Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

[4]. Another possible, and more direct, bacterial effect would be influencing the expression of parasite's genes involved in oxidative stress management and by doing so stimulating its intrinsic ability to cope with an intoxicating environment. Support for this comes from *E. histolytica*, where a direct bacterial effect on the regulation of parasite's genes was demonstrated [13]. Assuming that the intrinsic capacity of *H. meleagridis* to cope with oxidative stress is provided [8], such direct effects of bacteria might be feasible.

Impact of *H. meleagridis* on Bacteria

So far, only very few relevant studies are available, but molecular data point towards an intricate relationship between *H. meleagridis* and bacteria. On the basis of proteomic analyses of *H. meleagridis*, it seems that the presence of the parasite itself substantially influences the expression pattern of genes of cocultivated bacteria [9,10,14]. Due to the monoxenic nature of the *H. meleagridis in vitro* culture, the detection of a few *E. coli* proteins was anticipated. However, a substantial variation of their abundance, which could be associated with the parasite's phenotype, is remarkable and thought-provoking. Especially the exoproteome study demonstrated substantial changes in the expression of *E. coli* proteins. Considering that about one-third of bacterial proteins undertake their function outside the cytoplasm, it seems unsurprising that major differences in the exoproteome were of *E. coli* origin, whereas variations in protozoal exoproteins were almost nonexistent [9,15]. Analysis of detected divergence in *E. coli* exoproteins suggests that, during cultivation, *E. coli* relies on the consumption of bioproducts from the parasite's metabolism, indicating a mutual role as nutrient supply [9]. However, the data also reveal a potential resilience of prokaryotes to predation by the parasite. Whether bacteria themselves acquire some advantage from this tight interaction remains hypothetical and needs to be investigated in more detail. The obvious hypotheses are (i) the protection from external agents or conditions, (ii) the nutrient supply and/or (iii) the use of *H. meleagridis* as a Trojan horse for prokaryotes. Some evidence for the last hypothesis comes from animal experiments and case reports of histomonosis from the field, which often find a secondary *E. coli* infection [3].

Future Perspectives

Aside from a nutrition source and/or the creation of favourable environmental conditions, the need for bacteria in the turkey/chicken caecum to induce histomonosis might be seen as a cooperative aid in the disruption of the gut epithelial barrier. This 'eu-prokaryotic' interaction can have fatal consequences for the host, altogether a unique alliance in medicine. However, the underlying functional mechanisms are still to be resolved, considering that the host itself may trigger and contribute certain features inducing substantial consequences on the outcome. On the basis of available data, we hypothesise that the parasite–bacteria interplay is mutualistic and not of a predator–prey nature. Future research should focus on resolving the unknowns of this interaction in order to elaborate whether a targeted manipulation of the gut microbiome can be achieved in order to minimise clinical consequences. Similarly, such knowledge could also be used to optimise the infection of attenuated *H. meleagridis* strains used for vaccination.

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Forum

Spatial Lifecourse Epidemiology and Infectious Disease Research

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Spatial lifecourse epidemiology aims to utilize advanced spatial, location-aware, and artificial intelligence technologies to investigate long-term effects of measurable biological, environmental, behavioral, and psychosocial factors on individual risk for chronic diseases. It could also further the research on infectious disease dynamics, risks, and consequences across the life course.

Spatial lifecourse epidemiology is an emerging research field, aiming to utilize advanced spatial, location-aware, and artificial intelligence technologies, mainly geographic information systems, remote sensing, global positioning systems (GPS), location-based services, and machine learning, to investigate long-term effects and mechanisms of measurable biological, environmental, behavioral, and psychosocial factors on individual disease risk [1,2]. Despite a seeming focus on chronic diseases, this field could also further infectious disease studies, as many infections and their health outcomes present spatio-temporal and population heterogeneity and the risk for infections also varies across the life course.

Epidemiologic Triad over the Life Course

The epidemiologic triad, a classical model of infectious disease causation, describes the fundamental relationship among the disease-causing agent, the susceptible human and/or animal hosts, and an environment in which they reside and their interaction occurs, with the spread of infectious agents being direct host-to-host transmission or indirect transfer by vectors (e.g., mosquitoes). However, each of those components is dynamic: the environment is changing, such as daily weather variation and climate change that may affect the agent and the opportunity for exposure; the agent is evolving during its life and interacting with other agents in changing environments; and the host is also dynamic, influencing the individual's exposure, susceptibility, and response to the pathogen and environment. Also, the vector is moving around and interacting with different agents in varying environments. Thus, most if not all biological, social, and psychological pathways, as well as their combined processes (e.g., bio-social, socio-biological, and psycho-social), are to different extents influenced by spatio-temporally varying environmental factors. Investigating how those components may meet in respective dynamic processes could increase our capacity of monitoring and forecasting the outbreaks and health impacts of infections.

