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From the micro to the macro to improve health: microorganism ecology and society in teaching infectious disease epidemiology

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Chronic and emerging infectious diseases and antimicrobial resistance remain a substantial global health threat. Microbiota are increasingly recognised to play an important role in health. Infections also have a profound effect beyond health, especially on global and local economies. To maximise health improvements, the field of infectious disease epidemiology needs to derive learning from ecology and traditional epidemiology. New methodologies and tools are transforming understanding of these systems, from a better understanding of socioeconomic, environmental, and cultural drivers of infection, to improved methods to detect microorganisms, describe the immunome, and understand the role of human microbiota. However, exploiting the potential of novel methods to improve global health remains elusive. We argue that to exploit these advances a shift is required in the teaching of infectious disease epidemiology to ensure that students are well versed in a breadth of disciplines, while maintaining core epidemiological skills. We discuss the following key points using a series of teaching vignettes: (1) integrated training in classic and novel techniques is needed to develop future scientists and professionals who can work from the micro (interactions between pathogens, their cohabiting microbiota, and the host at a molecular and cellular level), with the meso (the affected communities), and to the macro (wider contextual drivers of disease); (2) teach students to use a team-science multidisciplinary approach to effectively integrate biological, clinical, epidemiological, and social tools into public health; and (3) develop the intellectual skills to critically engage with emerging technologies and resolve evolving ethical dilemmas. Finally, students should appreciate that the voices of communities affected by infection need to be kept at the heart of their work.

Introduction

Infectious diseases remain a global health threat and continue to lead government risk registers—eg, the current pandemic of coronavirus disease 2019 (COVID-19) and the development of antimicrobial resistance.¹ Chronic infectious diseases such as HIV and tuberculosis—together accounting for over 2·1 million deaths globally in 2017—and emerging infections with the potential for rapid expansion, remain a substantial and acute threat to humanity.^{2–5} Furthermore, there is growing acceptance that the body's resident microbiota plays an important role in non-communicable diseases. The role of a single pathogen in driving neoplastic disease is well established (eg, *Helicobacter pylori*, hepatitis B virus, Kaposi's sarcoma-associated herpesvirus, and human papillomavirus). However, in other diseases the role of the interactions between our microbiota and immune system remains under investigation.^{6–8} Infectious diseases have profound effects beyond health, especially on local and global economies, which exacerbates existing socioeconomic vulnerabilities.⁹ Moreover, any response to these infectious threats requires the development of new drugs, diagnostics, and vaccines, for which we are dependent on the pharmaceutical industry, whose interest might differ from those of public health.

To maximise improvements in human health, the field of applied infectious disease epidemiology needs to derive learning from ecology (the branch of biology that deals with the relations of organisms to one another and to their physical surroundings) and traditional epidemiology

Key messages

The field of infectious disease epidemiology is changing rapidly with:

- Better understanding of disease causation and the role of microbes in a wide range of diseases;
- Molecular characterisation of the microbe and the host, leading to better understanding of interactions in the ecology of each and the translation to transmission networks; and
- Better tools to measure and understand the social and environmental context

These changes require a response that brings new ways of thinking about teaching infectious disease epidemiology which includes the macro, meso, micro, and:

- Connects across basic science, clinical medicine, political and social science, sociocultural understanding, and population health statistics to decide on the right research questions;
- Incorporates emerging technologies to collect and understand complex, dynamic data with a critical approach of the limitations of these methods;
- Builds the intellectual skills to critically engage with disparate disciplines and new methods, including recognising their strengths and limitations, and new ethical dilemmas that may arise; and
- Keeps the voices of communities affected by infection at the heart of any enquiry

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(the branch of medicine concerned with distribution of disease in time, place, and person, their causes, and control). Infectious organisms thrive when they occupy a permissive ecological niche that enables them to reproduce and evolve.¹⁰ A wide range of interacting and dynamic systems determine whether an ecological niche is permissive, which includes the physical environment, social and cultural context, political and health-care systems, human behaviours, host and organism genetics, the host immune system, and interactions with other microorganisms competing for resources. Perturbations in any of these systems can alter the ecological balance. If we can understand the systems and their interactions better, we could identify opportunities to prevent and control infections.

