sequencing and analysis of a well-sampled population provide another method by which to derive similar fundamental epidemiologic parameters. One key measure of transmissibility is the basic reproduction number (R0), defined as the number of secondary infections generated from a single primary infectious case. When the basic reproduction number is greater than 1 (R0 >1), an outbreak has epidemic potential; when it is less than 1 (R0 <1), the outbreak will become extinct. On the basis of sequences from influenza samples obtained from infected patients very early in the 2009 H1N1 influenza pandemic, the basic reproduction number was estimated through a population genomic analysis at 1.2; this compared to estimates of 1.4–1.6 based on several epidemiologic analyses. In addition, with the assumption of a molecular clock model, sequences of H1N1 samples together with information about when and where the samples were obtained have been used to estimate the date and location of the pandemic's origin, providing insight into disease origins and dynamics. Because the magnitude and intensity of the public health response are guided by the predicted size of an outbreak, the ability of genomic methods to elucidate a pathogen's origin and epidemic potential adds an important dimension to the contributions of these methods to infectious disease epidemiology.

PROVIDING INSIGHT INTO PATHOGEN EVOLUTION

Beyond describing transmission and dynamics, pathogen genomics can provide insight into the evolution of pathogens and the interaction of selective pressures, the host, and pathogen populations, which can have implications for vaccine or therapeutic development. From a clinical perspective, this process is central to the acquisition of antibiotic resistance, the generation of increasing pathogenicity or new virulence traits, the evasion of host immunity and clearance (leading to chronic infection), and vaccine efficacy.

Microbial genomes evolve through a variety of mechanisms, including mutation, duplication, insertion, deletion, recombination, and horizontal gene transfer. Segmented viruses (e.g., influenza virus) can reassort gene segments within multiply infected cells. The pandemic 2009 H1N1 influenza A virus, for example, appears to have been generated through reassortment of several avian, swine, and human influenza strains. Such potential for the evolution of novel pandemic strains has precipitated concern about the possible evolution to transmissibility of virulent strains that have been associated with high mortality rates but have not yet exhibited efficient human infectivity. Controversial experiments with H5N1 avian influenza virus, for example, have defined five mutations that render the virus transmissible, at least in ferrets—the animal model system for human influenza.

The continual antigenic evolution of seasonal influenza offers an example of how studies of pathogen evolution can impact surveillance and vaccine development. Frequent updates to the annual influenza vaccine are needed to ensure protection against the dominant strains. These updates are based on an ability to anticipate which viral populations from a pool of substantial locally and globally diverse circulating viruses will predominate in the upcoming season. Toward that end, sequencing-based studies of influenza virus dynamics have shed light on the global spread of influenza, providing concrete data on patterns of spread and helping to elucidate the origins, emergence, and circulation of novel strains. Through analysis of more than 1000 influenza A H3N2 virus isolates over the 2002–2007 influenza seasons, Southeast Asia was identified as the usual site from which diversity originates and spreads worldwide. Further studies of global isolate collections have shed further light on the diversity of circulating virus, showing that some strains persist and circulate outside of Asia for multiple seasons.

Not only do genomic epidemiology studies have the potential to help guide vaccine selection and development; they are also helping to track what happens to pathogens circulating in the population in response to vaccination. By describing pathogen evolution under the selective pressure of a vaccinated population, such studies can play a key role in surveillance and identification of virulence determinants and perhaps may even help to predict the future evolution of escape from vaccine protection. The 7-valent pneumococcal conjugate vaccine (PCV-7) targeted the seven serotypes of *S. pneumoniae* responsible for the majority of cases of invasive disease at the time of its introduction in 2000; since then, PCV-7 has dramatically reduced the incidence of pneumococcal disease and mortality. Population genomic analysis of the sequences of more than 600 Massachusetts pneumococcal isolates from 2001–2007 has shown that preexisting rare nonvaccine serotypes are replacing vaccine serotypes and that some strains have persisted despite vaccination by recombining the vaccine-targeted capsule locus with a cassette of capsule genes from non-vaccine-targeted serotypes.

GLOBAL CONSIDERATIONS

While cutting-edge genomic technologies are largely implemented in the developed world, their application to infectious diseases offers perhaps the biggest potential impact in less developed regions where the burden of these infections is greatest. This globalization of genomic technology and its extensions has already begun in each of the areas of focus highlighted in this chapter; it has occurred both through the application of advanced technologies to samples collected in the developing world and through the adaptation and importation of technologies directly to the developing world for on-site implementation as they become more globally accessible. Genomic characterization of the pathogens responsible for important global illnesses such as tuberculosis, malaria, trypanosomiasis, and cholera has led to insights in diagnosis, treatment, and infection control. For instance, the nucleic acid–based test developed for rapid diagnosis of *M. tuberculosis* infection and detection of rifampin resistance is being priced for implementation in field settings in Africa and Asia where tuberculosis is most prevalent. The potential to diagnose multidrug-resistant tuberculosis in hours instead of weeks or months may truly revolutionize treatment and control of this common and devastating illness. High-resolution genomic tracking of the spread of cholera has yielded insights into which public health measures may prove most effective in controlling local epidemics. Overall, sequencing efforts have become exponentially cheaper with each passing year. As these technologies synergize with efforts to globalize information-technology resources, global implementation of genomic methods promises to spread state-of-the-art methods for diagnosis, treatment, and epidemic tracking of infections to areas that need these capabilities the most.

SUMMARY

By illuminating the genetic information that encodes the most fundamental processes of life, genomic technologies are transforming many aspects of medicine. In infectious diseases, methods such as next-generation sequencing and genome-scale expression analysis offer information of unprecedented depth about individual microbes as well as microbial communities. This information is expanding our understanding of the interactions of these microorganisms and communities with one another, with their human hosts, and with the environment. Despite significant progress and the abundant genomic data now available, technological and financial barriers continue to impede the widespread adoption of large-scale pathogen sequencing in clinical, public health, and research settings. As even vaster amounts of data are generated, innovations in storage, development of bioinformatics tools to manipulate the data, standardization of methods, and training of end-users in both the research and clinical realms will be required. The cost-effectiveness and applicability of whole-genome sequencing, particularly in the clinic, remain to be studied, and studies of the impact of genome sequencing on patient outcomes will be needed to clarify the contexts in which these new methodologies can make the greatest contributions to patient well-being. The ongoing efforts to overcome limitations through collaboration, teaching, and reduction of financial obstacles should be applauded and expanded. With advances in genomic technologies and computational analysis, our ability to detect, characterize, treat, monitor, prevent, and control infections has progressed rapidly in recent years and will continue to do so, with the hope of heralding a new era where the clinician is better armed to combat infection and promote human health.