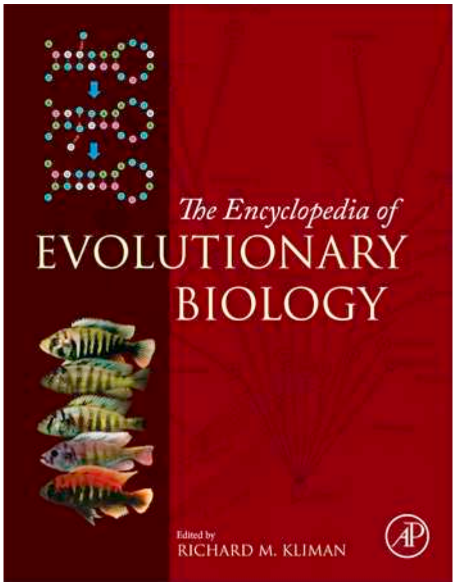

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Evolutionary Medicine IV. Evolution and Emergence of Novel Pathogens

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Glossary

Coalescent theory A retrospective, mathematical framework for relating genetic variation to historical evolutionary and demographic processes.

***De novo* phenotypes** New traits, which are present for the first time in a population.

Glycoprotein A molecule that consists of a carbohydrate and a protein bound together.

Influenza hemagglutinin One of the surface glycoproteins found on influenza viruses. Its primary function is for binding the virus to sialic acid binding sites.

Microparasites Parasites that can complete their life cycle within a single host and can be transmitted directly to other hosts of the same species, for example, influenza, HIV, and Ebola.

Phylodynamic models Theoretical population genetic models relating the complex demographics of pathogens to the structure of their phylogenetic trees.

Sialic acid Nitrogen or oxygen substituted derivatives of the nine-carbon monosaccharide, neuraminic acid.

Social contact networks A social structure made up of individuals and the contacts between them, which are often visualized as graphs.

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; Hotez, 2014). The critical factors uniting 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 McMichae, 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 McMichae, 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 Gabon. 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 McMichae, 2004; Holmes, 2009). In the next section, the author discusses

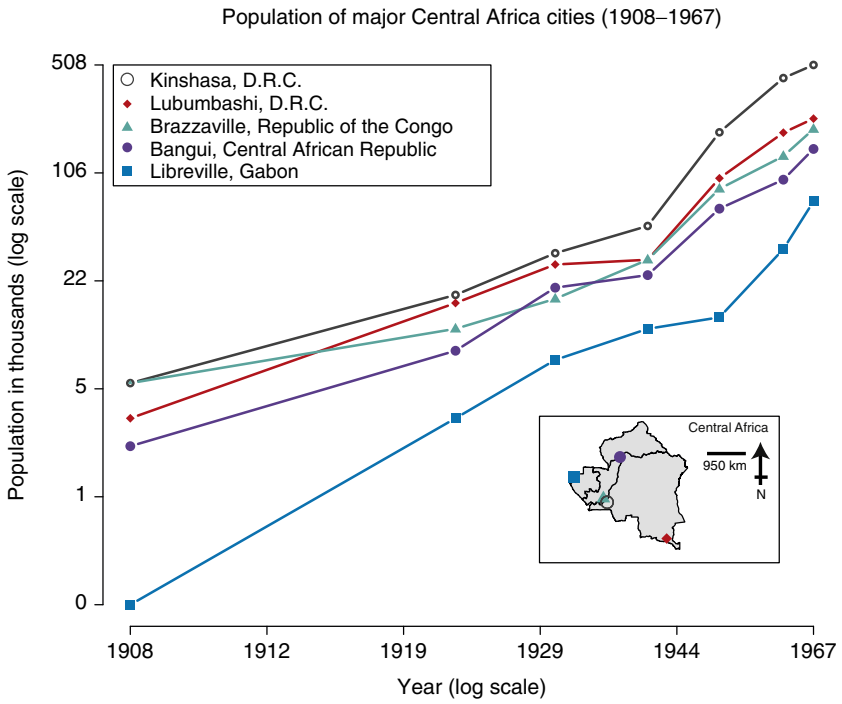

Figure 1 Between 1900 and 1970, the population size of the five largest central African cities grew by over 100-fold. This dramatic increase in size was due mostly to urbanization, where individuals migrated from rural areas to the cities, as opposed to population growth.

