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A report by the International Scientific Forum on Home Hygiene

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This is a summary of a report prepared by the International Scientific Forum on Home Hygiene to review the scientific and epidemiological evidence relating to the hygiene hypothesis with particular emphasis on examining the implications for hygiene and the prevention of infectious diseases and our overall relationship with the microbial world we live in. The full report can be downloaded from the IFH website at www.IFH-homehygiene.org

The International Scientific Forum on Home Hygiene (IFH; www.ifh-homehygiene.org) is a not for profit, non-governmental organisation which was established in 1997 to meet the need for an independent expert body who could develop and promote a science-based approach to hygiene in home and everyday life settings as a means to reduce the global burden of infectious diseases.

1. The hygiene hypothesis – what does it mean?

The hygiene hypothesis, as originally proposed by Dr David Strachan in 1989, proposed that a lower incidence of infection in early childhood could be an explanation for the 20th century increases in atopic [allergic]* diseases, particularly hay fever. Though a simple idea in itself, it raised the alarming thought that rising allergies may be an inevitable price to be paid for becoming free of the burden of killer infectious diseases. Strachan's proposal was based on research showing that larger family size appeared to protect against hay fever and, to some extent, eczema. Strachan suggested that smaller families provided insufficient microbial exposure because of less person-to-person spread of infections – but also because of "*improved household amenities and higher standards of personal cleanliness*". Others then extended the concept, suggesting that it could also be a reason for increases in the allergic form of asthma and other atopic disorders, such as food allergy.

From this the notion that "we have become too clean for our own good" has arisen and used to suggest we should return to the "good old days" before modern hygiene interventions. New knowledge about the hypothesis shows that this notion is very much misplaced and, if acted upon without reference to the risks of infection, would be dangerous for our health. There is no evidence to show that reducing hygiene would have any impact on rates of chronic inflammatory and allergic disorders, but there is a significant amount of evidence that it would increase the risks of infectious diseases.

The emerging research about the hygiene hypothesis is the subject of a new report by the International Scientific Forum on Home Hygiene[1] which reviews the scientific and epidemiological evidence relating to the hygiene hypothesis, with particular emphasis on examining the implications for hygiene and the prevention of infectious diseases and our overall relationship with the microbial world we live in. The main findings and conclusions from the report are summarised here.

2. How is our understanding of the hygiene hypothesis developing?

In the last 10 years or so, although a large number of new studies have considerably increased understanding of the hygiene hypothesis, they have shown that the issue is far more complex than originally thought. Although the concept began with allergic disorders such as hay fever, it is now recognised as potentially applying to a whole range of chronic inflammatory diseases (CIDs), including type 1 diabetes (T1D), multiple sclerosis (MS), and also inflammatory bowel disease (IBD) and some types of depression and cancers. In recent years we have seen numerous media reports on new studies related to these diseases that, at first, may appear unrelated.

Recent headlines include:

"Keeping children too clean could wreck their immune systems" *(Daily Mail, 2012)*

"Over-hygienic parents could be a cause of diabetes" *(Euronews 2012)*

**Atopic allergic diseases, typically asthma and hay fever, refer to conditions where people readily produce allergic antibodies, which cause them to react to common substances in the environment, such as pollen, house dust mite, etc. Similar symptoms of asthma and eczema can occur without evidence of an "atopic" reaction: these are known as non-allergic forms of the conditions and may be caused, for example, by direct irritant effects of various substances. Allergy can also involve totally different mechanisms, such as in allergic contact dermatitis to nickel, for instance.*

"Eating off the floor: How clean living is bad for you" *(2012, Scientific American)*

"Can eating worms banish asthma?" *(Daily Mail, 2011)*

"Are depressed people too clean? *(Science Daily, 2010)*

"Intestinal Parasites Protect Against Multiple Sclerosis Relapses" *(About.com, 2008)*

Closer inspection shows that a consistent finding of all these studies is that one of the underlying risk factors is altered exposure to microbes. Studies now show that our daily interactions with microbes, particularly in early life (and possibly even prenatally) are vital to health because they interact with the regulatory systems that keep the immune system in balance. Without this our immune systems may overreact, or react inappropriately, which is an underlying cause of these allergic and other CIDs. It is not that the immune system isn't working, but that sometimes it's overreacting. Often it is over-responding to minimal amounts of stimulus and things that should never cause an immune response. What's missing is the mechanism that regulates the immune reaction and shuts it off once a threat is eliminated, or what was seen as a threat is recognised not to be one – which is where the hygiene hypothesis seeks to explain what causes this. The hygiene hypothesis proposes that microbial exposure is a key part of the maturation of this regulatory mechanism

3. What sort of microbes do we need exposure to – when – and how?

Although the role of microbial exposure in immune regulation is now widely accepted by the scientific community and new data are giving us better insights, a key factor which we still do not fully understand is: to what sort of microbes do we need exposure?

The evidence still fails to show which exposures might be important: while one study suggests that a particular organism is beneficial, another study does not, but suggests other organisms.

Whereas epidemiological studies continue to confirm the protective effect of large family size, this appears to be a general effect with little consistency about the effect of family structure, the number of brothers and sisters or their position in the family. The evidence that being brought up in a farming environment is protective against asthma and allergies, and also early onset IBD, has similarly proved robust, yet also non-specific regarding which microbial species are involved. Recent studies on day care have not provided consistent evidence of protection against allergy, although there is now more interest in the influence of early mixing with other infants.

