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Review

From hidden outbreaks to epidemic emergencies: the threat associated with neglecting emerging pathogens

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ABSTRACT

Not all infectious disease outbreaks undergo full epidemiological investigations. In certain situations, the resultant lack of knowledge has led to the development of epidemics and public health emergencies. This review will examine six emerging pathogens including their history, present status, and potential to expand to epidemics. Recommendations to improve our understanding of these hidden outbreaks and others also will be provided in the context of health systems policy.

1. Introduction

Infectious disease outbreaks are common worldwide. While every occurrence deserves a proper epidemiological investigation, several constraints such as limited resources, political considerations, and an assumed familiarity with the pathogen may hinder the process [1,2]. This may result in what are known as “hidden outbreaks” in which spread is known to transpire in a localized environment (such as an endemic pathogen) but inquiries are not considered to be worthwhile in the larger context of global human health. This practice may be considered sound, however there is the potential an outbreak may expand to become an epidemic such that both caseload and costs are significantly increased [3,4].

The hidden outbreak begins no differently than isolated outbreaks with a single point-source such as a household, hospital, or restaurant. While several to dozens of people may be infected, the overall impact on society is considered to be low. Yet, as seen in several instances over the last decade, certain pathogens have become international juggernauts (Fig. 1). Public health authorities are caught off guard, calls for alarm are made by the scientific and medical communities, and the media must find a balance between objective reporting and the inevitable contagion of fear [5].

The quintessential example of such expansion is the Ebola virus epidemic in 2014 [6]. A small outbreak occurred in the small village of Meliandou in Guinea at the end of the previous year and eventually turned into a crisis in three West African nations and led to domestic cases in Europe and the United States. The spread was so troubling, the World Health Organization declared a Public Health Emergency of International Concern (PHEIC) [7]. The event eventually was controlled yet the virus was considered to be too volatile to ignore any further. Any sign of Ebola in the human population regardless of population size was deemed serious enough to be met with a significant response [8] to control spread.

In addition to understanding the biological nature of a pathogen as the etiology of an outbreak, an examination of the anthropogenic effects facilitating amplification to epidemic status is needed. These factors have been reviewed elsewhere [9] and include the grouping of susceptibles in both the healthcare environment as well as the community, changes in human consumption of natural habitats, territories, and food sources, increased amount and ease of international travel, globalized trade, and political strife. In the context of expanding hidden outbreaks, two factors are considered the most important, travel and trade [10,11].

One of the best known examples of travel-related spread of a hidden outbreak into an epidemic is the SARS coronavirus [12]. The outbreak began in the small village of Foshan in China and expanded to various areas of the country as well as Hong Kong, Singapore, Vietnam, and Canada. Although a lack of proper containment of the virus at the source may have facilitated the spread of the virus into the community [13], travel was deemed as the most influential anthropogenic factor in the development of this epidemic [14].

Another travel-related expansion began in the same year as SARS in the province of Quebec, Canada. Known as the toxinotype III, North American PFGE type 1, and PCR-ribotype 027 (NAP1/027) strain of *Clostridium difficile* [15], the bacterium was found to produce up to 20 times the amount of toxin of other known subtypes and led to over 1,000 deaths [16]. This should have sounded alarms, yet the emergency was considered to be localized with no other regions reporting such activity [16]. Eventually, the outbreak was