By treating the epidemiologic triad as a snapshot at every moment over a lifecourse process and the risk for infection as a function of all past snapshots (Figure 1), the spatial lifecourse theory can guide the understanding of many phenomena in pathogen spread, including: (i) the occurrence and transmission of infectious diseases (e.g., SARS and MERS); (ii) the re-infection (e.g., malaria) and co-infection with other pathogens [e.g., coronaviruses, hepatitis viruses, tuberculosis (TB), and HIV] or chronic diseases (e.g., diabetes); (iii) the burden of chronic infections (e.g., HIV and TB); (iv) long-term consequences of infections; and (v) the complex interaction between infectious and chronic diseases over the life course.

Risk Factors of Infections across Spatial Life Course

From a macroscopic point of view, the spatial heterogeneity of natural and socio-economic factors could alter the possibility of infectious disease outbreaks in different regions. Natural environmental factors, such as precipitation, humidity, and temperature, have been recognized as important factors of infectious disease spread, such as hand-foot-and-mouth disease and influenza [3]. The populations who are exposed to certain environmental factors can lead to an increasing contact to infectious agents. In particular, the hysteresis effect of the weather factors should be considered [4]. Socioeconomic factors, such as population density, human movement, urbanization, economic development, and communication technology development, are also connected to the transmission of infectious diseases. For instance, modern transportations have accelerated the spread of dengue and mosquito vectors across the world over the last six decades; human movement and urbanization have increased the frequency of communication among individuals and thus the risk for HIV transmission [5]. In addition, environmental amenities could facilitate the formation of behaviors, such as outdoor physical activities, which could increase the contact between people, motivating the outbreak of human-to-human transmission of diseases.

The microscopic perspective mainly involves the experiences and attributes of individual hosts, as well as the features of pathogens. Some infectious diseases are more likely to happen in specific age and/or gender groups. For example, the hand-foot-mouth disease more likely attacks children under 10 years [6]. Furthermore, a compromised immune status resulting from poor nutritional status in infancy may directly lead to an increased risk for infections in childhood, adolescence, and adulthood, as well as potentially elevated morbidity and mortality rates at each stage of life, especially in late adulthood. Additionally, long-term health impacts after infection may exist across the life course and across regions, such as the birth defects of children who are exposed to maternal Zika virus infection in America [7]. Infectious diseases caught in early childhood can also lead to malnutrition (e.g., stunting and overweight), which

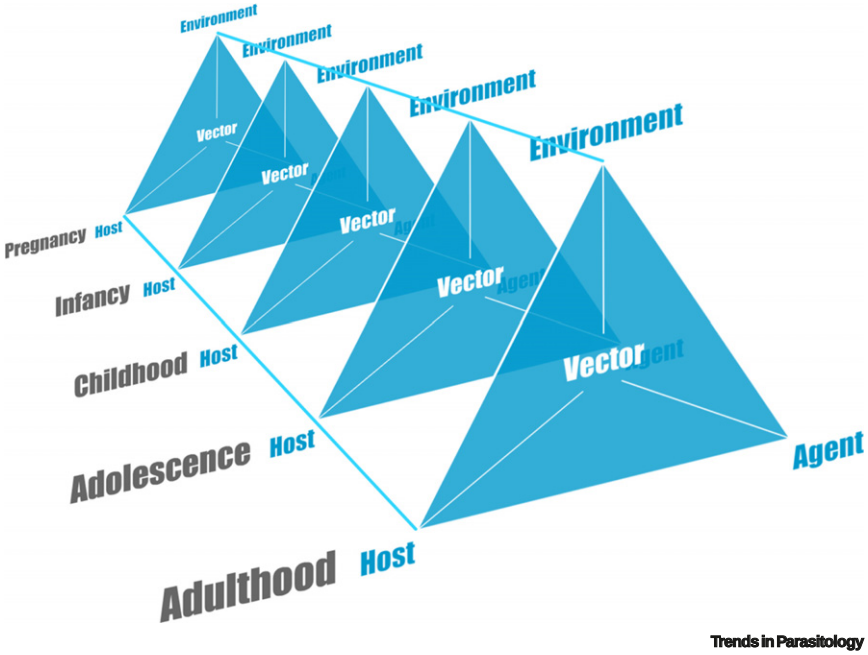

Figure 1. The Epidemiological Triad over the Life Course.

could still lead to higher risk for chronic diseases at a later stage of life.

