Title: From the micro to the macro to improve human health: Taking microorganism ecology and human society seriously in teaching Infectious Disease Epidemiology

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Abstract

Chronic and emergent infectious diseases and antimicrobial resistance remain a substantial global health threat, and our resident microbiota are increasingly recognised to play an important role in health. Infections also have a profound impact beyond health, including on global and local economies.

To maximise improvements in human health, the field of infectious disease epidemiology needs to derive learning from ecology and traditional epidemiology. New methodologies and tools are transforming our understanding of these systems, from better understanding of socio-economic, environmental and cultural drivers of infection, to improved methods to detect microorganisms, describe the immunome and understand the role of human microbiota. However, exploiting their potential to improve global health remains elusive.

We argue that to exploit these advances requires a paradigm shift in the teaching of infectious disease epidemiology to ensure students are well-versed in a breadth of disciplines, whilst maintaining depth in core epidemiological skills. We discuss the following key points illustrated using a series of teaching vignettes: integrated training in classical and novel techniques is needed to develop future scientists and professionals who can work from the micro (interactions between pathogens, their cohabiting microbiota, and host at a molecular and cellular level), with the meso (the affected communities), and to the macro (wider contextual drivers of disease); teach students to use a team-science approach to effectively integrate biological, clinical, epidemiological and social tools for public health impact; and 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 must be kept at the heart of their work.

Introduction

Infectious diseases remain a global health threat and continue to lead government risk registers, for example, with the threat of pandemic 2019 novel coronavirus (2019-nCoV) and the development of antimicrobial resistance (AMR).[1] Chronic infectious diseases such as HIV and tuberculosis, which together accounted 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 our resident microbes (microbiota) have an important role in non-communicable diseases. The role of single pathogens in driving neoplastic disease is well established (e.g. *H. pylori*, hepatitis B virus, Kaposi's sarcoma-associated herpes virus, and human papillomavirus) whilst the role of the interactions between our microbiota and immune systems in other diseases are under investigation.[6-8] Infectious diseases have profound impacts beyond health, including on local and global economies, exacerbating existing socio-economic vulnerabilities.[9] Moreover, any response to these infectious threats needs new drugs, diagnostics and vaccines, for which we are dependent on a pharmaceutical industry, whose vested interest may differ from ours.

To maximise improvements in human health in the coming decades, we believe that the field of applied infectious disease epidemiology needs to derive learning from both ecology (the branch of biology that deals with the relations of organisms to one another and to their physical surroundings) and traditional epidemiology (the branch of medicine concerned with distributions of disease in time, place, and person, their causes, and control). Infectious organisms thrive when they occupy a permissive ecological niche which enables them to reproduce and evolve.[10] A wide range of interacting and dynamic systems determine whether an ecological niche is permissive, including the physical environment, social and cultural context, political and healthcare systems, human behaviours, host and organism genetics, host immune system, and interactions with other microorganisms competing for resources. Perturbations in any of these systems may alter the ecological balance. If we can understand the systems and their interactions better, we may identify opportunities to prevent and control infections.

New methodologies are transforming our understanding of these systems, from better understanding of socio-economic, environmental and cultural drivers of infection, to improved methods to detect and characterise microorganisms, refined measurement of the immunome at scale, and improved understanding of the role of human microbiota.[11-13] Furthermore, our ability to study the genetic evolution of organisms alongside human host genetics and epigenetics brings new insights into disease susceptibility and the immune response. These biological insights alongside increasingly powerful bioinformatic methods allow us to reconstruct the evolution of outbreaks by combining molecular data with classical epidemiological and clinical data,[14] and provide powerful new tools to inform disease prevention,[15] including vaccine development.[16]

Working in silos is likely to limit the opportunities for change, but effective integration of these biological, clinical, epidemiological and social tools for public health programmes remains in its infancy. Moreover, new technologies bring with them new ethical and moral challenges,[17] which will require ongoing dialogue with communities and individuals affected by infectious diseases. We argue that there is an urgent need for education programmes that train a modern cadre of infectious disease epidemiologists who can integrate thinking across fields and methods in order to optimise the prevention of, and response to, infectious disease threats. This means incorporating training in classical and novel techniques to develop scientists and practitioners who can work **from the micro, with the meso, and to the macro** to improve human health.[18,19] Here we outline our proposal for a novel approach for training of epidemiologists and public health experts specialising in the field of infectious diseases.