New methodologies are transforming our understanding of these systems, from better understanding of socioeconomic, environmental, and cultural drivers of infection, to improved methods to detect and characterise microorganisms, a refined measurement of the immune at scale, and improved understanding of the role of human microbiota.^{11–13} Furthermore, our ability to study the genetic evolution of organisms alongside host genetics and epigenetics brings new insights into disease susceptibility and the immune response. These biological insights alongside the development of increasingly powerful bioinformatic methods allow us to reconstruct the evolution of outbreaks by combining molecular data with classic epidemiological and clinical data,¹⁴ and provide powerful new tools to inform disease prevention¹⁵ and vaccine development.¹⁶

Working in silos is likely to limit opportunities for change, but effective integration of biological, clinical, epidemiological, and social tools for public health programmes is still in the early stages. Moreover, new technologies bring new ethical and moral challenges¹⁷ which require ongoing discussions with communities

and individuals affected by infectious diseases. We argue that there is an urgent need for education programmes that train a modern group of infectious disease epidemiologists who can integrate thinking across fields and methods to optimise the prevention of, and response to, infectious disease threats. This change means incorporating training in classic and novel techniques to teach scientists and practitioners to work from the micro, with the meso, and to the macro, to improve human health.^{18,19} In this Personal View we outline our proposal for a novel approach to train epidemiologists and public health experts specialising in the field of infectious diseases.

Rethinking infectious disease epidemiology teaching—building on social epidemiology

Societal factors, including the environment, society, and health infrastructure (the macro), have long been understood to play a major role in determining the health of individuals and populations.^{20–22} This understanding led to the emergence of social epidemiology as a field of interest,²³ and the application of socio-ecological models from sociology to the public health field,²⁴ and WHO's focus on social determinants of health.²⁵ Social epidemiology is now extensively taught in traditional epidemiology and public health curricula, which has led to increased implementation of structural interventions that have substantially affected behaviours and health outcomes.^{26–30} Within the field of infectious disease control, sanitation, housing, accessible health care, and vaccine regulations have substantially reduced mortality and morbidity—first in young children^{31,32} and now for adolescents and adults.³³

There is also a better understanding of the dynamic interaction between these wider structural factors and the local community in infectious disease transmission (the meso). This improvement has primarily involved locating geographies or occupational communities with higher transmission of infection—eg, malaria in particular villages,³⁴ or HIV transmission in settlements next to major transport routes in sub-Saharan Africa,^{35,36} and among specific occupational communities (fishermen on Lake Victoria in Uganda; miners in sub-Saharan Africa).³⁷ There is an increasing understanding about how the communities (including individuals with interpersonal relationships, families, and households) experience, organise, and respond to the threat and reality of infectious disease, whether through political struggle to secure decent housing and clean water, or advocacy for access to prevention methods such as HIV pre-exposure prophylaxis, condoms, and vaccine funding.^{38–40} More recently,^{41,42} community mobilisation, community-based health care, economic empowerment, and gender-based violence reduction strategies are all seen as integral to controlling the global HIV epidemic. Communities can also be a barrier to effective interventions, as illustrated by the anti-vaccine movement.^{43,44} Infectious disease researchers and

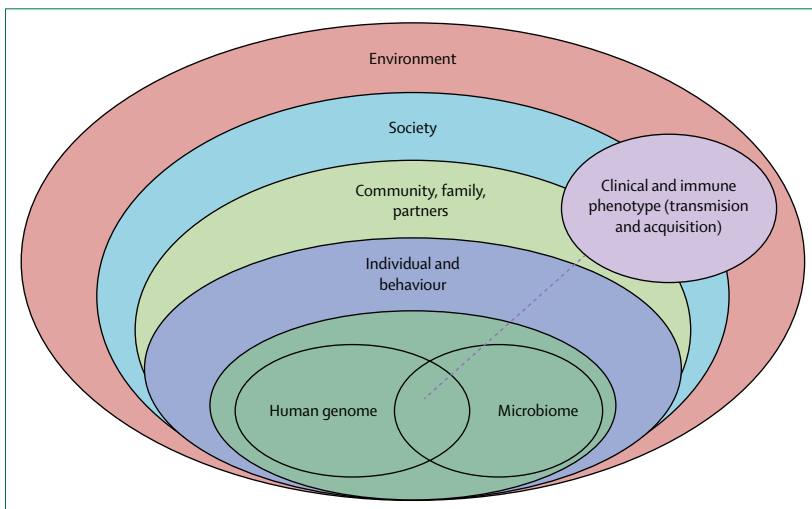


Figure: The socio-ecological-biological framework to integrate microbiota into human ecology

practitioners need to be trained to listen to the voices of affected patients, and to include and evaluate community-based solutions to infectious diseases.

