The Many Faces of Emerging and Re-emerging Infectious Disease

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Abstract

The emergence of disease threats can take many forms, from the adaptation of a traditionally zoonotic pathogen for efficient spread in humans, to the development of antibiotic resistance in well-known pathogens, to the creation of new niches for established disease through social and societal changes. In this commentary, the authors explore these various facets of disease emergence through the lens of the papers included in this issue of Epidemiologic Reviews. The authors explore multiple aspects of emergence, and the ways in which emergent pathogens can be controlled with the limited tools available. In doing so they put the papers in this issue in the context of the broader research agenda around understanding and combatting emergent pathogens.

Keywords: Infectious Diseases, global, vaccination, threat assessment, disease control, outbreaks, zoonotic

One of the most fundamental changes to the human condition over the past two to three centuries has been the decline in child mortality. While at one time it could be assumed that as many as one-third of all children would die before their sixth birthday, now, in all but the poorest countries, children are almost guaranteed to survive into adulthood (1). This accomplishment has numerous causes, but one of the most direct is incredible strides in infectious disease control through vaccination, treatment and improved sanitation. Even in this century substantial progress continues to be made; for instance, deaths from measles have decreased by 84% since the year 2000 through global vaccination efforts (2).

We should be proud of this accomplishment, but not complacent. The pathogens that cause infectious diseases are constantly evolving as they seek to survive. Zoonotic pathogens have the potential to evolve for efficient human-to-human transmission when they infect human hosts, as did HIV and many strains of influenza (3,4). Established pathogens can evolve to evade the drugs and other control measures on which we have grown to depend (5,6). As human society and the environment change, pathogens can find new niches in which to thrive, and cause disease. This constant evolution means that it is unlikely that infectious diseases will disappear as a threat to human health, as many thought they would a half century ago (7,8). The emergence of a truly novel pathogen or complete failure of our antibiotics could potentially undo much of what has been gained over the past couple of hundred years, though the probability of such an event may be rare.

This issue of *Epidemiologic Reviews* contains papers exploring various aspects of emerging and reemerging infections, from threat assessment to disease control. Combined, these manuscripts

take a broad view of what it means for a disease to be emerging, and explores the impact of both pathogens truly new to the human population, and new threats posed by well-established diseases. Below we summarize some of the key themes explored in this issue.

"True" Disease Emergence

True disease emergence usually occurs when a zoonotic pathogen that did not previously effectively circulate or cause disease in humans "jumps" the animal-human barrier and begins transmitting efficiently in the human population. Another path to true emergence is when a virus or organism present in the human population in a non-pathogenic form mutates to begin causing disease in the human population. These types of events are what people usually think of when they think about disease emergence, and have the greatest hold on the popular imagination, and for good reason. As sensationalistic as movies and books such as "Contagion" or "The Hot Zone" are, it is true that a truly novel pathogen could kill tens, or even hundreds, of millions before we could come up with an adequate response. One need only look to the HIV epidemic to see that this is true. Though the epidemic has not progressed at the pace of our worst fears, since jumping from apes to humans sometime around the turn of the last century (3), the virus has killed around 35 million people (9), and continues to spread despite substantial progress in treatment and control (10). Even more frightening is the 1918 strain of pandemic H1N1 influenza, thought to have jumped fairly directly from birds to humans (4), and is thought to have infected around 500 million people (about a third of the world population at the time) and may have killed more than 50 million people over the course of a few years (11,12).

Thankfully, true emergence events appear to be extremely rare. Limited outbreaks of Ebola,

SARS, MERS-CoV and Nipah, among others, are often headline grabbing and stoke fear globally. These outbreaks can be devastating to the populations involved, and each represents an opportunity for the pathogen to solve the puzzle of efficient transmission in humans; but since we have had the tools to detect it only a few, including Zika, HIV and various strains of pandemic influenza have successfully made the leap from a zoonosis to widespread, sustained human-to-human transmission globally. Further, those pathogens that do make the leap need not be as virulent as HIV or the 1918 strain of pandemic influenza. Though it can cause devastating birth defects when women are infected in pregnancy, and occasionally causes Guillain-Barre Syndrome in adults, the vast majority of Zika virus infections are mild or asymptomatic (13). Likewise, more recent pandemic strains of influenza have not been as virulent as the 1918 variety, and may kill fewer people than their seasonal counterparts (14,15). Still, if they become widely established in the human population, even a mildly virulent pathogen can kill millions over the long haul through the sheer number infected.

