Bayesian modeling examined the likelihood of transmission between patients within a CF center; the authors found nearly identical isolates in a number of patients and observed that these isolates were less diverse than isolates from a single individual. Because no clear epidemiologic link places the infected patients in the same place at the same time, this finding highlights a need to explore preexisting notions of circumstances required for transmission and a reconsideration of *M. abscessus* infection control guidelines. Similar studies of other pathogens—particularly those that share human, other animal host, and environmental reservoirs—will continue to advance our insight into the relative roles and prominence of sources of infection as well as the modes of spread through populations, thereby establishing evidence-based strategies for prevention and intervention.

As increasing numbers of studies aim to carefully define the origins and spread of infectious agents using the high-resolution lens of whole-genome sequencing, fundamental questions are arising with regard to our understanding of infection in a single individual and the process of a single transmission event. For example, a better understanding of a pathogen population's diversity within a single infected individual is a critical component in interpreting the relationship among isolates from different patients. While we have traditionally thought of individuals as infected with a single bacterial strain, a recent sequencing study of multiple colonies of *S. aureus* from a single individual showed a "cloud" of diversity; this finding raises a number of questions that will be important to address as this field develops: What is the clinical significance of this diversity? What are the processes that generate and limit diversity? What amount of diversity is transmitted under different conditions and routes of transmission? How do the answers to these questions vary by infectious organism, type of infection, and host and in response to treatment? More comprehensive descriptions of diversity, population dynamics, transmission bottlenecks, and the forces that shape and influence the growth and spread of microbial populations will be a critically important focus of future investigations.

RECONSTRUCTING THE ORIGINS AND DYNAMICS OF PATHOGEN SPREAD

In addition to reconstructing the transmission chains of local outbreaks, genomics-based epidemiologic methods are providing insight into broad-scale geographic and temporal spread of pathogens. A classic example has been the study of cholera, the dehydrating diarrheal illness caused by infection with *Vibrio cholerae*. Cholera first spread worldwide from the Indian subcontinent in the 1800s and has since caused seven pandemics; the seventh pandemic has been ongoing since the 1960s. An investigation into the geographic patterns of cholera spread in the seventh pandemic used genome sequences from a global collection of 154 *V. cholerae* strains representing isolates from 1957–2010. This investigation revealed that the seventh pandemic has comprised at least three overlapping waves spreading out from the Indian subcontinent (Fig. 146-4). Further, analysis of the genome of an isolate of *V. cholerae* from the 2010 outbreak of cholera in Haiti showed it to be more closely related to isolates from South Asia than to isolates from neighboring Latin America, a result supporting the hypothesis that the outbreak was derived from *V. cholerae* introduced into Haiti by human travel (likely from Nepal) rather than by environmental or more geographically proximal sources. A subsequent study that dated the time to the most recent common ancestor of a population of *V. cholerae* isolates from Haiti provided further support for a single point-source introduction from Nepal.

Increasing numbers of investigations into the spread of many pathogens—thus far including strains of *S. aureus*, *S. pneumoniae*, *Chlamydia*, *Salmonella*, *Shigella*, *E. coli*, *C. difficile*, West Nile virus, rabies virus, and dengue virus—are contributing to a growing atlas of maps describing routes, patterns, and tempos of microbial diversification and dissemination. Large-scale efforts like the 100K Foodborne Pathogen Genome Project, which aims to sequence the genomes of 100,000 strains of food-borne pathogens collected from sources including food, the environment, and farm animals, are possible because of advances in sequencing technologies. Such studies will yield a vast amount of data that can be used to investigate diversity and microbiologic links within distinct niches and the patterns of spread from one niche to another. The increasingly broad adoption of genome sequencing by health care and public health institutions will ensure that the available catalog of genome sequences and associated epidemiologic data will grow very rapidly. With higher-resolution description of microbial diversity and of the dynamics of that diversity over time and across epidemiologic and demographic boundaries and evolutionary niches, we will gain even greater insights into the relationships of transmission routes and patterns of historic spread.

PREDICTING EPIDEMIC POTENTIAL

Defining pathogen transmissibility is a critical step in the development of public health surveillance and intervention strategies as this information can help predict the epidemic potential of an outbreak. Transmissibility can be estimated by a variety of methods, including inference from the growth rate of an epidemic together with the generation time of an infection (the mean interval between infection of an index case and of the people infected by that index case). Genome

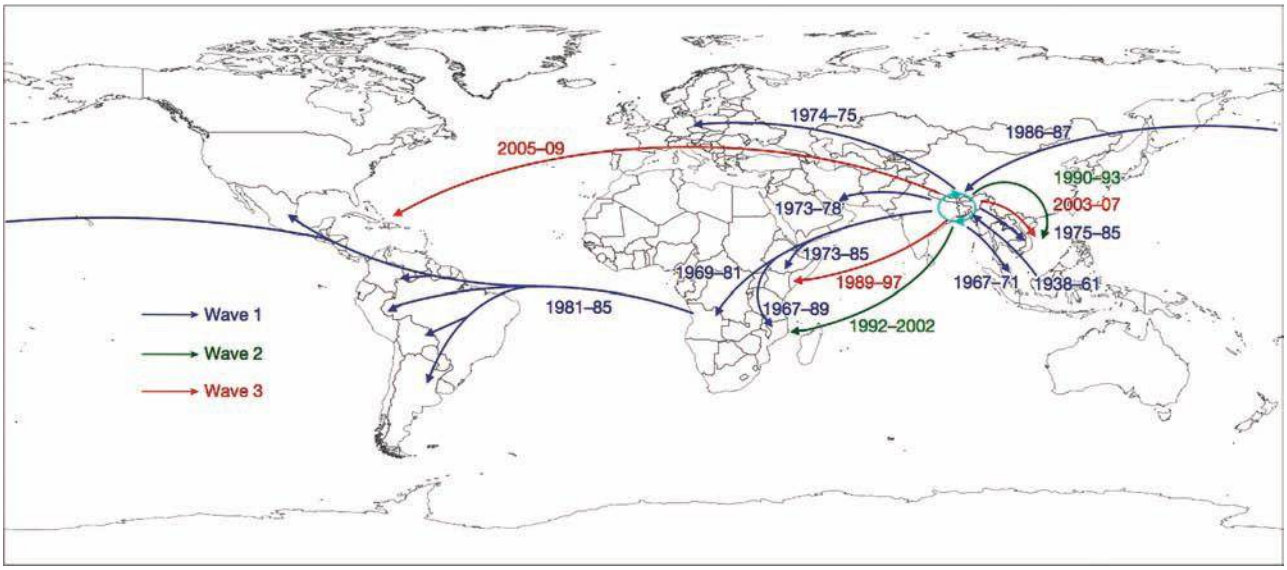

FIGURE 146-4 Transmission events inferred from phylogenetic reconstruction of 154 *Vibrio cholerae* isolates from the seventh cholera pandemic. Date ranges represent estimated time to the most recent common ancestor for strains transmitted from source to destination locations, based on a Bayesian model of the phylogeny. *(Reprinted with permission from A Mutreja et al: Evidence for several waves of global transmission in the seventh cholera pandemic. Nature 477:462, 2011.)*