microorganisms seem to comprise a greater proportion of the indoor air microbiome, particularly in well-ventilated spaces[64,66]. It is likely that the majority of microbial biomass dispersal from humans to the built environment occurs via skin-to-surface contact and/or direct shedding of larger biological particles. In support of this, a longitudinal study of surface-associated microbiota in a hospital, which comprised 365 consecutive days of observation in multiple patient rooms and staff spaces, and which included the staff- and patient-associated microbiota, highlighted the specificity of the surface-associated microbiota to the occupant of each room[67]. Although, maybe not surprisingly, the microbiota of an individual patient room initially resembled the microbiota of the previous occupant, within 24 hours of occupation, the surface microbiota originated from the new occupant entirely[67]. Patients also seemed to be a greater recipient of microorganisms from staff members than staff members were from patients. These results suggest a constant transfer of microorganisms within this environment, and although the majority of these organisms may not be active or even alive, it is still possible that this exchange could have health implications, such as from exposure to allergenic elements of dead organisms.

In fact, new understanding of the microbiology of the built environment and human health has shifted our perspective of microorganisms from a purely negative role (that is, being pathogenic or infectious) to a potentially positive role (that is, protective or preventive). Throughout history, most efforts to determine the influence of the indoor microbiome on health have focused primarily on the negative impact of fungi and other allergens on respiratory and skin diseases[68]. People inhale a considerable volume of indoor air daily, on average ~16,000 litres for adults[69]. Therefore, it stands to reason that the interactions between humans and buildings that facilitate microbial exposure will have a profound impact on human health.

Accepting that we are regularly exposed to ubiquitous microbiota necessitates research initiatives to elucidate the mechanism by which this exposure can influence health and disease. The concept of 'old friends' or the 'hygiene hypothesis', which suggests that improved hygiene is possibly linked to the rise in autoimmune conditions, is adaptable to this concept of beneficial microbial exposure[70]. For example, exposure to a complex microbial community in house dust has been inversely associated with the likelihood of developing asthma[71]. In another study, children exposed to household dust from homes immediately adjacent to a farming environment and who were actively working on the farm, presented with a statistically significant reduction in the risk of developing asthma compared with children who were not exposed to farming environments[72]. To investigate the biological underpinnings of that association, mice were exposed to house dust from the respective homes and then provided an allergic challenge. Farm home dust was protective against eosinophilia (asthma-associated inflammation), whereas the non-farm home dust was not protective. The association between this phenotype and exposure to particular species of bacteria (for example, taxa associated with mammalian gut-associated phyla Bacteroidetes and Firmicutes were more abundant in the farm-house dust) suggests that certain sources of bacteria may be better than others at offering protection[73,74]. Animal-associated microorganisms seem to offer some of the most effective protection against the development of asthma; for example, exposure of sensitized mice to dog stool-derived *Lactobacillus johnsonii* was associated with protection of these animal models against allergen challenge[75].

Microbial metabolism indoors

Besides direct infection, one of the primary concerns for the impact of microbial exposures in the built environment on human health is the influence of microbial metabolism. Although evidence for the associations between indoor dampness, mould odour and visible