Where epidemiological studies have singled out specific clinical infections for study (e.g. common childhood infections such as chickenpox or measles), the evidence that exposure to these infections may have a protective effect against allergies and other CIDs is now much less persuasive than was previously thought. As a result, the original proposition of a key protective role against allergic diseases for clinically apparent infections in early childhood is now largely discounted, possibly with the exception of a few disease-causing microbes and parasites. Measures of clinically diagnosed infections, such as episodes of respiratory or intestinal infections in childhood, have not been shown

to be generally protective against allergies and other CIDs. By contrast, immunological studies increasingly indicate that the normal human microbiota (commensal organisms in the human gut, skin and other sites) have an important role in developing and regulating the immune system.

The wide range of organisms that are implicated as protective has led to the conclusion that our microbial exposure needs for immune regulation are not confined to a single species. It is likely that there is considerable redundancy in the human immune system, which means that the needs of any individual person can be met by one or more of a range of quite diverse species; and that if any of these species are missing, their role may be met by other species.

Building on these findings, a number of refinements to the original hypothesis now seem to offer more plausible explanations. These include the "Old Friends" (OF) and closely related "diversity" hypotheses. The OF hypothesis has gained wide recognition because it addresses the problem of identifying protective microbial exposures, and also provides a unifying explanation for the impact of other increasingly implicated risk factors, such as modern diet and the urban environment.

The "Old Friends" hypothesis, as proposed by Rook in 2003,[2] proposes that the microbial exposures vital for immune regulation are not the infectious diseases (respiratory infections such as colds, influenza, measles etc. and gastrointestinal infections such as cholera, polio, Campylobacter, norovirus etc.) which have evolved and spread over the last 10,000 years as we came to live in ever denser urban communities, but rather the microbes with which we co-evolved, and that were already present in Paleolithic, hunter gatherer times – the era when the human immune system was developing, in close association with the abundant microbes present in that era.

Put simply, in the same way that we have evolved to become dependent on Vitamin C in our diet (something which most mammals could, and most non-primates can still, synthesise for themselves) because it became plentiful in our food, we have also evolved dependency on microbial exposure, such that our immune systems cannot now function properly without it.

It is hypothesised that the "Old Friends" include commensal organisms (the normal microbiota of the skin, gut and respiratory tract of humans and animals) and some potentially pathogenic organisms such as Hepatitis A Virus (HAV) and helminths (worms), which establish chronic infections or carrier states. These latter have to be tolerated, because attempts by the immune system to eliminate infections that it cannot eliminate only lead to pointless tissue-damaging inflammation. The OFs also include environmental saprophytes i.e. species which inhabit our indoor and outdoor environments).

Although the OF hypothesis, as currently postulated, includes potentially pathogenic species such as *Helicobacter pylori*, HAV and helminth infections, because of the "redundancy" in the system, it is unlikely that the immune system is dependent on exposure to these potentially harmful species; as with other biological processes, it has evolved alternative pathways which achieve the same effect. This means that increased risk of allergies and other CIDs need not be an inevitable trade off from reduced exposure to any particular pathogen, providing that a correct balance or mix of exposures to other immunoregulation-inducing organisms occurs.

The OF hypothesis is supported by increasing amounts of data from laboratory studies.[1,3] Recent data show that some helminths, and some members of the gut microbiota secrete molecules that directly drive proliferation of the class of lymphocyte that regulates the immune system, while others do this indirectly by causing other immune cells to mature into forms that drive immunoregulation. Other findings using mouse models show that allergies, IBDs, and disorders such as T1D and MS can be treated with helminth infections that act in this way. If altered microbial exposure is partly responsible for the recent rises in incidence of CIDs, there should be evidence for defective immunoregulation in these diseases. Such defects have been recorded in human allergies, MS, T1D and IBD.

The "**microbial diversity hypothesis**" as proposed by Professor Paolo Matricardi[4] is a further refinement of the OF hypothesis, which holds that diversity and turnover of bacterial species in the mucosa of the gut and other sites is a key factor for priming and regulating the immune system, rather than stable colonisation with a particular species. He proposes, not that a range of species CAN perform this function, but that diversity and turnover of species is a REQUIREMENT for immune regulation.

Some recent studies give support to this hypothesis, including a Swedish study showing that reduced diversity of faecal microbiota in infants at one week was associated with higher rates of atopic eczema at 18 months[5] and a Danish study showing that increased risk of allergic disease was associated with less gut microbiota diversity in infancy.[6]

Professor Lena von Hertzen[7] is now proposing that the adverse changes in the human commensal microbiota are partly attributable to reduced contact with the broader variety of microbial species found in the natural environment. The "biodiversity" hypothesis proposes that loss of diversity in human microbiota results from the observed loss of biodiversity in the outside environment.[8] Evidence of this is seen in a new study investigating bacteria on the forearms of Finnish teenagers. Participants who lived near farms or forests had a different composition of bacteria on their skins and were less sensitive to allergens than those living in built-up areas or near lakes and other water bodies. Many of the bacteria appeared to be species common in the environment on soil, plant surfaces, grass pollen and dust. Healthy teenagers had a greater diversity of these species on their skin and, amongst this group, the abundance of a particular species, *Acinetobacter*, was positively associated with levels of an important anti-inflammatory cytokine, in cells from the blood.