In this issue two papers discuss diseases that may be on the verge of making the leap to widespread human-to-human transmission. Carias *et al.* focus on the 2014-2015 West African Ebola epidemic, exploring how well we were able to forecast the progress of the epidemic (16). The authors review 26 papers that made forecasts of the course of the epidemic while it was ongoing. They find that while it was possible to produce forecasts of reasonable accuracy at time horizons under two months into the future, longer term forecasts were far less accurate. A particular challenge is that those models that did perform well over the longer term tended to be statistical, hence were of limited utility when it came to answering policy critical questions, such as the impact of proposed interventions. Grant *et al.* tackle another disease that is "on the

doorstep" of widespread circulation in humans, Middle East Respiratory Syndrome Coronavirus (MERS-CoV). While sometimes deadly, most MERS-CoV infections are mild or asymptomatic, and these undetected cases will play an important role if the virus achieves sustained transmission in humans. In this issue, Grant *et al.* review the evidence surrounding sub-clinical MERS-CoV infection in humans (17). They find a wide variety of levels of exposure among those with frequent camel contact and among exposed health care workers, with sero-prevalence in some studies reaching 67%. Importantly, these asymptomatic cases do shed virus, and likely can transmit; making MERS-CoV difficult to control should it gain the ability to spread widely.

A pathogen need not gain the ability to transmit between humans to be an emerging health threat, despite not fulfilling the classical definition of emergence. Lyme disease in the United States is a prime example; though transmission between human hosts is virtually unheard of, zoonotic infections are frequent enough to make Lyme disease a top health concern in many parts of the United States (18,19). In this issue we examine two such infections. While tuberculosis (TB) is not usually thought of as a zoonosis, people are still routinely infected by cows and other domestic animals, most commonly by unpasteurized milk (20). In this issue, Couto *et al*. review the literature on zoonotic tuberculosis through the lens of a one health approach (21). They find that the burden is concentrated in low-income countries, and that there is high variability in the quality of surveillance and control between countries. Coccidioidomycosis (AKA valley fever) is not a zoonosis, but is caused by the fungus *Coccidioides Immitis* that is found in the soil of certain parts of North and South America. In this issue, Pearson *et al*. review how land use, population movement and climate change have driven recent surges in incidence in California (22). They find that most research has centered around occupational exposures, but there is some

evidence of increased risk in some subsets of the general population. They conclude that much more needs to be done to understand the wider risk posed by this infection.

Alternate Paradigms of Emergence

While novel pathogens pose an ongoing threat to human populations, they are far from the only emergent disease threat. The evolution of novel traits in well-established human pathogens, particularly drug resistance, can pose a threat as big or bigger than truly novel infections (5,6). Likewise, societal changes, from the opioid epidemic to increasing global connectivity can increase the impact of established pathogens, introduce them into new populations, or otherwise change their distribution on a global scale (23,24). This edition of *Epidemiologic Reviews* has several papers exploring the changing impact from established diseases.

Hundreds of bacterial species cause diseases in humans, and we have effective antibiotic treatment to nearly all of these. However, antibiotic resistance is increasing at an alarming rate, and for several diseases, including tuberculosis and gonorrhea, strains have emerged that are resistant to nearly all available antibiotics (25,26). In this issue, Fridkin *et al*. review how data driven approaches and machine learning can be used to better coordinate the response to resistance events and prevent the emergence of resistance all together (27), observing that in an increasingly interconnected healthcare system it is critical to leverage streams of administrative data and electronic health records to implement more effective resistance control programs.

Biological changes in the pathogen itself are not the only ways by which a pathogen long established in humans can become an emerging disease threat. Social and environmental change

can also be drivers of an emerging disease threat. A prime example is how epidemics of injection drug use, such as the current opioid epidemic gripping the United States, are often accompanied by epidemics of hepatitis C virus (HCV) (23). The opioid epidemic has not spared indigenous populations in North America, where HCV transmission is understudied though these populations are disproportionately affected by the diseases. In this issue, Page *et al*. review the literature on HCV transmission on HCV transmission in indigenous populations of the US and Canada (28), finding an overall lack of studies and large differences in prevalence across studies and groups; highlighting the need for more regular surveillance in these populations.

The impact of environmental change can be seen in a number of diseases, particularly vector borne pathogens (29). Climate is equally important in governing the transmission of pathogens where its role is less obvious, such as influenza (30,31). Understanding how climate drives influenza transmission can allow us to better understand how the threat proposed by this globally endemic pathogen will change as the climate changes. This, in turn, will help us in determining how best to mitigate epidemics including optimal times for vaccination, and may also illuminate how emergent pandemic strains will spread. In this issue, Lee and Dave review the literature on how spatial and temporal patterns are associated with climates (32). While they found some important drivers, they found that large gaps remain in our understanding of the relationship between influenza and climate, particularly in tropical and sub-tropical regions.