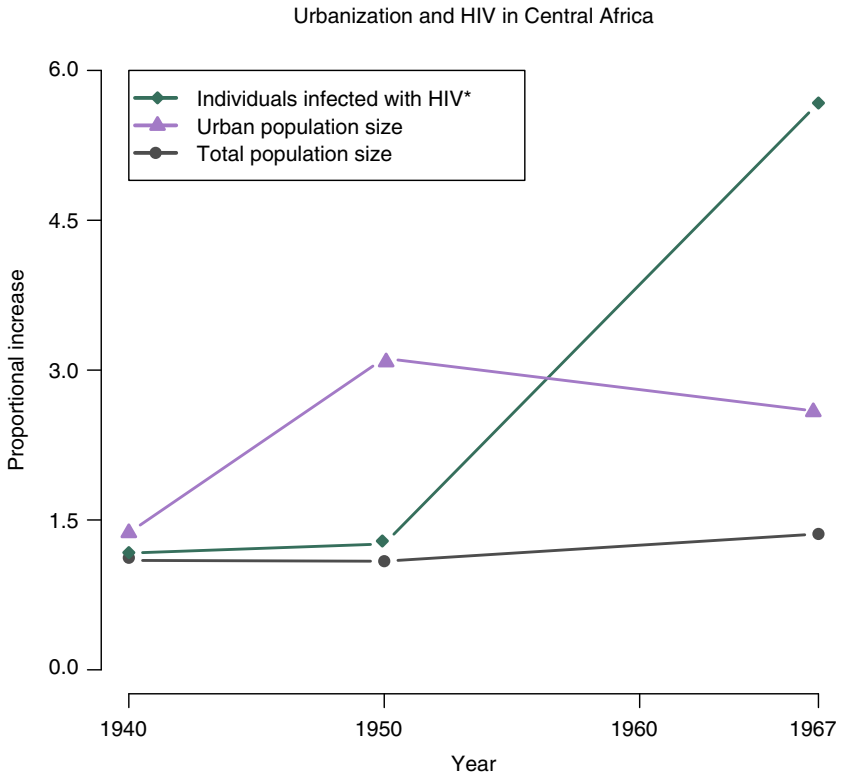

Figure 2 Estimates from genomic data suggest that HIV was already spreading rapidly in central Africa by the 1960s. As predicted by theory from epidemiology, there is evidence for a role of urbanization in the spread of HIV. The figure plots the proportional increase in growth rate by decade for individuals 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; Pybus 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 track 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 Phylodyanmics 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.

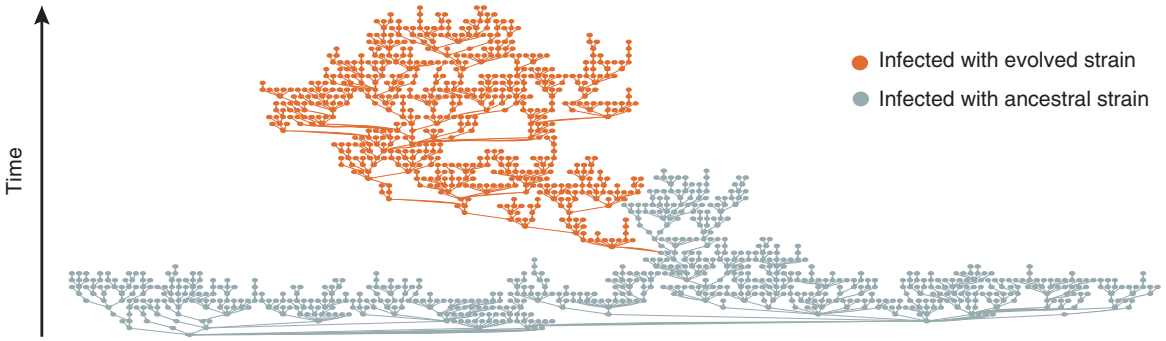

Figure 3 The results from a computer simulated emerging infectious disease outbreak. Hosts are represented as circles, with lines connecting individuals who infected each other. Time starts at the bottom of the plot. Approximately one-third of the way through the outbreak, a mutation occurred that increased 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 phylodynamic 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 phylodynamic 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 phylodynamic 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 phylodynamic 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.*, 2015; 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 phylodynamic 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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