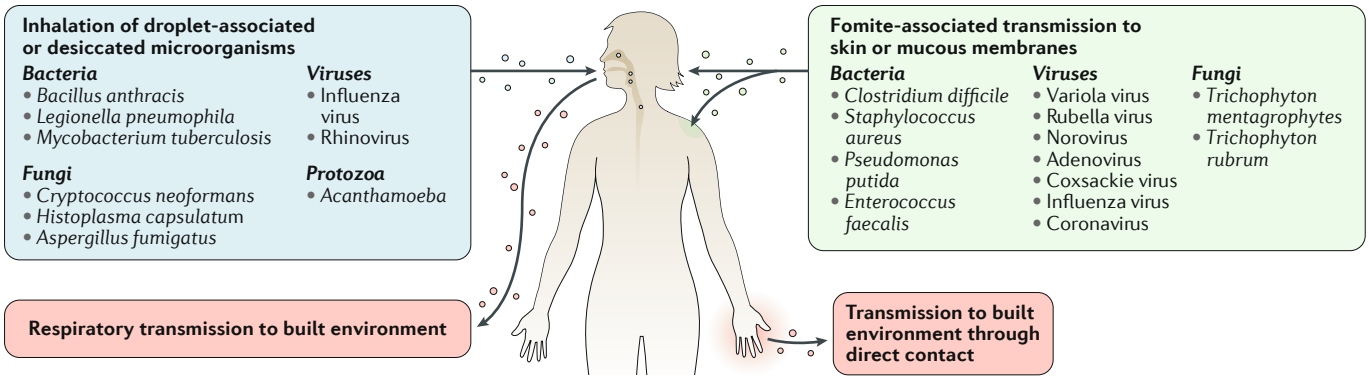


Fig. 2 | **Routes of microbial transmission.** Microbial transmission between human occupants and the built environment is reciprocal. For the majority of the history of this field, the emphasis has been on understanding the potential for human pathogens to be transmitted via air or surfaces in the built environment. For example, bacterial pathogens such as *Bacillus anthracis*[48], *Legionella pneumophila*[49] and *Mycobacterium tuberculosis*[50]; fungal pathogens such as *Cryptococcus neoformans*[51], *Histoplasma capsulatum*[52] and *Aspergillus fumigatus*[53]; and pathogenic viruses such as rhinovirus[54–56] and influenza virus[57–59], can be transmitted by direct inhalation. Other pathogens, such as *Clostridium difficile*[60], *Staphylococcus aureus*[61], *Pseudomonas aeruginosa*[61], *Pseudomonas putida*[61] and *Enterococcus faecalis*[61], as well as norovirus[61,62] and influenza virus[57,63], can be transmitted through surface contact. These same transmission routes also occur for usually benign microorganisms, although they have been investigated in much less mechanistic detail than possible human pathogens. Moreover, human-associated microorganisms are also being transmitted to the built environment.

mould, and disease states (including allergies and asthma[76–78]) exists, the links between the microbial community composition in the built environment, the abundance of their members, their metabolites and disease remain elusive. Bacterial and fungal toxins, allergenic components of the cellular wall and MVOCs have all been implicated in observed associations between indoor dampness and human health effects, but the evidence remains limited and inconclusive[79,80]. MVOCs are chemicals of low molecular mass, high vapour pressure and low water solubility, and as such are easily inhaled or can travel across the skin, and hence interact with human metabolic, immune and endocrine processes. Some studies have shown that MVOCs are enriched in damp buildings[81], and MVOCs have been associated with temperature and the type of building material, which functions as a nutritional and structural substrate for microbial growth[82]. However, the technical resolution of metabolomics has greatly improved in recent years, and prior confusion about whether MVOCs originate from microorganisms, plants or building material[82,83] is now being resolved. For example, a recent study under controlled laboratory conditions demonstrated the first attempt to combine advanced amplicon sequencing approaches with metabolomics to analyse samples from the built environment and showed that predicted microbial metabolites in periodically wetted environments correlate with changes in the microbial community structure and composition[43].

