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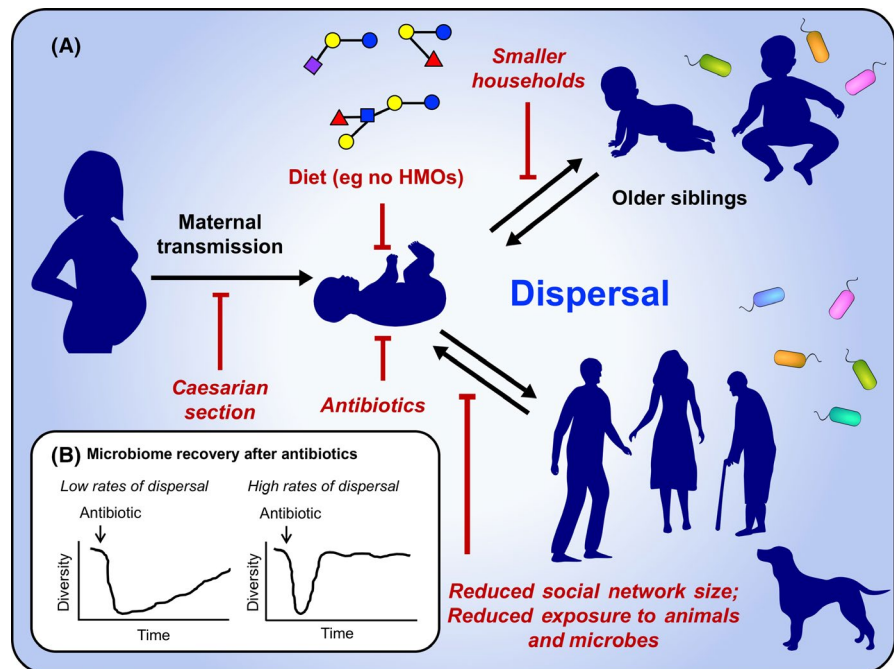
The importance of social networks—An ecological and evolutionary framework to explain the role of microbes in the aetiology of allergy and asthma

To the Editor,

The hygiene hypothesis was first proposed by Strachan in 1989, following his observation that hay fever was less common among children with older siblings.¹ Subsequent studies supported the association

of family size, and more specifically birth order, with allergic sensitization. While initially focused on exposure to infectious agents and later microbes in general, the hygiene hypothesis is now considered by some to be a misleading misnomer and the focus on “hygiene” has

FIGURE 1 Microbial metacommunity in early life. (A) Microbial dispersal events that influence early life exposure to microbes, their survival or extinction. (B) An example of an additive interaction between dispersal and extinction (eg antibiotics) events on microbial diversity is illustrated



Box 1 Ecological factors influencing development of an infant microbiota

Immigration/dispersal (D)

1. Delivery mode
2. Environmental conditions impacting dispersal (eg traditional rural environment and sanitation)
3. Network (number) of interactions with people and animals
4. Social interactions
5. Interaction frequency
6. Interaction duration

Extinction (E)

1. Medications (eg antibiotics)
2. Host phenotypes (eg inflammatory milieu and physiological changes)
3. Immune reactivity (eg antibody response and antimicrobial peptides)

Survival (S)

1. Dietary resources to justify energy requirements of microbes (eg HMOs and dietary fibre)
2. Medications (eg acid suppression)
3. Early colonization (eg competition for resources and niche construction)

been criticized for encouraging practices that might increase the risk of infection without providing clinically relevant changes in microbial exposures.² In fact, many of the risk factors associated with food allergy, allergic rhinitis, atopic dermatitis and asthma are not directly linked to hygiene (such as mode of delivery, antibiotic use, dietary practices and urbanization).³ Since these factors have been shown to alter microbial exposure and the composition and diversity of nonpathogenic microbial communities that inhabit the human host, researchers have shifted their focus to the role of the mucosal microbiome, which can influence disease risk due to effects on immune tolerance networks.^{3,4}

Several hypotheses have been proposed that link disease risk with the microbiome, or more specifically a depletion thereof, such as "missing microbes," "microbiome depletion," "microbiome diversity," "biodiversity," "overarching microbiome" and "old friends" hypotheses.⁵ However, although these hypotheses are well supported by numerous studies that confirm the role of microbes in modifying disease risk, especially early in life, a scientific consensus has not been reached and none of the microbiome-focused hypotheses have energized public imagination sufficiently to replace the original hygiene hypothesis. A major challenge that remains is

the lack of a simple and equally appealing theory that unites all aspects of the complex lifestyle factors that disrupt exposure to microbes.

We propose that ecological theory can reconcile the existing hypotheses and concepts into a unifying testable framework. Humans are exposed to a myriad of environmental microbes but have also evolved symbiotic relationships with highly specialized microbiomes that provide essential biological functions, such as aiding development of the immune system. Ecologically, the combined microbiome of a human population can be viewed as a metacommunity, in which individual humans represent island-like habitats that are colonized by spatially separated microbial communities separated by an inhospitable area. Metacommunity theory, which was developed from island biogeography theory, postulates that the dynamics within island-like communities are governed not only by the ecological processes that occur at local scale (eg competition for available resources) but also the ease by which microbes are transmitted between islands, a process ecologists refer to as dispersal.^{6,7} The relative strengths of dispersal, which is influenced by environmental factors, and the local ecological processes (ie within the human host) converge to determine the immigration, survival and extinction of individual members and thereby the patterns of species composition and diversity of the local communities.