The "Old Friends", Diversity and Biodiversity hypotheses are closely related and overlapping, all suggesting that exposure to a wide variety of organisms is necessary for correct immune regulation. But they also all indicate that relevant organisms are those with which we co-evolved. They had to be tolerated, so they evolved immunoregulatory roles. Very few pathogens are involved, and when they are it is because infection was inevitable and lifelong, so they had to be tolerated too.

A further important aspect of the OF and diversity hypotheses, is the critical timing for these microbial exposures. So far as allergies and asthma are concerned, it seems that the most important times

are very early in development, during pregnancy and the first few days or months of infancy, and that exposure needs to be maintained over a significant period: this applies, for example, to the protective effect observed from growing up on a farm. This fits with some evidence that Caesarean section may be associated with an increased tendency to allergies, whilst breastfeeding for six months or more can be protective. Although findings are still inconclusive, there is good evidence that the transfer of maternal microbiota to the baby may be critical for immune priming.

The importance of childhood exposure has recently been demonstrated in studies of population levels of C-reactive protein (CRP), a marker of inflammation that should fall to almost zero when there is no valid reason for the immune system to be active.[9] Research in people of the Ecuadorian Amazon showed that although CRP levels varied over time, background levels were very low in the absence of episodes of infection, indicating intact immunoregulation, presumably set up during childhood. In contrast, persistently raised CRP levels have been found in people living in affluent urban areas in the US even in the absence of infection, which may suggest failing immunoregulation, chronic low-level inflammation and increased risk of CIDs.

Answers are also needed to questions such as "to what extent do these exposures need to be maintained during childhood and adult life?" and "could these diseases be contained or reversed by ongoing exposure?" Despite a previous emphasis on studying childhood exposure there is now evidence that, at least in some cases, exposure during adulthood exerts ongoing effects on the immunoregulatory system. For autoimmune diseases such as MS, which develop in adulthood, we do not know whether the problem originates from microbial deprivation and immune dysregulation in early infancy, triggered only when other risk factors kick in, or whether it is due to sustained microbial deprivation, which causes immune dysregulation that eventually manifests as clinical disease. A 2007 study, for example, showed that, when adults with established IBD or MS undergo trials involving oral treatment with helminth eggs, significant improvement of symptoms is seen, and naturally occurring helminth infection can delay progression of established early MS.[10] This suggests that, in some respects, ongoing exposure from particular "Old Friend" organisms may be important for immune regulation throughout our lives, although more research is required to better understand this. Remedying the results of dysregulation, to the extent it becomes possible, is likely to involve specific, targeted, therapies rather than simply increasing general microbial exposure.

The route of exposure is important, because it impacts on possible remedial measures. Based on current evidence, the oral route seems the most likely candidate, which fits with the OF hypothesis, but study findings do not rule out other potential routes including inhalation, which is very effective in animal models, or even transdermal exposure. It is possible that all of these routes are involved.

In summary, it seems that the problem is not a general lack of microbial exposure, but a lack of exposure to the right kinds, doses and diversity of microbes.

4. What are the other risk factors for allergic and other chronic inflammatory disorders?

It is now becoming clear that, within modern society, increased risk of allergic and other CIDs for any particular individual depends on many factors in addition to microbial exposure. These include changes in diet (including vitamin D deficiency), interactions with pollution, climate change, less physical activity, obesity, socioeconomic factors and stress, all of which can interact with and amplify the immunoregulatory deficit resulting from the changes to our microbial environment.

Stress, diet and obesity can modify the gut flora, and both obesity and stress result in greater release of pro-inflammatory cytokines. Vitamin D is involved in driving immune regulatory cells.

Many of these factors seem to play a role, even if the main underlying problem is immunoregulation, and changing microbial exposures are fundamental aspects of the immunoregulatory deficit.

Genetic predisposition is a key factor that determines the risk of allergic or other CIDs. Increasing knowledge of underlying genetic factors is showing how many CIDs relate to particular genes. This, and the many factors in play over the last two centuries, may help to explain why we do not all suffer from these diseases. It seems plausible to assume that we all still get some of the requisite microbial exposure, but whereas for some this is sufficient for immune regulation, for others it is not. In these individuals, allergies and other CIDs may be triggered, particularly when one or more of the other factors outlined above causes further dysregulation of the immune system.

5. What medical, public health or other trends have caused our loss of exposure to microbes?

Despite considerable research, another aspect that is far from clear is: "what changes have occurred over the past two centuries that might have deprived us of beneficial microbial exposure?" Although various studies highlight some of the factors that may be involved, there are inconsistencies and conflicting results. This suggests that a whole range of inter-related factors are probably responsible, including improved water quality, sanitation, the environmental clean-up of our cities, reduced exposure to livestock animals or horse driven transportation, and changes in the design and operation of our indoor environments (heating, air-conditioning etc.). It may also include foods in our diet with different or less microbial content. Medical advances, such as vaccines or the use of antibiotics may have played a part in altering the way our bodies interact with microbes.

Allergy was so rare in the late 19th century that doctors mentioned difficulties in finding cases to study. Data suggest increasing levels from the late 19th century, followed by a rapid rise from the 1970s.