Rethinking infectious disease epidemiology teaching – building on the revolution in teaching 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 thus populations.[20-22] This led to the emergence of social epidemiology as a field of enquiry,[23] the adaptation of social ecological models in the field of sociology to public health,[24] and the World Health Organization's focus on the social determinants of health.[25] Social epidemiology is now extensively taught in traditional epidemiology and public health curricula and has led

to increased implementation of structural interventions that have substantially affected behaviours and thus health outcomes.[26-30] Within the field of infectious disease control, sanitation, housing, accessible healthcare, and vaccine regulations have substantially reduced mortality and morbidity – both historically 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 localcommunity, in infectious disease transmission (the meso level). This has primarily involved locating geographies or occupational communities with higher transmission of infection, for example malaria in particular villages,[34] or HIV transmission in settlements next to major transport routes in sub-Saharan Africa,[35,36] or amongst specific occupational communities (fishermen on Lake Victoria in Uganda; miners in sub-Saharan Africa[37]). However, there is also increasingly understanding about how communities (including individuals with their interpersonal relationships, families and households) experience, organise and respond to the threat and reality of disease. Whether through political struggle to secure decent housing and clean water, or advocacy for access to prevention technologies, such as HIV pre-exposure prophylaxis and condoms, and vaccine funding.[38-40] More recently, community mobilisation, community-based healthcare, economic empowerment, and gender-based violence reduction strategies are all being seen as integral to controlling the global HIV epidemic.[41,42] Communities can also be a barrier to effective interventions, such as illustrated in the recent antivaccine movement.[43,44] Future infectious disease scientists and practitioners need to be trained to listen to the voices of those affected, and to include and evaluate community-based solutions to infectious diseases.

At the other end of the spectrum (the micro), our 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 generally 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. These

include the possibility that social and community solutions become side-lined as glamourous molecular innovations attract investment, and unclear clinical and ethical issues associated with the technological advances.[17] It is also vital to apply the same degree of epidemiological caution, particularly regarding inferences about causality, to molecular data.[45] For example, the limited power to study the effect on disease of any one attribute that we measure (e.g. a single nucleotide polymorphisms in the human genome where there is no prior hypothesis of effect) has only recently been more widely appreciated and a lack of replicability remains a concern for these studies[46]

We argue that teaching current fundamental epidemiological skills will remain key to exploiting scientific and technological advances. Applied infectious disease epidemiologists will need the skills to define the problem, albeit within a socio-ecological-biological framework (figure 1). They will need to know the benefits and limitations of different epidemiological study designs for addressing the problem, their potential for biases (e.g. 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. They will still need to understand transmission dynamics (air, water, zoonosis, vector-borne, sexual, vertical and parenteral) within and across the life-course. Furthermore, they will need to understand how to apply this knowledge to design and evaluate interventions (including cluster randomised trials and quasi experimental methods); and understand how mathematical modelling of transmission can (and generally should) be used to inform scale-up and cost effectiveness.

However, over and above these concepts, infectious disease epidemiologists will need to understand the way that biologists and social scientists think, i.e. be familiar with pathology and clinical implications as well as the impact of the socio-economic and policy environment. They will need to understand the type of research questions that new methods can answer, their limitations, and how they 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 in developing and evaluating solutions[47,48] and translating findings into policy. While no single individual can be expected to have expertise in all of these disciplines, this

speaks to the importance of training in and rewarding a team science approach bring together well-matched inter-disciplinary groups of scientists.[49,50]