At the other end of the spectrum (the micro), the appreciation of microorganisms and their hosts at a molecular level has been revolutionised by advances in technology, including the tools to characterise genomes, describe the microbiota, and measure host immunity and inflammation. These advances have been technologically driven, often without clear models of future use, with computational biology and data science developments responding to vast increases in the generation of

high-density datasets rather than driving health-focused developments.^{12,13} Moreover, the omics revolution brings dilemmas which include the possibility that social and community solutions become side-lined as novel molecular innovations attract all the investment. Clinical and ethical implications might also be unclear.¹⁷ Applying the same degree of epidemiological caution to molecular data is vital, particularly regarding inferences about causality.⁴⁵ For example, the insufficient power to study the effect on disease of an attribute that we measure (eg, a single nucleotide polymorphism in the human genome when there is no previous hypothesis of effect), has only recently

Vignettes and related questions	Interdisciplinarity	Key learning points	
Identifying and explaining a HIV microepidemic in a high-prevalence setting	Phylogenetic analysis of HIV identified the emergence of a new HIV outbreak that was not picked up by routine surveillance in rural KwaZulu-Natal (South Africa); why did a microepidemic occur? what could be done to prevent or control it?	Epidemiological data connected the HIV outbreak to the opening of a new coal mine; ⁵⁶ rapid ethnographic methods adapted from anthropology showed how this new industrial development had changed local socioeconomic dynamics by bringing workforce and financial resources to a poor area; community and public engagement to establish HIV-prevention measures before the development of the coal mine could have prevented the outbreak	Although the HIV cluster was identified using phylogenetics—traditional epidemiological and social science methods were needed to understand why the outbreak occurred and how it could be controlled; responsive public health systems might need to layer multiple methods to inform effective and ethical intervention strategies in real-time
Causes and control strategies for an Ebola epidemic	Outbreak investigations—eg, for Ebola in west Africa—have used state-of-the-art phylogenetic methods to detect and understand clusters of infections; ⁵¹ why did the outbreaks happen? why has the national and international response been slow?	Anthropologists, social scientists, and health-system analysts have described the role of poor health infrastructure and cultural reasons for health-seeking behaviours in driving the epidemic; traditional epidemiology, statistics, computational biology, and modelling were used to plan the vaccine trials	The confluence of sociocultural conditions, health systems, and biology underlie the 2014 Ebola epidemic and all of these factors were needed to bring the Ebola epidemic under control; the effective deployment of a new vaccine will require combining epidemiology, mathematical modelling, public health, and social science understanding of the context and vaccine acceptability
The role of early infant microbial colonisation in subsequent health outcomes	Observational epidemiological studies have shown associations between early life events—eg, method of delivery and health outcomes such as childhood asthma and obesity; ^{52,53} other studies have suggested that microbial colonisation is mediated by the same exposures; what is the mechanism for these associations? how can we intervene?	Infectious disease epidemiologists had to collaborate effectively with microbiologists, geneticists, parents, clinicians, bioinformaticians, and statisticians to design longitudinal studies with early-life biobanking and life-long follow-up at sufficient scale to advance understanding of mechanisms and identify modifiable factors that might need intervention	What might be a clinically relevant difference at species-level in early life microbial colonisation is currently unclear; biology and epidemiology understanding will be needed to define these differences and translate findings into public health responses; public engagement will be key to understanding how and when to communicate these complex findings
Establishing an evidence base for digital technologies in controlling infections	The digital revolution is changing social relationships in ways that affect infectious disease transmission (eg, widening social and sexual networks), and provide new opportunities to intervene (eg, optimising real-time surveillance and revolutionising health-care delivery); however, many digital health interventions have an insufficient evidence base and might exacerbate social exclusion along the digital divide; can mobile health deliver effective HIV care and prevention remote from facilities? can social and sexual networks deliver this care? what will be the effect on transmission dynamics?	To develop a contextually-adapted intervention and safe clinical pathways, bioengineers have worked with human-computer interaction specialists, clinicians, members of the public, and social scientists; epidemiologists and statisticians use developments in social network analysis and mathematical models to measure the effect on transmission dynamics and estimate the cost and cost-effectiveness; scale-up and equitable access requires public engagement, economists, geographers, health systems, and health policy specialists	Digital health interventions are complex, requiring iterative theory-based development involving public and user engagement at each stage; we need to be able to evaluate the effectiveness, efficiency, and equity compared with traditional models of care, which can be achieved only using interdisciplinary measures across a wide range of disciplines
The changing transmission dynamics of shigella in high income settings	Shigellosis epidemics driven by transmission between adult men have been observed in Europe, Australia, and North America; ⁵⁷ traditional epidemiological studies including those using male to female ratios and case studies with interviews have shown that these epidemics are linked to sexual behaviours in men who have sex with men, including sexual activity under the influence of drugs and social media applications that facilitate sexual networking; how are these outbreaks sustained? how can we move from observation to control? what is the effect on propagation of antimicrobial resistance?	Epidemiologists used surveillance data to monitor shigellosis outbreaks and worked with social scientists to understand human behaviours; working with microbiologists, bioinformaticians, and comparative biologists has shown that repeated horizontal transfer of a single plasmid, containing multiple antibiotic resistance was associated with successful clonal strains; it seems probable that the shigella epidemics resulted from a combination of high-risk sexual behaviours, prescribing practices, and the ability of the pathogen to acquire selective evolutionary advantages, and exploit a new ecological niche; integrating advances in social network epidemiology with phylogenetic analysis can provide further insights into antimicrobial resistance and sexually transmitted infection outbreaks	There are major benefits from joining up the thinking between epidemiology (ie, observing the changing distribution of shigella); evolutionary microbiology (ie, identifying antibiotic-resistant strain evolution); sexual network analysis (ie, identifying who has sex with who); and health systems (ie, analysis of clinical policy and prescribing practices over time)