If the OF hypothesis is correct, i.e. that key microbial exposures from which we have become separated are not the "modern" infectious diseases, but those on which our immune systems evolved

dependence during ancient times, then the rise in more recent years needs an explanation. The OF hypothesis argues that significant deprivation from exposure to these "Old Friends" did not occur in western societies until the urbanisation of the early 1800s and the introduction of clean water, sanitation and cleaner cities in the late 19th century. Although the sanitary revolution acted to protect us from the infectious diseases caused by increasingly dense urban societies with poor standards of water, sanitation and hygiene, it also inadvertently reduced our exposure to the old microbial friends that are needed for regulating immune development.

If the OF hypothesis is correct, it nullifies the notion that allergies and other CIDs are the price for no longer suffering the burden of killer infectious diseases.

Public health trends

Comparing trends in public health measures against trends in infectious disease also challenges the idea that allergies and other CIDs are the ongoing cost of reducing the burden of infectious diseases, although temporal correlations must be interpreted with care: apart from difficulties in finding good data on the public health measures, epigenetics research suggests that the effects of environmental change may not be fully manifested in the first generation and might take two or more generations.

Improvements in water and sanitation occurred gradually dating from the early 1800s but, for example, whereas flushing toilets were available in England from the 18th century, widespread coverage did not occur until the late 19th century. Chlorination of drinking water was only introduced in England in the 1890s and did not become routine until the 20th century.

Until measures were introduced in the mid 1800s to clean up the cities, urban dwellers would have been constantly exposed both by faecal:oral transmission and by the inhalation of contaminated dust particles to both human waste and excreta from animals in the city streets.

In line with public health trends, a review of disease trends shows that the most rapid decline in mortality during the sanitary revolution occurred between 1900 and 1950, particularly for young children. Declining infant mortality rates of whooping cough, measles, diphtheria in the US and UK also date from around 1900.

Rapid decline in overall mortality rates was not observed in countries such as India and China until 1950s onwards. In the less industrialised countries the emergence of allergic and other CIDs seems to have occurred later, although they are now "catching up".

In "higher income" countries, the decline in mortality and morbidity during the last century from killer diseases such as cholera, typhoid, tuberculosis and diphtheria, and viral infections such as measles and mumps, has fostered the view that there has been an overall decline in infectious disease, which is not the case. The incidence of food poisoning rose during the critical period of the increase in atopic disorders (1970s-1990s). Respiratory infection remains common, with acute respiratory illness contributing 6% of global disability or death, including 1.5 million annual deaths of children aged under five and an estimated 3 to 6 episodes within the first year of life. Skin infections are

also a significant cause of morbidity: a UK study indicates a major general increase in pathogenic community-onset staphylococcal disease in the past 15 years. There is a broad correlation between trends in public health measures to reduce the infectious disease burden and the decline in life-threatening diseases, but these measures would seem to have occurred too late to have triggered the early emergence of allergies and other CIDs in the 19th century and too early to be associated with the epidemic rise in these diseases in the late 20th century.

Domestic cleaning and personal hygiene

Of all the candidate trends that might explain a general decline in microbial exposure, one of the weakest is the simplistic idea that the underlying cause is "being too clean in our own homes". Though this is how the hygiene hypothesis has most often been presented to the public, there is in fact no direct evidence linking the cleanliness of homes to increased risks of allergies.

If home and personal cleanliness contributes at all, its role is likely to be small relative to factors such as clean water, efficient sanitation, cleaner environments and food quality.

Even the cleanest-looking homes still abound with bacteria, viruses, fungi and moulds, as well as dust mites and other insects. Microbiological evidence indicates that routine daily or weekly cleaning habits have no sustained effect in reducing overall levels or altering the types of microbes in our home environment. The idea that we could create a "sterile" home through excessive cleanliness is implausible: as fast as they are removed by cleaning, the microbes in our homes are being constantly replaced, via dust and air from the outdoor environment, by commensal microbes that are constantly shed from the human body and our pets, and from contaminated foods brought into our homes. It is often assumed that "over cleanliness" is the root cause of the current epidemic of asthma and allergies but in reality home cleanliness has not been directly evaluated in relation to the risk of developing allergies or CIDs, the epidemiological studies mainly using crude measures based on the appearance or poverty of homes or, at best, hygiene activities such as self-reported frequency of cleaning or hand washing.

In his early proposition, Strachan suggested that, alongside home cleanliness, "*higher standards of personal cleanliness*" could be an underlying cause of reduced exposure to infection. Family size is relevant here: larger families give more opportunities for sharing gut, skin and respiratory microbiota, such as by close contact, or sharing towels, toothbrushes, food utensils and other personal items. Yet the hunt for the specific protective family factor against allergy has been unsuccessful.

Statistical analyses of data from the ALSPAC cohort of children born in 1991/2 have looked for evidence of a link between home and personal cleaning practices and atopic disease. An analysis in 2002[11] found an association between parent-reported frequency of hand and face washing, showering and bathing at 15 months and wheezing and atopic eczema at 30-42 months. The association with washing has not been reported in other studies.

While very frequent showering can aggravate existing skin disorders such as eczema, a recent study challenges this, reporting a lower risk of atopic eczema for infants who had been bathed or given a shower at least once a day, compared with those bathed less frequently.[12]

Research into causes of atopic skin disorders has also shown the influence of education, income and maternal history of allergic disorders. At present there is no conclusive epidemiological evidence regarding washing habits as having either a causal or a protective role for allergies/CIDs.