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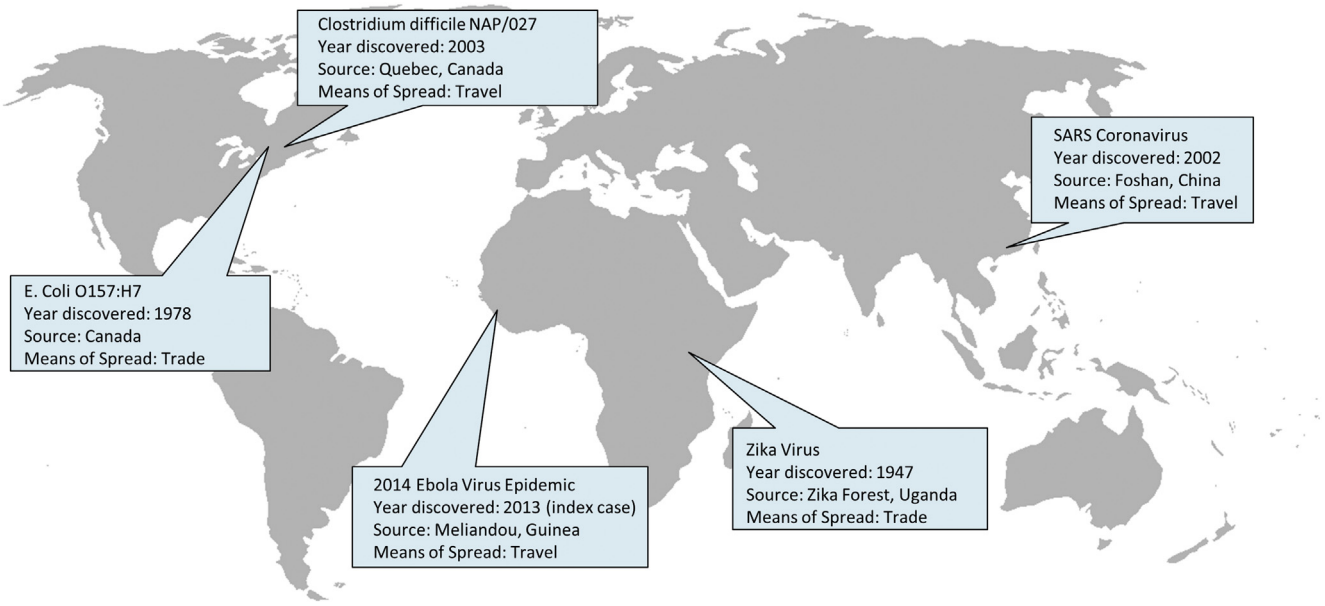

Fig. 1. Hidden Outbreak Source of Recent Global Epidemics. Source: Author edited copy of image, "The World Without Borders," Wikipedia Commons.

found to be part of a larger, unrecognized community-based spread of the pathogen. By 2010, NAP1/027 was found to be prevalent worldwide [17].

Travel of animals through trade has also proven to be a contributing factor. *Escherichia coli* O157:H7 was originally identified as a human pathogen in 1978 [18] but for many years thought to be a sporadic illness [19–22]. However, the strain spread throughout Canada and the United States and over time into other parts of the world due in part to travel as well as livestock movement through commercial routes [23,24].

Trade in general also can lead to inadvertent spread of a pathogen via arthropod vectors such as mosquitoes. This route has been seen as the means for the expansion of the Zika virus [25,26], which was originally found in Uganda in 1947. Due to international trade [25], the virus found its way to the Pacific and eventually the Americas leading to the now infamous epidemic in Brazil. While the exact vehicle has not identified, a possible route may have involved the importation of mosquitoes in high enough numbers to meet the minimum requirements for establishment in the new environment [27].

Due to lessons learned, increased surveillance for these infectious agents and other well-known species, such as avian influenzaviruses [28], polioviruses [29], and measles [30] are now in place. Yet, several pathogens given little attention have begun to show signs of expansion from hidden outbreaks into large scale epidemics. Although none currently poses a significant global threat, increased vigilance is needed to ensure history does not repeat itself. This review will examine six hidden outbreaks that have for the most part eluded widespread attention and will explore their potential to form epidemics. These analyses will include a list of questions that require answering to gain a better understanding of the potential of each pathogen to expand into significant pathogens of concern.