(Table continues on next page)

Vignettes and related questions	Interdisciplinarity	Key learning points	
(Continued from previous page)			
Malaria transmission and endemicity in central Myanmar	Myanmar represents an important country for artemisinin-resistant malaria and yet few data exist to inform control efforts and achieve the WHO malaria elimination target for southeast Asia; internal economic migrants might be important to the ongoing endemicity of malaria in Myanmar, but are also a politically sensitive population; what is the prevalence of malaria and artemisinin resistance in central Myanmar? what are the risk factors associated with malaria infection?	Epidemiologists needed to work with in-country clinicians, microbiologists, and politicians to access remote and politically sensitive regions with appropriate ethical oversight to design and implement a cross-sectional prevalence survey; ⁵⁴ the blood samples collected were tested for parasites and drug resistance using molecular diagnostics, and for malaria serology; a combination of clinical parasitology, immunological, and biostatistical expertise was needed to interpret the molecular data; social science observations provided insights about the movements of working age men and their involvement in the forestry industry	The value of molecular data can be substantially enhanced with individual-level clinical, behavioural, and sociodemographic data; any interpretation (of the finding that seroconversion to <i>Plasmodium falciparum</i> was 16-times higher in men older than 23 years) needs contextual information about behaviours and the wider socioeconomic and political environment to design effective and ethical public health responses; community engagement and acceptance will be key to sustainable and scalable solutions
Creating evidence-based tuberculosis screening policies for migrants in the UK	In high-income countries an increasing proportion of all tuberculosis cases are detected in migrants; in response to this changing epidemiological pattern, several countries have developed pre-migration tuberculosis screening programmes; understanding the epidemiology of tuberculosis in migrants to improve the evidence base of these screening policies is a public health priority; can probabilistic linkage methods be used to identify migrants across datasets where no standard unique identifier exists? can molecular strain typing data infer the incidence of active tuberculosis disease in pre-entry screened migrants which might be preventable using additional latent tuberculosis-infection screening?	Epidemiologists, computer scientists, and mathematicians worked together to develop and validate probabilistic methods that could be used to identify non-UK born individuals across separate datasets; these newly validated methods were used to construct a population-based cohort of 519 955 migrants screened before entry to England, Wales, and Northern Ireland; ⁵⁵ working with molecular epidemiologists and using these newly linked data improved the understanding of epidemiology in migrants previously screened for active tuberculosis; this new evidence was then used by public-health experts, and national and international policy makers to improve global screening policies	This work required a public health data-science approach that combined the skills of epidemiologists, computer scientists, and mathematicians to develop and understand new methods and apply them to newly linked datasets, which gave new insights and actionable evidence to improve screening for tuberculosis in the migrant population; public engagement and community advocacy were key to translating the evidence into effective policy and practice

Table: Using vignettes to teach students to use a socio-ecological-biological framework to apply infectious disease epidemiology to improve human health⁵⁴⁻⁵⁷

been more widely appreciated and the inadequate replicability remains a concern for these studies.⁴⁶

We argue that teaching fundamental epidemiological skills will remain key to exploiting scientific and technological advances. Infectious disease epidemiologists will need the skills to define the problem, albeit within a socio-ecological-biological framework (figure). They will need to know the benefits and limitations of different epidemiological study designs for addressing the problem, the potential for bias (eg, through informative missing data and measurement bias), the role of chance and often unmeasured or unknown confounding, and complex statistical methods including those for causal inference. Infectious disease epidemiologists will still need to understand transmission dynamics (air, water, zoonosis, vector-borne, sexual, vertical, and parenteral) within and across the life course. They will also need to understand how to apply this knowledge to design and evaluate interventions (including cluster randomised trials and use of quasi experimental methods), and understand how mathematical modelling of transmission can be used to inform scale-up and cost-effectiveness.