Analyses of ALSPAC data on frequency of household chemical use found an association with persistent wheezing in non-atopic children which, it was concluded, was "*unlikely to be mediated through increased hygiene in the home*".[11] The association was attached to all products, not just those for cleaning / disinfection, and while some types contain irritants other suggested explanations include over-reporting of both symptoms and "chemical" use by certain people.

Although the use of soap, detergents and cleaning products has risen over the last 50 years, though at a lower rate than in the first quarter of the 20th century, trends in consumer cleaning and home hygiene practices over the past 100 years show no evidence of a correlation with the rapid rise in allergies and other CIDs from the 1970s to the 1990s. To date, there is no confirmed evidence of a link between domestic cleaning products or activities and the increased risk of atopic disease.

The key point here may be that the microbial content of our modern urban homes has altered considerably relative to that of earlier generations, not because of home and personal hygiene habits, but because, prior to the 1800s, people lived in predominantly rural surroundings. "Home microbes" used to be similar to "farm microbes" but now differ significantly because they interact with a very different outside environment. People also have different diets, lifestyles and so on which affects the nature of our gut, skin and respiratory microbiota. All of this means that we now live and interact with an altogether different and less diverse mix of microbes than we did prior to the 1800s and the subsequent rise in allergies and CIDs. Although gut and skin microbiota are constantly shed from family members onto surfaces, into the toilet, or through contact, such that other family members are constantly exposed to them, it is likely that this exposure lacks many of the organisms from our rural past with which we co-evolved.

The ways in which dietary changes can shape changes in gut microbiota have been demonstrated in a 2010 comparative study of children from Europe and rural Africa.[14]

These ideas are supported by recent research into the microbial profile of indoor environments.[15] Studies of migrants who have moved from rural to urban environments also show that first generations may be protected by immunoregulation induced during their childhood in a rural environment, and retention of former dietary habits and other factors providing a different ecosystem from the indigenous urban dwellers. These effects may "protect" against the reduced diversity in the new environment. Meanwhile, the reduced diversity of microbes entering the home appears to be a factor in "urban" asthma, and unrelated to apparent cleanliness of the home.

Changes to the outdoor environment

von Hertzen's proposal implies that, ultimately, reduced exposure to important microbial species has happened largely because of changes in, and reduced contact with, our outdoor environment: though much microbial exposure takes place indoors, the outdoor environment must substantially influence the microbial mix of the indoor environment.

von Hertzen cites data showing that asthma and allergic rhinitis among military conscripts from 1966 to 2003 rose while indices of biodiversity declined. The concept that the outdoor environment is important fits with the protective "farm effect" – although the evidence has not so far identified specific factors, other than a more consistent effect for children brought up on farms with animals, as opposed to crop farms.

Antibiotics and vaccines

It is notable that antibiotic usage trends, (although also trends for many other drugs), show a fairly good temporal fit with the critical rise in allergies and CIDs documented since the 1970s. Antibiotics are relevant here because there is evidence that they affect immunoregulation by reducing the diversity of gut microbiota. Antibiotic use increased rapidly after the development of penicillin in the 1940s. Although several studies show associations between antibiotic use and later development of asthma or allergy, other studies suggest that the effect is due to more frequent antibiotic use in asthmatic children. It has been suggested that trends in vaccine use may also be relevant, since immunisation against tetanus and diphtheria was introduced during the 1930s to 1940s, followed by vaccines against several childhood infections. But epidemiological studies provide no consistent support for a detrimental effect of vaccination/immunisation on atopy rates. Indeed vaccination is a microbial exposure that might be just as likely to protect against CID.

The impact of public health and other measures on exposure to "Old Friends"

Looked at from a different perspective, the time trends comparing rates of infectious disease with the introduction of public health and therapeutic measures show us that whilst these measures have been very successful in reducing exposure to pathogens as a by-product, they have presumably been equally successful in reducing or altering our exposure to microbes such as the OFs, since they inhabit the same human, animal and other environments. Decline in diarrhoeal diseases transmitted by the faecal:oral route over the critical period since the late 1800s shows how these measures successfully separated us from exposure to GI pathogens: this must have also reduced exposure to the commensal species that make up the human gut microbiota. Recent studies provide clues regarding alterations in gut and skin microbiota in the last few decades, but do not show what was happening 50 or more years ago. Another example is the decline in helminth infections, probably due to provision of indoor plumbing and less exposure to muddy areas. Colonisation of humans with helminths, widespread until recently, is now relatively rare in developed countries: it is estimated that around 50% of young children of Europe and North America were infested with pinworm up to the mid 20th century. Both the decline in helminth and HAV infections occurred later and thus may be relevant to the late 20th century increase in atopic disease.

The particularly rapid increases in allergies and CIDs since the 1970s remains difficult to explain, particularly as there is evidence that the incidence (new cases) of asthma is now levelling off in some countries. This also applies, but less consistently, to consultations for hay fever in the UK, meanwhile the CIDs have generally increased. Without doubt, the last two centuries have dramatically changed our lives in relation to water, food, diet, sanitation, medical interventions (antibiotics and vaccines), personal cleansing and home cleaning, and to factors such as urban living and less outdoor physical activity, all of which may have contributed to altered microbial exposure and to a greater or lesser extent in the trends of these disorders. Hygiene, with its vague definition, may have been the easiest suspect to blame, and remains the most frequently cited cause in the populist media.