A different way to view emergence is as itself a social process, rather than a biological one. That is, a disease threat may have long been present, but is an emerging issue because its health impacts are only now becoming apparent (33). Cancers caused by infectious agents are one such

class of disease, as we have only become aware of their impact through the confluence of new medical research and more people living long enough for cancer to develop. Human papillomavirus (HPV) is the poster child for infectious cases of cancer (34); and the success of the HPV vaccine in reducing rates of cervical cancer is one of the great public health accomplishments of recent decades (35,36). However, HPV is far from the only infectious cause of cancer, and *Helicobacter pylori*, hepatitis B virus, and HCV are also notable carcinogens (37). In this issue, Brown *et al*. review the literature on cancers associated with infectious agents in the United States (38). They find that the literature is lacking; there are few observational studies that can be used to estimate the mortality attributable to infectious causes of cancers. Such studies are critical if we are to prioritize development of new ways to prevent these causes of cancer. Prevention of infectious cancers is the focus of Wang *et al*., who review the impact of *H. pylori* eradication on gastric cancers in these pages (39). They find a marked impact of *H. pylori* eradication on such cancers, suggesting that early intervention against the bacteria could play an important role in the prevention of such cancers.

Control of Emergent Pathogens

The key tools of infectious disease control are vaccination, chemotherapy and prophylaxis and limiting opportunities for transmission through quarantine, isolation and other social distancing measures. To be effective, all of these tools rely on effective surveillance and case finding during epidemics. Because emergent pathogens are, by definition, new, we may not have vaccines or drugs at our disposal at the time of the emergence to combat the disease threat; hence, we must rely on measures aimed at limiting transmission. Vaccines, in particular, are unlikely to be available for newly emergent diseases. However, efforts are underway to change this landscape

so that we have vaccines at the ready if a pathogen makes the leap from animals to humans. As detailed by Gouglas *et al.* in this issue (40), the Coalition of Epidemic Preparedness Innovations (CEPI) aims to guarantee that we have vaccines at the ready to respond against some of the pathogens thought to be most likely to emerge in the human population, including Nipa virus, Lassa fever and MERS-CoV. Even when a vaccine is available, a critical challenge in its effective use is getting the vaccine to at risk populations before they are exposed to the disease. This may be especially difficult in an emerging epidemic, where vaccine supplies may be limited and the course of the outbreak may be uncertain. However, as highlighted in a review by Gallagher and Lipsitch in this issue (41), it might not always be necessary to beat the disease to the punch. For diseases ranging from hepatitis B to smallpox, they find that post-exposure vaccination can have marked effects in preventing both disease and death. Whether this type of post-exposure protection exists in new vaccine products aimed at potentially emergent pathogens is an important question, and could affect how these vaccines could be most effectively used. Post-exposure prophylaxis is most likely to be effective against longer incubation period infections although as shown in the review, vaccines even may be able to protect against shorter incubation diseases if administered soon following exposure.

Any disease control program lives or dies based on the quality of the disease surveillance system. Surveillance systems in turn rely critically on the willing participation of those who might be infected with the disease, particularly for those pathogens such as HIV that can asymptomatically infect hosts, and still be transmitted in this asymptomatic period. In this issue, Choi *et al*. review what is known about what makes people participate in screening programs (42), with a particular focus on chlamydia. They find that the most important determinant of participation was age, and

identified several interventions, including the use of home-testing kits, that can have a measurable impact on participation. Likewise, the natural history of disease plays an important role in the effectiveness of surveillance, both in the sense of its ability to identify cases and its ability to do so in time to inform meaningful interventions (43–45). In this issue Awofisayo-Okuyelu attempt to shed light on the natural history of one important infection by reviewing information on the incubation period of Shiga-toxin producing *E. coli* (46).

Conclusion

Despite the broad range of topics covered, the areas included in this issue of *Epidemiologic Reviews* represent only the tip of the iceberg when it comes to understanding the epidemiology of disease emergence. As highlighted by the diversity of papers here, one critical challenge is the variety of processes that can cause a disease to be an emergent health threat. While the emergence of a truly novel pandemic virus or bacteria presents a dramatic, and existential, threat to the global community; the slow boil of increasing drug resistance and the creation of new niches for known diseases that might ultimately kill more people is important to consider. As the global population increasingly ages, we may also face emergent threats from established diseases that are not really new threats at all, but rather clinical outcomes that were always present but were missed or deemed unimportant when few lived long enough to experience them. Understanding the unique epidemiologic issues associated with the many facets of emergence is critical to ensuring population health in the face of new disease threats. We hope that the papers contained within this issue of *Epidemiologic Reviews* makes some small progress in achieving this goal.

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