2. Current hidden outbreaks

2.1. Candida auris

In 2009, Satoh et al. [31] discovered a strain of yeast in the ear canal of a Japanese individual. Genetic analysis revealed the isolate was a new species which was named *C. auris*. The species was closely associated with *C. ruelliae* and *C. haemulonii*, the latter of which had been known to cause fungemia [32]. *C. auris* was later isolated in other South Korean patients with otitis media [33]. The discovery was concerning yet assessing the significance in terms of risk for an epidemic was difficult at best. Two years later, the first cases of *C. auris* fungemia in South Korea [34] were detected, including one from an isolate taken 15 years earlier in 1996. The findings suggested the species already could possibly be endemic in the country. Moreover, an increased tolerance to fluconazole was identified suggesting future cases could be more difficult to control. Over the next three years, antimicrobial resistant strains of *C. auris* healthcare-acquired infections were observed in Kuwait [35] India [36], and South Africa [37]. In 2017, the yeast was discovered in the United Kingdom [38], South America [39], Europe [36] and Canada [40]. Genetic rDNA analysis of 24 isolates in the UK demonstrated several geographic origins [38] highlighting the importance of human travel in the spread of the species.

To date, *C. auris* remains for the most part a health-care associated infection affecting immunocompromised individuals. While there is increasing attention in the healthcare field to the risk of this pathogen [41], the international surveillance program SENTRY has demonstrated the contribution of *C. auris* to the overall burden of *Candida* species remains small and limited to healthcare facilities. However, the nearly simultaneous emergence of the species across several continents suggests the yeast is ubiquitous in the environment and may pose a threat to an increasingly immunocompromised population [42]. Additionally, the increase in antimicrobial resistance seen in numerous isolates confers significant hurdles to combat fungemia [43]. Guidelines to deal with *C. auris* are either in place [44] or in development [45] but as seen in the case of *C. difficile*, this may only have a limited effect in controlling its spread in the community and through travel. Public surveillance is necessary to determine the as of yet unknown prevalence of the yeast in the community and potential routes of transmission should also be examined to determine whether preventative strategies such as hygiene measures in the community may help to reduce the burden.

2.2. Coccidioides

Coccidioidomycosis has been a recognized disease since 1892 [46] although it is better known as Valley Fever [47] due to the geographic location of the first American cases, the San Joaquin Valley in California. The disease is caused by the fungal pathogen *Coccidioides immitis* [48] and is marked by skin lesions and the potentially fatal formation of granulomas in numerous organs. At first, the pathogen was considered to be limited to arid desert regions in the United States and Argentina [49], however, wider surveillance has detected the fungus in other geographic regions of the United States including Arkansas [50], Utah [51], Arizona [52], Texas [53] as well as in Canada [54,55], Central and South America [56]. In addition, a retrospective analysis of coccidioidomycosis in China revealed 38 cases involving no history or travel to endemic areas [57] suggesting the fungus already may be spreading globally with no defined routes identified.

Although the mortality of this pathogen is quite low at less than one case per million person-years [58], its expansion over the last half century highlights the potential for an increase in prevalence not only in the Americas but also Asia. Should the species become endemic in China, there is a greater potential for a rapid increase in outbreaks, and possible epidemics as evidenced by SARS. Moreover, the ability of the fungus to infect animals, such as dogs, cats, bats, rodents, and armadillos [48], potentiates even greater spread via domesticated and possibly feral reservoirs. Combined with a noted increase in planetary temperature and resultant increases in desertification [58], there is a need to increase surveillance and explore the modes of transmission including environmental dissemination of dust through wind currents [59].

2.3. *HTLV-1*

Human T-Lymphotrophic Virus was first isolated in 1978 [60] from skin cancer and was considered an atypical oncovirus. Other diseases were eventually associated with this virus including adult T-cell leukemia, HTLV-1 associated myelopathy, tropical spastic paraparesis, uveitis, dermatitis, psychological disorders, and general immunosuppression [61]. Though the virus was detected worldwide, until recently, it was considered sporadic. That view has changed due to epidemics in several regions including Brazil, Spain, Sub-Saharan West Africa, the Middle East, the Caribbean, Japan, and Australia [62]. Due to the bloodborne nature of the virus, which can only be transmitted efficiently through unprotected sexual contact [63–65], the virus typically remains endemic to a region without significant geographic spread. However, historical analyses of HTLV-1 reveal the virus can be introduced into another area through large scale population movements from endemic regions [66,67]. For example, Trevino et al. [68] examined HTLV in Spain and discovered HTLV-1 has entered the country as a result of migration. While the virus has yet to become endemic in the Spanish population, the authors suggest this will occur in time.