6. How could we tackle the problem of allergies and other CIDs?

Ultimately, if the OF and diversity hypotheses are correct, the key question is "what measures could be put in place to reverse the trend in CIDs and other disorders related to lack of exposure to microbes?" At present there is little to suggest that there might be a single "magic target" within the immune regulatory system that could form the basis for developing drugs to prevent or treat these diseases. Since translation of immune dysregulation into disease involves many factors, a single breakthrough clinical solution is unlikely. As with diseases such as cancer, success will be a slow process, using emerging data to try out new treatments. Various therapeutic approaches are being investigated, as yet at an early stage. Using probiotic strategies (such as probiotic drinks or foods) to reintroduce key microbes to our bodies seems an obvious approach, but further work is required to identify protective organisms, and progress is unlikely until there is much better understanding of which "Old Friends" are truly friendly – and safe.

In her recent paper, von Hertzen[7] argues that immune-stimulating treatments to address the burden of CIDs will be "*only paltry substitutes of nature*", stating that a greater need is to consider measures reconnecting us with nature, along with changes to food production. For Hanski also, the notion of distributing microbes artificially is not enough. He suggests[16] that their findings indicate a need to retain contact with natural habitats and "*highlight the importance of green space in urban areas, and of opportunities for urban children to spend some time in the countryside*".

Children spend much more time indoors than in previous generations – estimated at around 15 hours a day some 20 years ago. Increased exposure to natural habitats since then is hardly likely.

Implementing remedial public health measures seems an unlikely option unless the key microbial exposures can be identified. Without this, any relaxation of standards related to water, sanitation and hygiene would have no guarantee of success and would only serve to increase infectious disease risks. Although the benefits of healthier lifestyles in terms of diet, exercise, smoking, and alcohol are now widely promoted, encouraging us to abandon our modern obsession with cleanliness and hygiene is not the answer to replacing our microbial exposure needs.

Encouraging lifestyle changes which could increase exposure to "Old Friends" is a huge challenge and would likely meet with opposition, without more robust evidence of a real health benefit.

Lifestyle changes which could increase exposure to OFs range from encouraging natural childbirth, sustained breast feeding and physical interaction between siblings, to designing and running our homes to ensure more interaction with our environment, or encouraging more sport and other outdoor activities. It could mean persuading local authorities that green spaces in urban areas have a direct physiological action on our immune system.

Measuring the extent to which such measures might impact on rates of allergies and other CIDs is probably unachievable, due to the complex interaction between microbial exposure and other factors, as well as the difficulty in conducting intervention studies to investigate presence or lack of benefit from individual elements. It is more likely that any evidence to support public health policy changes will come from better understanding how microbes interact with the immune system.

7. Why is hygiene in home and everyday life so important?

At the same time that concerns about allergies and other CIDs have been increasing, there has been an equivalent increase in concern about infectious disease. A 2009 IFH report[17] showed that infectious gastrointestinal (GI), respiratory tract (RT) and other diseases circulating in the community continue to exert a heavy toll on health and prosperity. This is being driven mainly by the growing immuno-compromised population living in the community and the unremitting emergence of new pathogens. We live in an increasingly crowded and mobile world where new infectious agents and antibiotic resistant strains spread easily and quickly. It is a world where widespread resistance to antibiotics is making infections increasingly difficult to treat. In a 2012 conference address, Margaret Chan, WHO Director General, warned that bacteria were becoming so resistant to antibiotics that it could bring about "the end of modern medicine as we know it".[18] The consequence of this is that we would become even more reliant on preventing infectious disease. Looking in more detail:

- Food-related, waterborne, and non-food-related infectious intestinal diseases remain at unacceptable levels, despite food-borne infectious being largely controllable through good food and kitchen hygiene. The WHO reported a study of OECD countries in 2003, indicating that about 31% of reported food-borne outbreaks occur in private homes**. *Salmonella* is estimated to cause around 38,000 annual cases in the UK, while the number of *Campylobacter* infections is estimated at 600,000. Norovirus affects an estimated 3 million in the UK and 20 million in the US: the majority of cases are spread from person to person via aerosols, hands and surfaces.**
- Evidence increasingly shows how good respiratory hygiene (summarised in a recent UK campaign as "Catch it, bin it, kill it") can limit the spread of respiratory infections, most particularly colds, but also influenza. Promotion of good respiratory hygiene is internationally recognised as a first line of defence in preventing an influenza pandemic. **Respiratory infections remain common: A study of 1,314 German children recorded an average of 21.9 respiratory infections by the age of 12 years, with up to 11 episodes a year the norm for infants.**[19]
- The proportion of people with reduced immunity to infection, currently estimated at around 20%, is likely to increase. **This includes the 300,000+ diagnosed annually with cancer and the 91,000+ living with HIV in the UK, but it is the elderly that make up the largest numbers of the "at higher risk" population.** Many of this growing group have chronic ill health with associated vulnerability to infection. Family members carry out much of their care, so they need better understanding of infection prevention – both for themselves and for their vulnerable relatives.
- Populations with a low education level, income level, or occupational class are at higher risk of infection. These factors initiate a vicious cycle of infection predisposing to malnutrition and poor growth, which in turn leads to increased risk for further infection.
- Tackling antibiotic resistance is a global priority and hygiene is a means to reduce the silent epidemic spread of resistant strains (e.g. MRSA, ESBL and NDM-1-producing strains) in the community. By reducing the burden of infectious diseases, hygiene can reduce the need for antibiotic prescribing, which is the major underlying contributor to antibiotic resistance. As persistent nasal or gut carriage of these strains in the healthy population spreads across the world, this increases the risk of both hospital and community infections. Infection control measures are now central to strategies to reduce the spread of drug-resistant infections.

