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Evolutionary Medicine IV. Evolution and Emergence of Novel Pathogens
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Introduction

The evolutionary history of humans is characterized by dynamic shifts in population density and the structure of our social contact networks. Agriculture, the advent of City-States, European expansionism, and modern globalization have all had profound effects on the ecology of humans (McMichael, 2004). Our changing dispersal, demographic, and contact patterns have impacted both commensal and pathogenic organisms. Fruit flies in the genus Drosophila, numerous Yeast species, Escherichia coli and other human commensals tracked our expansion throughout the world (Keller, 2007; Pamer, 2007). However, pathogenic species followed too. In the 1700s and 1800s, smallpox and measles – spread to the Americas by European explorers – decimated indigenous populations (McMichael, 2004; Cliff et al., 1993). At the turn of the last century, the 1918 flu killed between 20 and 40 million people worldwide in little over a year (Noymer and Garenne, 2000). Troop movement during WWI played a critical role in the emergence and spread of that virus (Oxford et al., 2002). Today, we are beset by the human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) epidemic, the threat of pandemic avian influenza, hepatitis C, Ebola, tuberculosis, and myriad neglected tropical diseases (McMichael, 2004; Morse, 1995; Worobey et al., 2008; Hotze, 2014). The critical factors unifying the spread of commensal and pathogenic species, the emergence of new diseases, and the rapid spread of pandemic strains are the increasing density and connectivity of our populations, coupled with the evolutionary lability of many parasites, for example, bacteria and viruses (Scarpino et al., 2015; Galvani and May, 2005; Pourbohloul et al., 2009; Stoddard et al., 2009).

Modern travel patterns, heterogeneity in population density, variable immunity, and changing proximities to wild and domesticated animals interact to drive complex patterns of disease transmission and emergence (Galvani and May, 2005). SARS and SO-H1N1 spread rapidly around the globe, but because of heterogeneity in contact patterns and immunity, these diseases were not the disasters predicted early in the epidemics (Pourbohloul et al., 2009; Meyers et al., 2005). A similar situation also occurred during the 2014–15 Ebola outbreak in West Africa, where models with more realistic human contact patterns predicted yielded more accurate predictions (Scarpino et al., 2015). The threat of wildlife disease and its spillover to humans and our food is also becoming an increasing concern (Weiss and McMichael, 2004; Frenzen, 2004; Chua et al., 1999; Daszak, 2000). Changes in hunting and agricultural practices alter contact patterns between wildlife and domesticated animals (Daszak, 2000; Köndgen et al., 2008). The result has been both the spillover of highly virulent diseases, such as Nipah virus and Ebola, and recombination between human and animal strains of influenza (Weiss and McMichael, 2004; Chua et al., 1999; Daszak, 2000).

The emergence of HIV in central Africa illustrates both the importance of evolution and changing ecology on the epidemic potential of novel pathogens. The European reorganization of central Africa – from a dispersed collection of villages to a system with large urban areas – fundamentally changed human social contact patterns in the region (Figure 1; Hance, 1970; Worobey et al., 2008). Recent genetic evidence suggests that in some of these emerging cities, HIV epidemics were raging by the late 1950s or early 1960s (Worobey et al., 2008). Using historical census data (Hance, 1970), the author compared the rates of population growth, urbanization, and HIV infection – as reconstructed from HIV genomic data by Worobey et al. (2008) – in the Democratic Republic of the Congo (DRC), the Republic of Congo, the Central African Republic, and Cabon. Strikingly, the rate of increase in HIV infections lags the rate of urban growth, while the rate of population growth remains essentially constant (Figure 2). This result highlights the importance of both changing host ecology, in this case the urbanization of central Africa, and pathogen evolution in the emergence of new diseases (Schrag and Wiener, 1995; Antia et al., 2003; Weiss and McMichael, 2004; Holmes, 2009). In the next section, the author discusses...
Figure 1  Between 1900 and 1970, the population size of the five largest central African cities grew by over 100-fold. This dramatic increase in size was due mostly to urbanization, where individuals migrated from rural areas to the cities, as opposed to population growth.