Most of our knowledge of microbial metabolism in the built environment comes from studies of indoor microbial isolates in vitro. However, a number of studies have attempted to determine the influence of moisture and other environmental variables on microbial metabolic activity. Studies of house dust have provided evidence of the moisture-dependent metabolic activity of the microorganisms in this particulate material[84,85]. Dust is a rich, heterogeneous mixture of materials, providing plentiful substrate for microbial growth. When exposed to moisture, the resulting germination of fungal and bacterial spores or dormant cells leads to an increase of metabolic products, which can include chlorinated hydrocarbons, amines, terpenes, alcohols, aldehydes and ketones, as well as sulfuric and aromatic compounds[86] (FIG. 3). However, metabolic activity is dependent on the amount of available water, whereby a relative humidity of 84–86% will cause an 8-day lag in CO_2 production (which is evidence of microbial respiration) compared with a relative humidity of 96–98%[84]. In a study of 40 homes with evidence of mould damage and 44 homes where mould damage was not found, most MVOCs could not be linked to the presence of mould[87]. The exceptions were 2-methyl-1-butanol (black truffle smell) and 1-octen-3-ol (so-called mushroom alcohol), which were weakly enriched in the presence of mould. It is possible that large variability in local environmental conditions, including local weather, building materials, humidity, temperature and household activities, could have contributed to the lack of statistical power in this study[87]. Another potential explanation is that variation in the species or strain of mould, and maybe in the co-associating bacterial organisms, could have affected the metabolic activity of these mould species, as well as the quantity of MVOCs in the air. Molecular detectors (such as mass spectrometers) could be used to detect the presence of fungus by association with high levels of fungal secondary metabolites in the absence of visible growth[88]. However, these approaches remain limited with little practical success thus far, as real life applications involve a large number of confounding factors and low concentrations near the detection limits of many analytical methods[89]. In most environments,

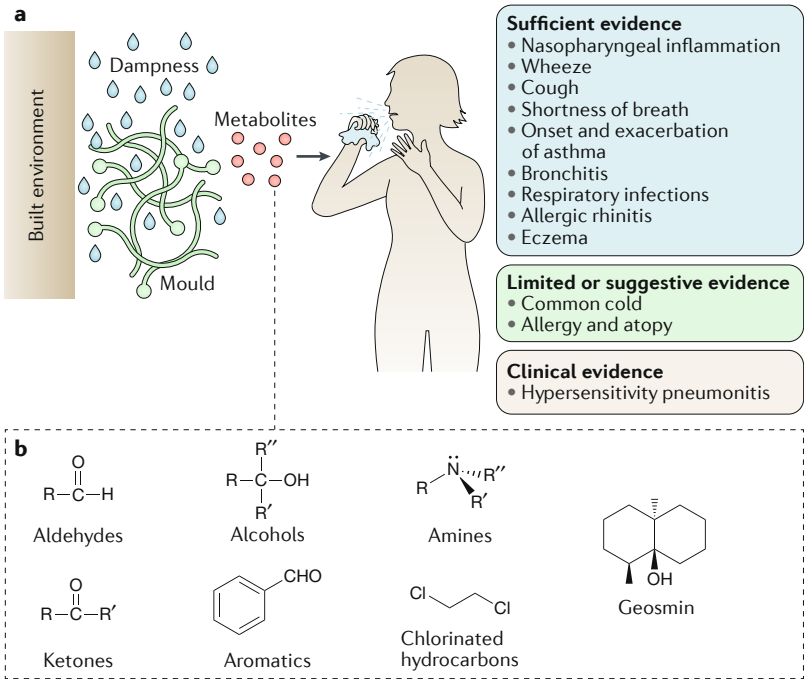


Fig. 3 | **Effects of the microbial metabolic products on human health. a**,**b** | Indoor air and surfaces are associated with dust and microbial chemical products. Increased relative humidity in the environment results in an increase in the amount of microbial metabolites in dust and on surfaces. Indoor dampness and mouldy conditions (for example, visible mould and mould odour) have been associated with many different disease states, but associations between the composition and concentration of microorganisms and their metabolites in the built environment and disease remain elusive[168] (part **a**). When exposed to moisture, the resulting germination of fungal and bacterial spores or dormant cells leads to an increase in metabolic products, which can include chlorinated hydrocarbons, amines, terpenes, alcohols, aldehydes, ketones, and sulfuric and aromatic compounds (part **b**).

short-chain fatty acids and medium-chain fatty acids were mainly detected as persistent MVOCs on periodically wetted surfaces, whereas amides, pyridine, dimethylsulfide, ethanethiol and benzothiazole were mostly detected in the kitchen environment, and sulfoxides, cyclic amides and other acids and esters mainly in the bathroom[43]. Interestingly, metabolic derivatives of phenyl acetic acid have been found on kitchen surfaces; it has been reported that this compound is produced by skin-associated bacteria, which supports the notion that those bacteria, now colonizing the built environment, exhibit metabolic activity[43].