Due to the continued effect of mass migrations from endemic areas into naïve ones, the risk for an increase in the prevalence of HTLV-1 exists. Surveillance for this virus needs to be recognized as a priority in countries receiving these individuals. While halting the spread of the virus requires a focus on safe sexual practices, there is a need to identify possible warning signs such as those in Spain prior to expansion of the virus.

2.4. Mycobacterium ulcerans

Discovered in 1948 as an atypical mycobacterium species, *M. ulcerans* has been widely seen as a rare infectious agent in comparison to other species such as *M. tuberculosis* and *M. leprae*. According to Käser et al. [69], two different lineages of the bacterium exist with one being far more virulent than the other. The virulent strain is known to cause painful skin lesions known as Buruli ulcers, named after the Ugandan region where this infection was first described [70]. The bacterium and associated disease has subsequently been found in several other areas of Africa including Angola [71], Benin [72], the Democratic Republic of the Congo [71], Côte D'Ivoire [73], Ghana [74], Nigeria [75], and Togo [76]. The infection also has been identified in Australia [77], and most recently Jordan [78]. While the association between the bacterium and the symptoms are well established, the mode of transmission has yet to be elucidated. The infection is self-limiting and several reports suggest the highest risk is associated with living in a riverine region [79–83]. As to the potential route for inoculation, several theories have been suggested such as bites from water bugs [84,85] and the potential for colonization with the bacterium through contact with soil [86] and watersheds [87,88].

Without knowing the exact route of transmission, determining the risk of spread from one environment to another is difficult at best. In a genetic analysis of the spread of the pathogenic branch in Africa, Vandelannoote et al. [89] suggested the bacterium spread at the same time as populations were divided by European colonial rule. Infected individuals contaminated pristine water sources allowing for the growth and dissemination of the species. In this regard, the potential for spread of the bacterium relies on migration of those who are infected. While the morbidity associated with this disease should prevent such movements by those infected, political and socioeconomic strife may lead to forced travel during infection. Surveillance for ulcers should be conducted in healthcare facilities to identify new cases in non-endemic regions. In the event a case is discovered, efforts to minimize the potential spread to watersheds need to be in place to prevent the development of endemicity.

2.5. *Invasive* Streptococcus pyogenes

S. pyogenes has been a significant pathogen for centuries in the form of Scarlet Fever [90]. However, the bacterium has the ability to invade systemically causing bacteremia, endocarditis, toxic shock syndrome, necrotizing fasciitis and endometritis [91,92]. Several contributing factors are associated with these complications [93,94] including fibronectin binding proteins to facilitate invasion, cysteine proteases to escape immune attack, and superantigens that trigger a massive immune response leading to the potential for tissue damage and organ failure.

For the last two decades, a significant increase in the number of invasive infections has been seen in certain regions of North America and Europe. Gheradi et al. [95] have shown several serotypes have increased their circulation in these areas. While between 50 and 70% have been associated with one particular serotype, *emm1*, the risk of complications associated with the other serotypes, including known invasive members such as *emm3*, *emm12* and *emm28* [96] as well as *emm59* [97] and *emm89* [98].

The inability to identify a single serogroup to explain the rise in cases suggests the risk factors associated with the rise of this infection lies in the nature of the susceptible population. Nelson et al. [96] examined 9557 cases of invasive Group A *Streptococcus* infection and found several human factors associated with invasion and mortality including early childhood, advanced age, underlying chronic illness, and immunosuppression.

Given the population-based obstacles regarding prevention of invasive infection, emphasis needs to be placed on surveillance of all *S. pyogenes* infections. While this does occur in many regions of the developed world, more needs to be done to prepare for the inevitable introduction of an invasive serotype into a community. Although this likely will not prevent illnesses and small outbreaks,

public health authorities will have sufficient information to warn the public of a new invader and emphasize hygiene guidelines aimed at prevention of spread.