Figure 2  Estimates from genomic data suggest that HIV was already spreading rapidly in central Africa by the 1960s. As predicted by theory from epidemiology, there is evidence for a role of urbanization in the spread of HIV. The figure plots the proportional increase in growth rate by decade for individuals infected with HIV (green), urban population size (purple), and total population size (black). Note how the HIV epidemic lags urbanization, while the population growth rate remains essentially constant.
modern methods for studying the dynamics of infectious diseases using genomic data and then in the following sections the author illustrates the role of these new methods in studying emerging infectious diseases.

The Phylodynamics of Emerging Infectious Diseases

Pathogen host shifts are responsible for outbreaks of severe disease in wildlife, livestock, and human populations (Antia et al., 2003; Dobson and Foufopoulos, 2001; Morens et al., 2004; Daszak et al., 2000b; Altizer et al., 2003). Despite the biological importance of such host shifts, many gaps remain in our understanding of how and why they occur. Because many pathogens – especially RNA viruses – mutate so rapidly, their evolutionary and ecological processes are inextricably linked (Antia et al., 2003; Koelle et al., 2009; Pybus and Rambaut, 2009; Levin, 1999). Therefore, studying epidemics requires models able to connect evolution to ecology. The emerging field of phylodynamics seeks to leverage the genetic variation of pathogens to investigate their complex, epidemiological dynamics through the use of mathematical transmission models (Grenfell, 2004; Holmes and Grenfell, 2009; Volz et al., 2009).

Linking these models with the genetic sequence data – now routinely collected during disease outbreaks – provides an unprecedented opportunity to advance our scientific understanding of how evolution affects epidemics and pathogen establishment (Antia et al., 2003; Holmes and Grenfell, 2009; Volz and Rambaut, 2009; Leventhal et al., 2015; Woolhouse et al., 2005).

What are the drivers of pathogen emergence and reemergence? How are microparasites able to cause epidemics in novel hosts? These questions have been the focus of epidemiology since its inception and remain of immediate importance for wildlife, human, and livestock populations (Anderson and May, 1992; Daszak et al., 2000a). It has become clear that answering these questions requires an understanding of how rapid evolution contributes to epidemic potential (Antia et al., 2003; Pepin et al., 2010; Pybus and Rambaut, 2009; Leventhal et al., 2015; Woolhouse et al., 2005). For emerging infectious diseases, the key evolutionary event is often the generation of de novo phenotypes in pathogens (Altizer et al., 2003; Woolhouse et al., 2005; Parrish et al., 2008). These phenotypes might include a strain with increased transmissibility, or immune escape variants. Because of the large population sizes and high mutation rates of many viruses, it is hypothesized that selection on de novo variation may be a critical factor during viral adaptation to novel hosts and coevolution with existing hosts (Crill et al., 2000; Eshelman et al., 2010; Pybus and Rambaut, 2009; Altizer et al., 2003; Woolhouse et al., 2005; Parrish et al., 2008).

Since its inception, the field of phylodynamics has seen significant advances in theoretical population genetic models relating the complex demographics of pathogens to the structure of their phylogenetic trees (Koelle et al., 2006; Norström et al., 2012; Volz et al., 2009). These include mathematical models describing how deterministic epidemic dynamics shape neutral genetic variation (Volz, 2012), models describing how rates of coalescence can be related to epidemiological model structures (Koelle and Rasmussen, 2012), and powerful statistical models to estimate the parameters of those mathematical models (Rasmussen et al., 2011). However, the existing mathematical models are insufficient for investigating the role of de novo evolution in epidemics. The emergence of novel pathogen phenotypes, such as a strain with higher transmissibility or increased virulence, during an outbreak necessitates a dynamic model structure. Although capable of incorporating selection and allowing for stochasticity, the current models have a static structure and are thus unable to account for newly arising phenotypic variants (Koelle and Rasmussen, 2012; Rasmussen et al., 2011; Volz, 2012).