Whether bacterial and fungal metabolites actually metabolically or physically interact remains a key question. Fungal–bacterial interactions have important roles in plant productivity and human disease, and thus there has been substantial research on how soil-associated and human-associated fungi interact with bacteria[90]. The potential for bacterial–fungal relationships, especially in biofilms, to alter the phenotypic characteristics of the isolated taxa makes these relationships so important for the built environment[91]. Fungal growth is a great concern in the modern home, owing in part to the impact of inhaling spores and the MVOCs released during active growth on human health. It has been suggested that bacteria can alter the virulence of clinically relevant fungal infections. For example, *Enterococcus faecalis* has been shown to inhibit hyphal formation and hence the virulence of *Candida albicans*; in fact, this relationship is bidirectional, whereby *C. albicans* can suppress the virulence of *E. faecalis*[92]. It was shown that inhibition of hyphal formation, biofilm formation and virulence of *C. albicans* is mediated by the *E. faecalis* bacteriocin EntV, which could represent a valuable clinical antifungal agent[93]. It is possible that the same mechanism could control the growth and lifestyle traits of indoor fungal and bacterial biofilms.

Culture-dependent and culture-independent studies suggest that the most common microorganisms associated with indoor surfaces belong to the fungal genera *Cladosporium*, *Penicillium*, *Aspergillus* and *Stachybotrys* (in damp buildings) and the bacterial taxa *Corynebacterium*, *Staphylococcus*, *Lactobacillus*, *Streptococcus*, Enterobacteriaceae, *Acinetobacter*, *Sphingomonas*, *Mycobacterium*, *Methylobacterium*, *Bacillus* and *Pseudomonas*[94,95]. However, the growth potential of these organisms is determined by the water activity (a measure of water availability in a material), chemical composition, pH and the physical properties of surfaces. Keeping building materials dry (that is, with water activity below 0.7) completely limits microbial growth for most known organisms on most materials[96]. Water activities above 0.7 are typically not observed in most built environments unless there are active moisture sources, such as water leakage or water vapour diffusion[97]. For example, a recent study of microbial communities on office surfaces in three climate zones in the Unites States reported water activities ranging from ~0.1 to ~0.7 (REF.[14]). Temperature affects both water activity and microbial growth, and although warmer temperatures probably promote more rapid growth, many psychrophilic organisms, especially bacteria, can still flourish at lower temperatures. The surface material is also very important; although all surfaces can function as a physical substrate, the chemical composition of the material provides a food source for the colonizing microorganisms and potentially selects for different species. Studies have demonstrated that cellulose-based surface materials, such as, for example, wood, can stimulate microbial growth more rapidly than inorganic materials such as gypsum, mortar and concrete[98,99]. pH is also important, as many metabolic processes are more energetically favourable at neutral pH; therefore, materials with an alkaline or acid pH can retard microbial growth. Moreover, the physical composition of the surface material will affect which organisms can access the surface. As in many decomposition processes, the physical and chemical disruption of a surface material by a fungus may be essential for bacterial colonization or growth, as the surface material might become more accessible for bacterial degraders. Even the surface roughness, porosity and its position in the environment (for example, the ceiling or the floor) can influence the dynamics of microbial colonization and growth[14]. However, how these variables influence microbial metabolism and fungal–bacterial interactions remains to be elucidated and is an active area of research.