2.6. Yellow fever

Yellow Fever has been known for over four centuries as a serious illness with the potential to cause death [99]. The virus is present in both Africa and South America although limited to a few regions on these continents. However, due to the ubiquity of its mosquito vectors, *Aedes* and *Haemagogus* species, there is potential for escape from these regions.

Shearer et al. [100] performed a modeling analysis of this virus and determined numerous areas of the world including Southeast Asia, and Central America may be receptive to the virus. In addition, the virus may be transported to non-traditional regions such as the southern regions of China and the United States. In another example, Ibañez-Justicia et al. [101] reported on the introduction of *Aedes aegypti* into a Netherlands airport. While only six insects were identified, as Saarman et al. [27] point out, the number of mosquitoes required to develop a potentially endemic population may be as little as 25. Moreover, yellow fever can develop an urban transmission cycle in an unvaccinated population [102].

Historically, yellow fever has not caused significant widespread concern due to the usually remote nature of endemicity both in Africa and South America [103] and the availability of a vaccine. However, a recent outbreak in Brazil has raised the concerns for those traveling to the region [104,105]. Hamer et al. [106] describe 10 cases of yellow fever in travelers of whom 4 died. None were vaccinated. Moreover, due to the precedent of Zika virus [107], concerns have been raised regarding the potential of the virus to move north into Central and North America where populations are not vaccinated against the virus. The resultant scare has led to a concern for vaccine supply [108] as there is not enough to cover the entire American population living within zones where *Aedes* may thrive.

The most important tool in determining the risk of yellow fever expansion is surveillance. The identification of mosquitoes in Amsterdam [101] is one example of how proper environmental screening of packages from endemic areas may serve to prevent the introduction and eventual reception of a pathogen. In addition, promotion of vaccination will help to reduce the likelihood of infection in travelers. While human to human transmission has not been demonstrated for this virus, the virus may be brought into a region where competent mosquitoes thrive allowing for the initiation of the sylvatic and/or urban transmission cycles.

3. Future directions

The abundance of infectious disease outbreaks worldwide outnumbers the resources available to perform extensive investigations, mitigate morbidity, and determine prevention strategies. Decisions are not easy to make in light of the potential for misjudging a potential epidemic-causing strain as an isolated or sporadic case. Though these occurrences are rare, as demonstrated by previous epidemic of worldwide concern, the consequences may be drastic.

Moving forward, each outbreak associated with these six pathogens needs to be seen as a potential epidemic and algorithms for management need to be in place. Developing these decision-based policies require the use of advanced methods to improve confidence in results. The use of advanced molecular analysis techniques such as whole genome sequencing may provide a wider perspective on the nature of the outbreak and whether it truly is isolated or is a part of a larger problem. Molecular and syndromic surveillance in at-risk areas can provide real time assessments and provide predictive information. The latter may be aided through the use of social media, which is currently being examined for its power in identifying and predicting outbreaks [109–112]. Mathematical modeling of anthropogenic effects apart from travel and trade, such as climate change, urbanization, and food supply and demand can enhance the fidelity and accuracy of these calculations. Finally, the appreciation of social and cultural practices can offer valuable insight into how healthcare workers and the community may react in the event of pathogen detection. This information also can offer best practices for collaborative efforts to reduce the chances for amplification and spread to wider areas.

In the case of the six pathogens listed in this review, there has yet to be an expansion of cases to epidemic status. However, this situation quickly can change and lead to an expansion into a larger public space. While we may be able to vaguely predict how such escapes may occur, they are only guesses with little contributory value to policy and health systems development. For this to occur, appropriate algorithms need to be put in place and used to assess each outbreak as it happens. This may require valuable resources and could be met with resistance from numerous levels of government and the public in general. However, in light of the economic burden already seen with what amount to preventable epidemics, the cost may be fully justified.

Conflict of interest

None.

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