A Short Primer on the Coalescent

The primary tool for modern population genetic inference is coalescent theory, which provides a retrospective, mathematical framework for relating genetic variation to historical evolutionary processes (Wakeley, 2008). Coalescent theory permits the study of the evolutionary history of a population by sampling individuals in the present (Drummond et al., 2005; Wakeley, 2004, 2008). Consider a population in which individuals are related by a shared ancestry rooted at their ‘most recent common ancestor’ (MRCA). Going forward in time and starting from the MRCA, the population diverges with lineages forming and dying. Looking backwards, lineages fuse, reducing in number until only a single lineage remains; the coalescent is a quantitative, probabilistic framework for determining when lineages join, or ‘coalesce,’ backwards in time (Wakeley, 2008; Fu and Li, 1999). Because the coalescent considers neutral genetic variation, all pairs of existing lineages are equally likely to coalesce (Wakeley, 2008; Kingman, 1982a,b). The result is a genealogy tracing the current individuals backwards in time to the MRCA. The parameters of a coalescent model describe this stochastic, genealogical process. The rate that these lineages are born and die is also a function of the nonneutral evolutionary forces acting on the population and demographic processes (Wakeley, 2008). Therefore, selection, demography, and other evolutionary processes will leave signatures in the shape of genealogies (Wakeley, 2008; Drummond et al., 2005; Parsch et al., 2001; Nei and Takahata, 1993). The expected coalescent time and the rate of coalescent are both highly sensitive to changes in ecological and evolutionary dynamics. As a result, coalescent theory can be used to extract information about phenotypic evolution from the genetic variability of populations.

The Coalescent and Infectious Diseases

Applying coalescent theory to the study of infectious disease dynamics presents a number of challenges (Frost et al., 2015). First, sequences are typically sampled serially, as opposed to the classical application of coalescent theory where sequences are collected from a single time-point (Koelle and Rasmussen, 2012; Volz, 2012; Stadler et al., 2012). Second, unlike many traditional applications, often a large fraction of infected individuals are sampled (Volz, 2012). Third, complex population dynamics emerge from an epidemic process. In two recent papers, Volz et al. (2009) and Volz (2012) derived the coalescent for structured pathogens undergoing complex population dynamics. The models in (Volz, 2012; Volz et al., 2009) allowed for: (1) the nonlinear growth rate of pathogen populations during
epidemics, (2) birth and transmission rates that change during an epidemic and are not always proportional to population size, and (3) the changing variance in the number of transmissions per infected individual. Using the novel coalescent framework developed by Volz et al. (2009), Rasmussen et al. (2011) demonstrated that with a model for the rate of coalescence, it was possible to infer historical epidemiological patterns from simulated sequence data. The statistical methods developed by Rasmussen et al. (2011) are Bayesian particle filter methods, which, once an equation exists for the rate of coalescence, can approximate the likelihood of a model given a genealogy.

Selection acting on genetic variants arising from *de novo* phenotypic evolution adds an additional layer of complexity to the coalescent process (Frost et al., 2015). This form of evolution will result in new disease model compartments that arise stochastically. Therefore, modeling selection on *de novo* variation requires a dynamic model structure. The Volz et al. (2009) and Volz (2012) coalescent models can have arbitrary structure, but critically this structure must be static during the course of evolution. Consider a mutation increasing the transmissibility of a pathogen. As this mutation spreads, the transmission dynamics change. This effect can be easily visualized in the transmission tree, where hosts are connected if one host’s pathogens seeds infection in an uninfected host (Figure 3). Because two pathogen lineages cannot coalesce unless they come from a shared host, changes in the transmission tree will affect the rate of coalescence for pathogens.

**How Does Selection for Increased Transmissibility Affect Influenza Phylogenies?**

In 2004, an influenza outbreak in greyhound dogs had a case fatality rate close to 40% (Crawford, 2005). Sequencing of viral isolates determined that the virus responsible for this outbreak, influenza A/H3N8, arose from a recent spillover from horse populations (Crawford, 2005). Subsequent phylogenetic analysis provided early evidence for viral evolution during adaptation to a novel host. Molecular changes in the A/H3N8 hemagglutinin gene, encoding the viral surface glycoprotein, indicated evolution of increased transmissibility in canines (Crawford, 2005).