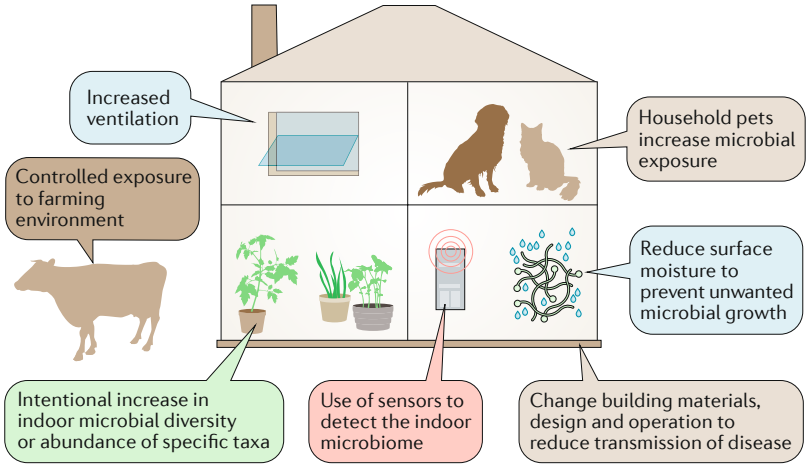


Fig. 4 | **Shaping the indoor microbiome.** Sensors that can detect the indoor microbiome will be valuable in increasing our understanding of which organisms or microbial antigens are associated with disease onset or prevention. Practices that promote possible health-promoting microbial exposure while minimizing the influence of disease-associated metabolites and organisms include, but are not limited to, increasing the proportion of outdoor air in the indoor environment through increased ventilation, changing the type of building material used in construction and reducing moisture. Exposure to pets and plants presents a relatively simple way to increase microbial diversity in indoor environments. Controlled exposure to farming environments has been shown to be effective, but implementation will require more insights into the underlying mechanisms. These approaches represent a possible way to advance human health outcomes based on understanding microbial colonization, activity and host interaction in buildings.

Microbial adaptation

The physical and chemical properties of buildings and the surface materials encountered by microorganisms in the built environment are for the most part very different compared with materials and surfaces in natural environments. Even wooden surfaces are often treated with chemicals to preserve them. Gypsum, fibreboard, drywall, synthetic carpets and surface lacquers, as well as a myriad of other unique hydrocarbons and polymers, create ecosystems unlike any other. The diversity of novel niches provides unique selection pressures that could shape microbial evolution, especially when one considers the short generation times of many microorganisms[100]. Even before the advent of genomic sequencing, culture-based studies routinely demonstrated that different surface chemistries and physical structures promote the growth of different organisms[95]. Even early studies using genomic sequencing technologies found that carbon chemistry can drive microbial evolution on synthetic surfaces. For example, shower curtains are mainly colonized by bacterial taxa associated with *Sphingomonas* and *Methylobacterium*, which are known to be readily adaptable to the availability of multiple chain length carbon compounds[4,101]. In addition, physical surfaces in buildings have been shown to be primary sites for bacterial adhesion and biofilm formation. For example, biofilm adhesion and/or formation on catheter tubing combined with antibiotic selection pressure resulting from the administration of antibiotics to a patient can lead to the acquisition of antibiotic resistance genes within these material surface-associated biofilms[102,103].

Using whole-genome and metagenomics sequencing, it is possible to reconstruct last common ancestors and explore the selective pressures that shape functional attributes necessary for adaptation and that are of relevance to human health[104]. Hospital environment-associated bacterial genotypes seem to acquire antibiotic resistance and virulence genes over time, although this trend was not statistically significantly associated with antibiotic administration[67]. This suggests that microorganisms that have survived antibiotic treatment and that are being released from patients into the hospital environment, which is very clean, dry and cold compared with the host, are likely to be experiencing environmental stress that selects for cells in the population with the characteristics necessary for survival or may trigger horizontal gene transfer events that facilitate the acquisition of new genes and hence new phenotypes. A similar impact on microbial phenotype has been observed in the International Space Station[105–107] and in clean-rooms used for space craft manufacturing[108]. This suggests a mostly unexplored influence of the built environment on microbial stress with potential health implications for humans as a result of the evolution of harmless microorganisms into opportunistic pathogens.