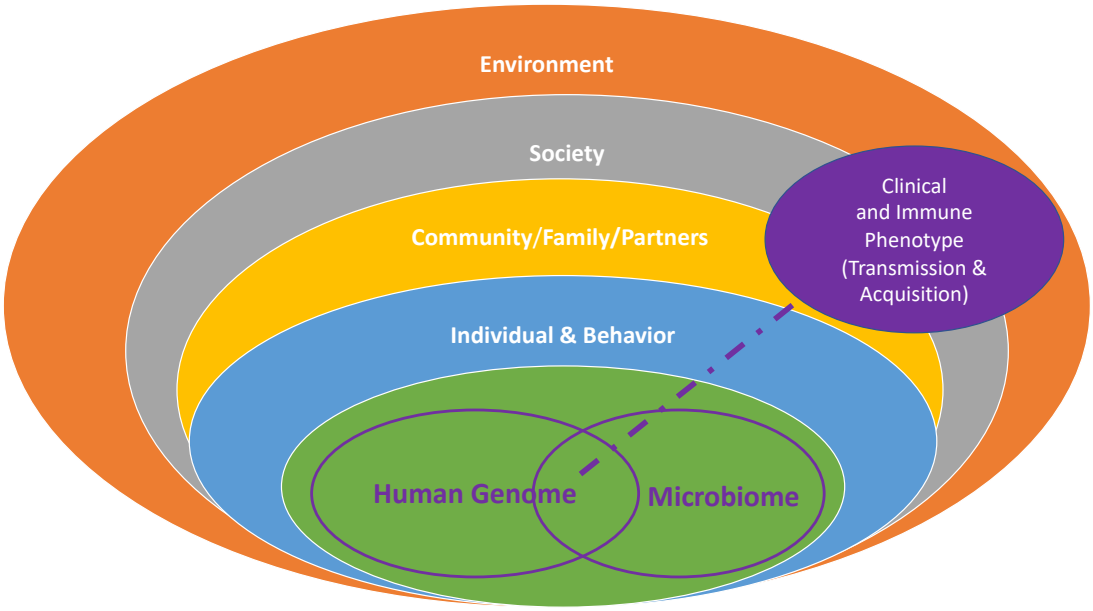

Figure 1: The socio-ecological biological framework to integrate microbiota into human ecology

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

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

To assist conceptualisation, we propose an expanded socio-ecological framework that includes the interactions between hosts, pathogens and the wider microbiome as depicted in Figure 1. This socio-ecological-biological framework provides a model to facilitate how we

include and critically appraise the range of factors that influence disease. To operationalise this approach in training the next generation of infectious disease epidemiologists requires teaching a basic understanding of biological sciences (basic 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.

Our aim is not a dilution of the discipline of epidemiology and its established methods. Rather we aim to increase students'appreciation of the range of disciplines that contribute to the field of infectious disease epidemiology, and how they can develop their intellectual skills to critically engage across the disciplines. One way we have found to do this is to engage our postgraduate students in inter-disciplinary problem solving through the use of experiential learning techniques , such as vignettes (case studies that illustrate a problem). By using facilitated group work with students simulating "disciplinary" roles, we have found that we can illustrate the practical use of team-science approach, i.e. the need to be an expert in one area, but responsive to and aware of the role of other disciplines in solving complex problems. Furthermore, we ask students to apply the principles of basic immunology, microbiology and pathogenesis to describe micro-organisms' adaptions to transmit (e.g. air-borne, faecal-oral route, sexually transmitted, vector bourne and hospital acquired) as well as the implication for clinical manifestation and thus measurement and case definitions. We present several exemplar teaching vignettes to demonstrate how this integrated socio-ecological-biological framework can be applied in infectious disease epidemiology teaching (Table 1).

226 Table 1: Using vignettes to teach students to use a socio-ecological-biological framework to apply infectious disease epidemiology to improve

227 human health[51-55]