This theory can be applied to the human microbiome, especially as it relates to the acquisition and assembly of microbial communities during infancy (Figure 1). During birth, the sterile infant emerges like an unoccupied island that becomes exposed to a variety of potential microbial colonists through direct vertical transmission from the mother and horizontally from other family and community members, animals and environmental sources, which is facilitated by dispersal. Infant exposure to sources of potential colonists (eg older siblings, family and community members and pets) is critical as the more dispersal is limited, the less likely it is to receive new immigrants in a timely manner, which will delay colonization and also introduce inter-personal variability. It is safe to say that certain aspects of modern lifestyle have generated hurdles to microbial acquisition that would influence assembly of the microbiome. Epidemiological factors linked to allergy risk, such as caesarean sections, small families, absence of animals and urban environments, constitute mechanisms of dispersal limitation, while antibiotics lead to losses of bacterial species and extinction events that cannot be "rescued" due to low rates of dispersal from nearby sources (Figure 1B). In addition, dietary intakes that lack appropriate substrates (eg human milk oligosaccharides and dietary fibre) result in a nutrient deficit for acquired microbes impacting their survival. In combination, these factors result in disturbed microbial communities that are unable to function adequately and fail to provide their evolutionary-routed benefits to the host. Therefore, a framework to understand the developing infant microbiome based on metacommunity theory would include factors related to immigration or dispersal (D), extinction (E) and survival (S) to explain microbiome diversity or microbiome stability (MD). The allergy relevant exposures for this framework are summarized in Box .The ecological perspective described above provides a theoretical and testable

framework for how lifestyle and environmental factors contribute to immunoregulatory diseases. Humans have evolved over millions of years in an environmental and social context that enabled reliable transmission and dispersal of symbionts, accompanied by appropriate nutritional support. While exposure to biodiverse environments is important, membership of the human microbiome metacommunity has also been evolutionary driven and these human-adapted symbionts might only be acquired from contact with other humans. Hallmarks of these evolutionary relationships can be observed in the microbiomes of nonindustrialized human populations and nonhuman primates, whose microbiomes are shaped by dispersal and social behaviour.^{8,9} Recent changes in lifestyles and social interactions have altered these metacommunity processes, disrupted the human microbiome and, as a consequence, increased risk of immune-mediated diseases such as allergy and asthma. This framework could explain how diverse and seemingly unconnected factors (eg smaller households, absence of older siblings, antibiotics, C-sections, breastfeeding, rural versus urban living and diet) can modulate disease risk through their ecological effects on microbiome assembly. It therefore provides an understandable rationale to facilitate communication with the lay public on the health effects of lifestyle choices and social behaviours. It can further aid the scientific community in elucidating causal mechanisms and interactive factors that influence disease risk and can support the development of clinical practices and strategies to redress early life microbiome alterations. For an ecological framework to be maximally beneficial, future research on the aetiological role of microbes in inflammatory disorders should consider their exact biological relationships with the human host and differentiate between co-evolved symbionts, pathogens or environmental microbes to which humans are merely exposed. While such a differentiation is not always easy to make, this information would provide essential information to the question whether disease risk is primarily determined by microbial exposure in general or whether specific microbes (or microbiomes) are required.

CONFLICTS OF INTEREST

LOM is a consultant to Alimentary Health Ltd and has received research funding from GSK. JW is a co-owner of Synbiotics Solutions, a consultant to Alimentary Health, and has received research funding from industry sources involved in the manufacture and marketing of probiotics, prebiotics, dietary fibres and food ingredients.

KEYWORDS

allergy, asthma, ecology, hygiene hypothesis, microbiome, microbiome hypothesis, old friends hypothesis

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The health and economic benefits of approaches for peanut introduction in infants with a peanut allergic sibling

To the Editor,

Peanut allergy (PA) is a growing public health problem affecting between 1.4% and 4.5% of individuals in westernized countries, which can be lifelong in approximately 75% of individuals, and is often severe.^{1,2} Despite new potential for both PA prevention and desensitization treatments, there are still unknowns regarding who is at risk of developing PA.^{3,4} Newer studies have focused on egg allergy and/or severe eczema as a specific risk for developing PA, whereas older studies highlighted a parental or family history of atopic disease as a risk factor.⁴⁻⁶ There has been speculation that PA has a potential genetic inheritance pattern and that PA in a primary relative (especially a sibling) may impart risk to other family members, prompting questions if younger siblings of peanut allergic individuals should be screened prior to peanut introduction.^{1,7,8} To better understand the potential health and economic benefits of screening younger siblings of PA children prior to peanut introduction (Figure S1), we

conducted a 20-year computer-based mathematical Markov simulation (Tree Age Pro, Williamstown Mass).

In this model, infants with PA siblings were assigned to home peanut introduction without in-office assessment or peanut skin prick test (SPT) screening by an allergist. Skin prick test positive infants (wheal size ≥ 3 mm) either received PA diagnosis or underwent supervised oral food challenge (OFC). Rates of positive peanut SPT were based on Hourihane et al.⁷ Sensitivity analyses were performed to validate assumptions shown in Table 1 from US, Canadian, and European societal perspectives. Study outcomes included costs, quality-adjusted life years (QALYs), and allergic reactions. Cost-effective care is defined as care costing $< \$50\,000$ – $\$100\,000$ per QALY in the United States (but may vary in other countries and currencies).^{e1-e29} This study was exempt from IRB approval. A full description of the methods is detailed in e-supplement 1.

Table 2 describes model outcomes of the base case simulation, demonstrating that the SPT screening strategy was dominated by an approach of at-home peanut introduction without screening. However, if it was assumed that reactions occurring during observed

Abbreviations: CAD, Canadian dollar; ICER, incremental cost-effectiveness ratio; OFC, oral food challenge; PA, peanut allergy; QALY, quality-adjusted life years; SPT, skin prick testing; USD, US dollar.