Implications and translation

The finding that the ecology, metabolism and transmission pathways of microbial communities in indoor environments are dynamic has led to renewed interest in refining how we practise health care, how we design, operate and build buildings, and how we shape our built environments. Examples include identifying the types and sources of microorganisms in homes that influence the development of asthma in children, changing surface materials to reduce the transmission of pathogenic viruses and bacteria, controlling water activity to reduce mould growth and changing ventilation rates or filtration requirements to reduce the accumulation of bacteria that are being dispersed from humans in work spaces and homes (FIG. 4). Although there is substantial evidence that some bacteria can influence the onset of asthma, we still do not know whether it would be possible to intervene in homes of at-risk children with microbial probiotics (that is, the introduction of health-promoting microorganisms) to reduce the risk, although an ongoing study in Finland called PROBIOM is attempting to determine whether the introduction of microorganisms associated with forest soil could influence human health outcomes. Similarly, although large-scale efforts have shown that it is possible to map potential transmission routes for microorganisms in hospitals, it is not yet possible to determine how the ubiquitous distribution of bacteria in the hospital influences health outcomes, through either infections or immune activation. Research is also focused on investigating whether the microbiome left behind at a crime scene by a perpetrator can be used as trace evidence in forensic cases[109,110]; however, we are many decades away from being able to apply this technology to create support for a legal case.

The largest potential translational impact from the field of the indoor microbiome may be the idea of manipulating the building design and material choices to influence human health outcomes[6,68,111,112]. The primary route for manipulating human health is to alter human

exposure to the environmental microbiome and metabolome. Importantly, this is not proposed to be a direct way of manipulating the human microbiome but a subtler approach focused on influencing the human immune system. As studies have shown that neutrophil ageing can influence the onset of inflammatory disorders[72,113], it is paramount that we understand how to target the stimulation of immune responses leading to positive health outcomes. This includes understanding the timing and dosage of such exposures, as well as what components are required (for example, exposures to various microorganisms, antigens and chemicals)[114]. While we now understand that pets[75], occupant density[115], geography[14], moisture, building materials[116] and building operation[117] are associated with the structure of indoor microbial communities, and likely with human health outcomes, we are still unable to accurately manipulate these parameters to fine-tune exposures and promote human health. As a result, the default approach is to ensure the indoor environment is as hostile to microbial life as possible to prevent exposure to harmful microorganisms (FIG. 2). However, we simply do not yet know what the right balance is between too little and too much microbial exposure.

There is an immediate need for the development of accurate real-time microbial sensors to detect exposures for individuals within the built environment. Developing sensors that can detect the airborne microbiome will be especially valuable in yielding a more refined understanding of which organisms, functions or microbial antigens are associated with disease onset or prevention. Large-scale studies to provide the statistical power to assess these exposures at the level of resolution needed to make these associations are lacking. Regular longitudinal detection and analysis of the microbiome and metabolome of the built environment will help architects and building operators to understand the impact of their decisions; meanwhile, personal environmental sensors will help people who regularly move between different indoor settings to track their exposure and correlate it with health and disease metrics. In combination, these new data streams would have a profound impact on the future of our indoor lives.

Conclusions

The microbiome of the built environment is still very much a nascent field. This is despite considerable investment in research from both private foundations and federal programmes across the globe. Owing to the complexity of this environment, it has been profoundly difficult to determine the microbial characteristics that directly or indirectly influence human health and disease. However, there is substantial and compelling evidence that microbial exposures influence the onset and exacerbation of disease. In addition, evidence that microbial exposure can have beneficial health impacts has sparked interest in how to manipulate indoor environments to refine such exposures. We have spent the past few hundred years attempting to make the built environment as hostile to microbial life as possible to prevent microbial infections. However, there is also a need for balance to stimulate the human immune system and possibly to prevent the onset of non-communicable disease. To achieve this, continued investment in this field is essential to understand the ecology and evolution of indoor microorganisms.

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