Additionally to these concepts, infectious disease epidemiologists will need to understand the way that biologists and social scientists think—ie, be familiar with pathology and clinical implications, and the effect of socioeconomic and policy environment on human health. Epidemiologists will need to understand the type of research questions that new methods can answer, their limitations, and how these methods can be integrated with more traditional approaches. Moreover, they will need to

embrace and critically appraise complex data and knowledge from a wide range of sources, and learn to include the communities and individuals affected by infection when developing and evaluating solutions,^{47,48} and translating findings into policy. Although no single individual can be expected to have expertise in all of these disciplines, these concepts show the importance of training and rewarding a team-science approach to bring together well-matched interdisciplinary groups of scientists.^{49,50}

Applying the socio-ecological-biological framework to infectious disease epidemiology

We propose that the next generation of infectious disease epidemiologists need to move beyond the dichotomy between communicable and non-communicable diseases, and use epidemiological methods at the interface between population health and microorganisms. The key to this shift is the expansion of the individual-level focus of many infectious disease epidemiology programmes to include the commensal microbiota that cohabit with potential pathogens in the host ecological space (the micro), the expression of this framework into communities (the meso), and the wider contextual drivers of disease (the macro), and the interactions between these factors. Such shifts are already happening in some training and research programmes, but a systematic approach is essential to ensure that all the key factors are included.¹⁸

To assist conceptualisation, we propose an expanded socio-ecological-biological framework that includes the interactions between the host, pathogens, and the wider

microbiome (figure). This socio-ecological-biological framework provides a model to facilitate how we include and critically appraise a range of factors that influence disease. To apply this approach to training, the next generation of infectious disease epidemiologists needs to develop a basic understanding of biological sciences (immunology and microbiology), clinical medicine, social sciences, data science and bioinformatics, engineering, politics and economics, and public engagement in relation to health, disease, and transmission.

The ultimate goal is not to broaden the field of epidemiology and its established methods. Rather we advocate for an increase in students' appreciation of the range of disciplines that contribute to infectious disease epidemiology, and how these areas can develop their intellectual skills to engage across different fields. One way to increase appreciation is to engage postgraduate students in interdisciplinary problem solving using experiential learning techniques such as vignettes (case studies that illustrate a problem). By using facilitated group work with students simulating disciplinary roles, we have shown that the practical use of a team-science approach is feasible and acceptable—ie, the need to be an expert in one area, but responsive to and aware of other disciplines in solving complex problems. Furthermore, we want students to apply the principles of basic immunology, microbiology, and pathogenesis to describe the microorganisms' adaptations to transmission (eg, airborne, faecal-oral route, sexually transmitted, vector-borne, and hospital acquired) and the implication for clinical manifestation, and thus measurement and case definitions. We present several teaching vignettes to show how this integrated socio-ecological-biological framework can be applied in teaching infectious disease epidemiology (table).

Conclusion

The field of infectious disease epidemiology is changing rapidly because of improved understanding of disease causation and the role of microbes in a wide range of non-communicable and communicable diseases. Molecular characterisation of the pathogen and the host are enabling better understanding of transmission and host networks; however, there are major challenges in bringing these different disciplines together while ensuring critical appraisal of data. Moreover, the environment needs to be assessed and included in disease models to understand complex infectious disease problems. Finally, epidemiologists need to engage with the affected communities if they are to successfully intervene on complex infectious disease problems at a population level.

New approaches to teaching need to account for the developments in our understanding of infection-related ill health, incorporate emerging technologies, and encourage collaboration across disparate disciplines including basic science, clinical medicine, statistics, and social science. Achieving these goals will require innovative ways of

teaching infectious disease epidemiology, at the core of which lies the need for familiarity and openness across a range of disciplines, expertise in one or two areas, and much practice in team-based problem solving. We believe that this approach will provide awareness of related disciplines and the ability to make connections between fields. Such change is feasible, but will require active adaptation and robust evaluation of the outcomes of future training programmes.

Contributors

MS and NF conceived the manuscript. MS, GuH, CEMC, CK, and NF were involved in early discussions and mapping the concepts that led to this Personal View. MS, GuH, CEMC, HB, CK, JG, RWA, and NF contributed to the vignettes. MS, GuH, CEMC, and NF wrote the first draft of the manuscript. All authors read and critically reviewed drafts of the manuscript.

Declaration of interests

We declare no competing interests.

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