- Infectious diseases can act as co-factors in other diseases that manifest at a later date, such as cancer and chronic degenerative diseases. Under some circumstances respiratory diseases can act as triggers for development of allergic diseases.
- Governments are now emphasising infection prevention as a means to reduce health spending. Increased homecare is a favoured approach, but gains are likely to be undermined by inadequate infection control at home. Healthcare workers recognise that reducing the burden of infection in healthcare settings cannot be achieved without also reducing the circulation of pathogens such as norovirus and MRSA in the community.

Taken together these issues indicate a need for greater investment in prevention strategies such as vaccination programmes and hygiene promotion which are now seen as the most sustainable approaches to containing the burden of infectious disease.

8. How could we address the issues of infectious disease prevention and reducing the risks of allergies and other CIDS at the same time?

Since infectious disease is still a major problem that needs increased effort, and if the "right kind" of microbial exposure needs to be encouraged, it poses the question "how do we address both issues at the same time?" How might we persuade people to develop lifestyles which reconnect with their environment in a way which could replace the necessary microbial exposures, whilst also protecting themselves against infection? To begin tackling these questions, we need to stop regarding them in isolation. For example, it must be confusing for the public to, on one day, read about a study suggesting that cats or dogs in the home can be beneficial to health because they may protect against allergies in children but, on the next, a report of an infection outbreak where domestic animals were identified as the most likely source. The significant numbers of reports of infectious disease outbreaks associated with domestic pets are detailed in a recent IFH review.[20]

We need to re-focus away from the misleading message that "we have become too clean for our own good". Where simple messages are needed, the concept that we are "missing some of the right kind of dirt" or have become "afraid of getting dirty" would help focus thinking on the right lines. We need to question the idea of separateness, that modern Homo sapiens, as a species, can exist quite separately from the rest of the biological kingdom.

We need to develop health promotion messages that help people to distinguish between letting children interact with their environment while also protecting them, as far as possible, against potentially harmful microbes. It is vital that, alongside messages about the need for healthy exposure to our environment, we promote the need for hygiene at appropriate times. We might, for example, encourage children to play and interact freely with each other and their environment, which exposes them to a wide range of microbes (but inevitably also some exposure to potential pathogens, because there will always be some risk), but rigorously enforce the need for actions such as hand washing after visiting the toilet, before eating food, after farm visits and so on, where there is a risk of exposure to levels of pathogens which cause clinical disease. We may encourage pet ownership as potentially

beneficial to health, but at the same time we must stress the importance of good pet hygiene to reduce risks of infection. This means giving clear messages about the chain of infection transmission and targeted food, water, respiratory and other aspects of hygiene to prevent the spread of GI, skin and RT infectious agents.

This is the basis for a more rational approach to home hygiene, developed by the IFH, known as "targeted hygiene". The basis of the IFH approach is that it seeks to protect against infection whilst sustaining normal exposure to human, animal and environmental microbes. This approach involves identifying the critical points (or actions) and times in the chain of infection transmission (for example washing hands after visiting the toilet, or decontaminating the chopping board after preparing raw meat or poultry) and targeting hygiene measures at these points to prevent ongoing spread of pathogens.

Risk assessment shows that the "critical points" for spread of infection in the home are the hands, together with hand and food contact surfaces, cleaning cloths and cleaning equipment. These are the "superhighways" for spreading pathogens around the home, such that healthy family members become exposed, directly or via the food they eat. Any surfaces that come into contact with the body, such as baths and hand basins, clothing and household linens can also act as vehicles of infection, as can hand-contact surfaces associated with the toilet.

Risk assessment is now the accepted approach for controlling microbial risks in food and other manufacturing environments and also in hospitals or other healthcare settings. If background exposure is proved to be the important factor, the targeted approach to hygiene allows a focus on preventing exposure to infectious doses of pathogens, but is more relaxed about other exposures, with a clear understanding that one of the greatest (and very important) benefits of living in a clean-looking home is its effect on our sense of well-being, which also impacts on our general health.

An often-voiced assumption, (possibly because this trend peaked in the 1990s, around the same time as the increased publicity about rising allergies in children), is that the reason for the "increased cleanliness" and loss of microbial exposure has been the trend towards adding antibacterials to cleaning products, chopping boards, clothing and so on. Studies are now showing that, although disinfectant products (also called antibacterials) used at specific times, for a purpose such as food preparation, can reduce infection transmission risks, non-targeted use of these products for general day-to-day cleaning has no measurable impact on ongoing microbial levels in the home. Just as there is no evidence that people living in cleaner homes have more allergies, there is no evidence that adding antibacterial agents to cleaning products is a risk factor for reducing the microbial exposure that we seem to require for immunoregulation.