The totality of all internal (e.g., having certain chronic diseases) and external (e.g., built and food environments in residential neighborhoods) exposures at all places and over the life course, termed as exposome, is a useful target to measure in not only chronic disease studies (i.e., cumulative exposure for dose–response estimation) [8,9], but also in infectious disease research. For instance, intensity of exposures to pulmonary TB, measured as individual contact time with the TB index case, has been positively associated with the increased risk for TB infection and diseases among household contacts [10].

Spatial Lifecourse Approaches for Infectious Disease Epidemiology

Spatial lifecourse epidemiology is an enabling field for the exposome [8]. Spatial approaches have been increasingly used to study the determinants of and the risk for infections for two decades [11]. For example, the changing spatio-temporal distribution of variant virus strains (e.g., influenza A viruses), has high impacts on the risk for influenza infections in populations across the world [12]; phylogeographical methods hold great potential for understanding the epidemics, spread routes, as well as the changing risks from origins to destinations (e.g., Zika and seventh cholera pandemic), by combining geolocations and genetic data, etc. Although these researches, as well as some other themes such as early detection and warning of disease outbreaks, could be partly under the concept of life course, they mainly stay at the regional instead of individual level (e.g., focusing on what types of climatic and meteorological factors may be risk factors). Many individual-level factors could be confounders for the detected associations. This problem needs to be solved in a longitudinal study design, which, in turn, requires spatial technologies to provide temporally frequent measurements of external environmental factors to enrich cohort data and hence investigate causal relationships between environmental exposure and disease occurrence.

From a lifecourse perspective, the risk assessment of infection should also be conducted according to age, gender, and other natural characteristics. Individuals' social characteristics, such as occupation, daily activities, and social interactions, also affect individuals' risk for infection. Modern ways of collecting those data include using location-based services (e.g., smartphone or mHealth applications) to ease the survey process [13]. Therefore, survey questions on infectious diseases could be combined into the prospective cohort studies that have been mainly designed for studying chronic diseases. In turn, data collected in infectious disease surveys could also be used to supplement the local cohort studies. Furthermore, if there is a sufficient sample size, infectious disease surveillance, surveys, and reports (e.g., the National Notifiable Diseases Reporting) could all be used to construct study populations for spatial lifecourse epidemiologic research.

Modeling the spatio-temporal trend of infectious diseases is an important issue because an accurate prediction of outbreaks can serve for early preparedness and responses. Lifecourse analyses for infectious diseases from macro to micro levels are helpful to improve the accuracy of the dynamic transmission model, as they provide additional information for simulation of the progression of infectious diseases. Some dynamic models from a lifecourse perspective have been developed, such as climate-driven dynamic models, age-dependent dynamic models, and human mobility-based models [5,14]. Propagation dynamics models could be used to predict the changes of infectious populations during an epidemic, which divide a population into different groups, such as susceptible population, infected population, and recovery population [15]. Different groups of the population are interchanged by a proportion within a

period. Two directions of improvements may be considered from a spatial lifecourse perspective. One is that a susceptible population could be estimated more accurately, according to the distribution of the population and corresponding infectious factors. The other is related to the adjustment of model parameters, such as transmission rate and recovery rate.

In addition to data analysis, presentation of disease maps also needs to be more dynamic, moving from static disease mapping to continuously updated maps of contemporary disease risk. Several approaches were summarized to quantify human mobility at different spatial and temporal scales, including long-term international and within-country migration census, flight and commuting networks, cell-phone data, and logging devices (e.g., GPS). Although long-term time series of these data are still challenging, they are becoming increasingly available from different novel and open data sources. Those approaches and data sources could also be used for designing new or supplementing existing spatial lifecourse epidemiologic studies [2,8].

Concluding Remarks

More attention should be paid to estimate the lifecourse risk of individuals for infections after considering variable environments, dynamic hosts and their behaviors, and the spatio-temporal interaction between the environment and individuals. The concept of spatial lifecourse epidemiology can include all those factors and considerations in one research framework, which will revolutionize the infectious disease research to improve 'One Health' at the interface of humans, animals, and their various environments.

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