Over the period of 4 months in 2011, nearly 200 New England harbor seals died of pneumonia caused by an avian influenza, also of the influenza A/H3N8 subtype (Anthony et al., 2012). The H3N8 strain had acquired a mutation that increased its ability to transmit between mammalian hosts (Anthony et al., 2012). Because influenza infects the gastrointestinal tract of birds and the upper respiratory tract in mammals, transmissibility had been a barrier to species jumping. Variation in infection location is primarily caused by differences in the sialic acid binding site of influenza infecting avian and mammalian hosts (Fergusson et al., 2003; Smith et al., 2009; Suzuki et al., 2000). However, reassortment of influenza strains with different cell-type specificity and evolution in hosts with mixed sialic acid types, such as pigs, can facilitate spillover (Fergusson et al., 2003; Smith et al., 2009; Suzuki et al., 2000). Sequence data from the harbor seal outbreak suggests this as a mechanism for increased transmissibility (Anthony et al., 2012).

**Using Phylodynamic to Study Disease Reporting During the 2014 Ebola Outbreak**

Infectious disease surveillance data can be unreliable during unfolding crises in which resources are limited and public health authorities have poor access to affected communities. During the 2014–15 Ebola outbreak in West Africa, surveillance efforts primarily detected cases that were treated in healthcare facilities, and may have missed a sizable fraction of infections (Meltzer et al., 2014; WHO Ebola Virus Response Team, 2014). Initially, the CDC estimated for every Ebola case reported in Sierra Leone and Liberia, as many as 2.5 times as many cases went unreported (Meltzer et al., 2014). Accurate outbreak projections and assessments of intervention strategies depend on reliable estimates of underreporting rates. However, underreporting can be a very dynamic process, potentially varying in time, space, and/or with outbreak size, and driven by intrinsic properties of the pathogen, human behavior, diagnostic practices, and the healthcare infrastructure.

The primary difficulty the public health community faced in estimating underreporting is the limited data commonly available during an outbreak, namely confirmed and suspected cases and mortalities. From these data alone, one cannot estimate the rate of underreporting without making strong modeling assumptions and, even with such assumptions, we often lack statistical power to make precise estimates.

![Figure 3](image-url) The results from a computer simulated emerging infectious disease outbreak. Hosts are represented as circles, with lines connecting individuals who infected each other. Time starts at the bottom of the plot. Approximately one-third of the way through the outbreak, a mutation occurred that increased the transmissibility of the pathogen. Individuals infected with this new strain are colored in orange.
However, underreporting can cause a mismatch between incidence estimated from case data and incidence reconstructed from genetic data using phylogenetic methods. For example, if there is a constant level of underreporting, case count data will reflect lower transmission rates and lead to underestimation proportional to the underreporting rate. However, the extent of genetic variation among viral sequences taken from the same set of cases will reflect the true, larger population size of circulating viruses, and lead to estimates closer to the true incidence. This is true even if viral sequences are only collected from reported individuals, assuming reported and unreported individuals are mixing with each other. In a phylogenetic analysis of Ebola virus genome sequences, Scarpino et al. (2015) estimated that underreporting of cases may be between 0–70%, with the most likely value being 17%.

Beyond underreporting, leveraging phylogenetic methods during emerging infectious disease outbreaks can potentially address a range of important, but historically challenging, questions. These include, but are certainly not limited to, the potential for evolution to alter the virulence or transmissibility of the pathogen, the role of subclinical or asymptomatic infections in transmission, the importance of cross-border transmission, and the relative role of various transmission routes in sustaining an outbreak. During the next pandemic, or emerging infectious disease outbreak, deploying phylogenetic methods and next-generation sequencing to improve surveillance and decision-making will be essential.

### Conclusions

In this article we have seen the emergence of novel pathogens is a complex process and one affected by host ecology and behavior, as well as, pathogen evolution (Leventhal et al., 2013; Woolhouse et al., 2005). For some diseases, such as influenza, it seems clear that the most important determinant is pathogen evolution. However, for others, such as SARS, Ebola, and Middle East respiratory syndrome corona virus host factors seem to play a larger role in regulating spread. Although a pathogen’s often rapid rate of evolution can contribute to its epidemic potential, these high rates also facilitate the application of phylogenetic methods to the study of emerging infectious diseases. Future work in the rapidly expanding field of evolution and the emergence of novel pathogens will undoubtedly provide numerous scientific insights, but hopefully, better prepare us for the next pandemic.

### See also

Coalescent and Models of Identity by Descent. Pathogen Epidemiology. Predation and Parasitism. RNA Viruses, Evolution of

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