9. Conclusions and recommendations

During the last decade, support for the role of microbial exposure in immune regulation has continued to increase, so that a "microbial exposure hypothesis" is now widely accepted by the scientific community. It is now clear that it makes no sense to claim that the increase in allergies and other CIDs is caused entirely by changed exposure to microbes, or entirely by vitamin D deficiency, or entirely by diet and obesity etc. Many of these factors are likely to play a role, although it seems that

the essential underlying problem is immunoregulation, and our changing microbial exposures are fundamental aspects of the immunoregulatory deficit.

The primary aim of this review is to better understand the implications for hygiene and other behaviours in our homes and everyday lives, relative to other factors that have altered exposure to microbes over the last two centuries. Increasingly the evidence indicates that the extent to which we suffer from clinical infectious diseases is not the key to immune regulation. We are thus *not* faced with the difficult choice between infectious disease and allergy/CIDs.

If we define "hygiene" as the practices we use to protect us from exposure to infectious disease agents, this puts home and everyday hygiene practices (food hygiene, respiratory hygiene and hand hygiene) as an unlikely cause of allergy and other CIDs. We can also dismiss the idea that "too much cleanliness" in relation to the general domestic cleanliness of our homes, is the cause of the reduced microbial exposure that has fuelled the rise in allergies and other CIDs. If this factor contributes at all, its contribution is likely to be very small relative to factors such as clean water, good sanitation, cleaner environments and food quality. Frequent showering and bathing may be a contributing factor, but there is no good evidence of a link, other than in worsening an existing risk of eczema.

It is time we recognised that using home and personal cleanliness as a scapegoat for a problem that has a much more complicated set of causes is not only unjustified, it is also ill-advised since it is diverting effort and attention from finding the true causes and workable solutions.

Changing public health policies associated with clean water, food and effective sanitation in order to increase our exposure to "Old Friends" is not currently a viable option. Unless we can identify the "Old Friends" and find ways to selectively reintroduce them without re-exposing ourselves to serious infections this would only turn back the clock; quite apart from the potential impact on the infectious disease burden, any attempt to return to lifestyles and public health systems which existed prior to 1800, would not re-establish the ecosystems particularly in urban areas. As stated by Professor Rook in a 2011 review "in the modern urban environment, relaxing hygiene would not expose us to "Old Friends" – only to new enemies like *E. coli* O104".

In the longer term, there is a prospect for drug therapies, and "probiotic" approaches to nutrition to provide us with the required microbial exposures, but any public health or medical approaches require much further research to gain clear understanding of how selective microbial exposure might be used to stimulate immunoregulatory systems without exerting pathogenic or toxic effects.

In the immediate term, promoting a more effective approach to hygiene in home and everyday settings offers a strategy that could impact on both issues. The principle of targeted hygiene is that it focuses on identifying the key routes by which pathogens are transmitted, and intervening at critical points at the appropriate time to reduce the risks of transfer of infection, but also recognising the value of maintaining exposure to our environment. Encouraging people to develop lifestyles that reconnect with the natural environment, while also understanding and using targeted hygiene as the means to protect ourselves from infectious diseases, is a challenge for our time. One of the problems in trying to communicate clearly with the public, in order to change attitudes and understanding, is that the terms "hygiene" and "cleaning" convey different meanings to different people, and are often used interchangeably, which may confuse the important differences.

There is already clear evidence showing that getting people to adopt a targeted approach to home hygiene is likely to have a significant health benefit by reducing the risks of infectious diseases. This

is sufficient in itself to warrant investment in the development and promotion of this approach. On the other hand, although the OF and diversity hypotheses now offer a plausible theory with growing scientific support, we are still some way from conclusively demonstrating how we can begin to reverse the rise in allergies and CIDs though exposure to the right kinds of microbes. It may be that promoting behaviours that reconnect us with our biological environment, including getting dirty more often, could contribute. While this would not conflict with targeted hygiene, we need a clearer understanding before particular approaches could be strongly advocated.

To make practical progress from this wealth of research, there are three key points to get across:

- The expanded hygiene hypothesis is an increasingly important issue for health. It is not confined to issues of day-to-day home and personal cleanliness, but rather to a broader range of lifestyle choices, and measures introduced to protect us from infectious diseases. Together, these have inadvertently also reduced exposure to the microbial friends that regulate our immune systems.
- The organisms identified as "Old Friends" that appear to protect against CID are distinct from the pathogens causing most infectious diseases in the modern world. Relaxing hygiene would NOT increase our exposure to the protective "Old Friends"… but would increase exposure to the pathogens. The problem is not one of being too clean: it's one of reduced contact with the right kind of dirt
- We need to distinguish between routines associated with cleanliness, in the sense of absence of dirt, appearance, social acceptability and freshness, and practices required to protect us from exposure to infectious disease. This indicates a need for clearer guidance on how to target hygiene practices effectively where and when they are required.

To reduce the health burden of both infectious diseases and allergies and other CIDs at the same time requires a co-operative effort between the different national and international health bodies and other departments, such as environmental agencies: at present, those with responsibility for these disparate issues tend to address them separately. All aspects of public health strategy must take into account the fact that the need for infection prevention through hygiene is as great as it ever was. The ongoing burden of infectious diseases, the greater numbers of people more vulnerable to infection, the problem of antibiotic resistance and lack of effective vaccines against many infectious diseases mean that infection prevention is, once again, a high priority health issue. Keeping the burden of infectious disease within economically sustainable limits means a shared responsibility and changing attitudes, understanding and behaviour at all levels of society.

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