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Title	Vignette and questions	Interdisciplinarity needed	Key learning points
Identifying and explaining an HIV micro-epidemic in a high-prevalence setting.	Phylogenetic analysis of HIV successfully identified the emergence of a new HIV outbreak not picked up through routine surveillance in rural KwaZulu-Natal, South Africa. *Why did micro-epidemic occur?* *What could be done to prevent or control it?*	**Epidemiological** data connected the outbreak to the opening of a new coalmine. Rapid **ethnographic methods** adapted from anthropology showed how this new industrial development had changed local socioeconomic dynamics by bringing men and money to an area of poverty. **Community and public engagement** to establish HIV prevention measures prior to the development may have prevented the outbreak.	Whilst the cluster was identified through 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 may need to layer multiple methods to inform effective and ethical intervention strategies in close to real-time.
Causes and control strategies for an Ebola epidemic.	Recent outbreak investigations such as 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 been able to describe the role of poor health infrastructure and cultural reasons for health seeking behaviours in fuelling the epidemic. Traditional **epidemiology**, **statistics**, **computational biology** and **modelling** were used to plan vaccine trials.	The confluence of sociocultural conditions, health systems, and biology underlie the recent Ebola epidemic and all of these disciplines were needed to bring it under control. The effective deployment of a vaccine will require epidemiology, mathematical modelling, public health, and social science understanding of the context and acceptability.
The role of early infant microbial colonisation in driving subsequent health outcomes	Observational epidemiological studies have demonstrated associations between early life events (e.g. mode 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 changes?* *How might we intervene?*	**Infectious disease epidemiologists** have needed to collaborate effectively with **microbiologists**, **geneticists**, **lay 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 be subject to intervention.	It is currently unclear what might be a clinically relevant difference at a species level in early life microbial colonisation. Biology 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 the role of digital technologies in controlling infections	The digital revolution is changing social relationships in ways that both impact on infectious disease transmission, e.g. widening social and sexual networks, and provide new opportunities to intervene, e.g. optimising real-time surveillance and revolutionising healthcare delivery. However, many digital health interventions, lack a strong evidence base and may exacerbate social exclusion along the digital divide. *Can mHealth deliver effective biomedical 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 modellers** can measure the impact 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 every stage. We need to be able to evaluate the effectiveness, efficiency, and equity compared to traditional models of care. This can only be achieved through inter-disciplinary working across wide range of disciplines.
The changing transmission dynamics of shigella in high income settings.	Recent shigellosis epidemics driven by transmission between adult men have been observed in the UK, other parts of Europe, Australia and America. Traditional epidemiological studies, including those using male: female ratios and case finding studies with interviews, have demonstrated that these epidemics are linked to sexual behaviours in MSM, including chemsex (sexual activity under the influence of drugs) and social media apps that facilitate sexual networking. *How are these outbreaks sustained?* *How can we move from observation to control?* *What is the effect on propagation of AMR?*	**Epidemiologists** used surveillance data to monitor shigellosis outbreaks and worked with **social scientists** to understand the human behaviours. Working with **microbiologists**, **bioinformaticians** and **comparative biologists** has provided an additional layer of understanding by demonstrating that repeated horizontal transfer of a single plasmid containing multiple AMR determinants was associated with successful clonal strains. It seems likely that the shigella epidemics result from a combination of high-risk sexual behaviour, 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 this and other AMR and STI outbreaks.	There are major benefits from joining up thinking between epidemiology, i.e. observing the changing distribution of Shigella, evolutionary microbiology, i.e. identifying antibiotic resistant strain evolution, sexual network analysis i.e. understanding who has sex with who, and health systems, i.e. analysis of clinical policy and prescribing practices across time and space.

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 realise the WHO malaria elimination target for South East Asia. Internal economic migrants may 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 on the ground 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 (in this case of the finding that seroconversion to *P. falciparum* was 16-fold higher in men older than 23 years old) needs contextual information about human behaviours and the wider socio-economic and political environment in order to design effective and ethical public health responses. Community engagement and buy-in will be key to sustainable and scalable solutions.
Building evidence-based screening policies for tuberculosis in migrants to 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 that is potentially preventable through additional latent tuberculosis infection screening?*	**Epidemiologists, computer scientists and mathematicians** worked together to develop and valid 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 it was possible to improve our 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 in order develop and understand new methods and apply these to newly linked datasets that gave new insights and actionable evidence to improve screening for tuberculosis in this population. Public engagement and community advocacy were key to translating the evidence into effective policy and practice.

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In conclusion:

The field of infectious disease epidemiology is changing rapidly due to improved understanding of disease causation and the role of microbes in a wide range of non-communicable as well as communicable diseases. The molecular characterisation of both 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 and ensuring critical appraisal in doing so. Moreover, we need to measure and include the environment in disease models if we are to understand complex infectious disease problems. Finally, we need to engage the affected communities, if we are to successfully intervene on complex infectious disease problems at a population level.

New approaches to teaching need to account for 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 infection disease epidemiology, at the core of which lies the need for familiarity and openness across a range of disciplines, expertise in one or two, and much practice in team-based problem solving. We believe this approach will provide awareness of allied 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 training programmes.

Key messages box:

- 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 disease;
  - Molecular characterisation of the microbe as well as the host, leading to better understanding of interactions in the ecology of each and translation of this to transmission networks;
  - 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 that includes the macro, meso and micro and:
  - Connects across basic science, clinical medicine, political and social science, socio-cultural understanding, and population health and statistics in asking and answering the right research questions;
  - Incorporates emerging technologies to collect and understand complex and dynamic data with a critical approach to 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.
  - Keep the voices of the communities affected by infection at the heart of any enquiry

Contributors:

MS and NF conceived the personal view. MS, NF, GHarl, CC, CK were involved in early discussions and mapping the concepts that led to the paper. MS, NF, GHarl, CC, HB, CK, RWA and JG contributed the vignettes, MS, NF, GHarl, and CC wrote the first draft of the manuscript. MS, NF, GHarl, CC, HB, CK, RWA, JG, JS, AP, CAS, PS, GH, MR, DP, AMJ, IA, read and critically revised drafts of the manuscript.

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We declare that we have no conflicts of interest."

Ethics

Not applicable

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