Commentary

Emerging Challenges and Opportunities in Infectious Disease Epidemiology

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Much of the intellectual tradition of modern epidemiology stems from efforts to understand and combat chronic diseases persisting through the 20th century epidemiologic transition of countries such as the United States and United Kingdom. After decades of relative obscurity, infectious disease epidemiology has undergone an intellectual rebirth in recent years amid increasing recognition of the threat posed by both new and familiar pathogens. Here, we review the emerging coalescence of infectious disease epidemiology around a core set of study designs and statistical methods bearing little resemblance to the chronic disease epidemiology toolkit. We offer our outlook on challenges and opportunities facing the field, including the integration of novel molecular and digital information sources into disease surveillance, the assimilation of such data into models of pathogen spread, and the increasing contribution of models to public health practice. We next consider emerging paradigms in causal inference for infectious diseases, ranging from approaches to evaluating vaccines and antimicrobial therapies to the task of ascribing clinical syndromes to etiologic microorganisms, an age-old problem transformed by our increasing ability to characterize human-associated microbiota. These areas represent an increasingly important component of epidemiology training programs for future generations of researchers and practitioners.

infectious diseases; methods; modeling; surveillance

Abbreviation: EBOV, Ebola virus.

The priority afforded to infectious diseases within epidemiologic research has been fluid over the past 200 years or longer. Despite the lasting prominence of early investigations into measles, cholera, plague, typhoid fever, malaria, and yellow fever (1–6), the intellectual tradition of modern epidemiology stems largely from studies of chronic diseases dating to the post-World War II era, when such conditions came to surpass infectious diseases in morbidity and mortality in high-income countries amid improvements in living conditions and the introduction of numerous antibiotics and vaccines. This epidemiologic transition co-occurred with a shift in focus for epidemiologic research (and training programs) toward the multifactorial etiology of chronic conditions (7). In parallel, early 20th-century work on the "dependent happenings" of communicable diseases (8–11) yielded to the development of today's core biostatistical methods for chronic diseases, premised on the independence of outcomes among subjects (12–14).

Since the late 20th century, the emergence of human immunodeficiency virus and acquired immunodeficiency syndrome and other infections has renewed interest in infectious diseases and their health, economic, and security implications (15). Outbreaks of severe acute respiratory syndrome, pandemic influenza A H1N1, Ebola virus (EBOV), and Zika virus have prompted international responses, whereas influenza A H7N9 and H5N1, Lassa fever virus, Nipah virus, and Middle East respiratory syndrome coronavirus, among other agents, have been a source of regional concern. The incidence and endemic range of "neglected" infections, including dengue and cholera (16, 17), have expanded, and antimicrobial resistance has threatened to derail the control of tuberculosis, typhoid, malaria, gonorrhea, yaws, and invasive bacterial infections (18–23). Although highly effective vaccines are available, measles and yellow fever have resurged on multiple continents, due to gaps in vaccine coverage (24, 25), while short-lived vaccine-induced protection has facilitated unexpected resurgences in diseases once on the path to elimination, such as pertussis and mumps (26, 27).

After decades of relative obscurity in the mid-20th century, infectious disease epidemiology has experienced an intellectual rebirth in response to disease emergence. Repopulation of this field by scientists trained not only in clinical medicine but

ecology, demography, and quantitative sciences has led to the adoption of methods scarcely addressed in traditional public health training programs. Cluster-randomized trial designs, for example, have become commonplace for evaluating infectious disease interventions, quantifying indirect effects resulting from contagion (28). Classical models of ecological dynamics have been adapted to address the transmission and control of infectious agents, while our expanding ability to integrate such models with epidemiologic data through Bayesian statistics has enhanced their relevance to policymaking (29–31). Most recently, sequencing and phylogenetic analysis have afforded an unprecedented view into the population structure and dynamics of pathogens (32, 33).

Here, we review developments in infectious disease epidemiology together with their implications for research and practice, and for the training of future epidemiologists. We first consider the role of epidemiologic surveillance in the context of pathogen emergence and the integration of surveillance data into quantitative studies of transmission. Next, we discuss challenges in causal inference, including the evaluation of public health interventions against emerging pathogens and the difficulties of attributing clinical syndromes to microbial agents.

SURVEILLANCE OF EMERGING INFECTIONS

Public health practice

Surveillance justifiably has been seen as a core public health function, with its important role articulated by Langmuir in 1963 (34). In the United States and elsewhere, surveillance for diverse infectious (and noninfectious) diseases has typically relied on an essentially passive system of reporting by healthcare providers or laboratories, often mandated by public health laws. Although such passive systems of disease reporting have proven invaluable, their limitations, such as incomplete, often inconsistent detection of cases and delayed detection of outbreaks, are well documented (35). As a result, active surveillance systems that do not depend on providers and laboratories to report have been developed and promoted.

The Centers for Disease Control and Prevention–funded Emerging Infections Program and its components (e.g., Foodnet, ABCs), initiated in 1994, is 1 notable example of such a system, as are international versions promoted through the Centers for Disease Control and Prevention's Global Health Security initiative (36). Such systems, while expensive to develop and maintain, are of great value, especially when they collect biological specimens (e.g., isolates of bacterial and viral pathogens) for typing and support analytic epidemiologic studies (e.g., case-control studies of vaccine effectiveness (37)). Nevertheless, these systems, too, may have limitations, particularly in their ability to detect in a timely fashion outbreaks caused by novel microbial agents, prompting interest in alternative methods. In this article, we consider proposed alternatives, highlighting their benefits and challenges.

Surveillance for disease emergence

Beyond efforts to quantify the incidence of infectious diseases of known etiology, disease surveillance has been advocated as a means of mitigating the threat posed by novel pathogens. Large-scale efforts to identify pathogens with the potential to spill over from animals to humans have received notable investment, for instance from the US Agency for International Development Emerging Pandemic Threats program (38). More recently, metagenomic sequencing has enabled the number of known viruses to be multiplied in such studies (39). The aim of those working on the Global Virome Project, launched in 2018, to characterize within 10 years all 1.6 million viruses thought to exist (40).

However, the pathway for translating data sets produced by such activities into actionable threat-reduction programs remains unclear. That only approximately 250 viruses are known to infect humans (and an even smaller handful to cause major epidemics) may constrain the value of large-scale virus discovery for identifying high-risk pathogens, as well as viral determinants of pathogenic potential (41). Spillover events causing recent epidemics—including H1N1 in Mexico, Middle East respiratory syndrome in Saudi Arabia, and EBOV in West Africa—have been poorly predicted by factors long believed to drive disease emergence (42). Accordingly, interest in expanding our catalogue of potential pathogens should be weighed against our persisting need to enhance the detection and control of outbreaks of known pathogens (43). For instance, 2 EBOV epidemics in the Democratic Republic of the Congo in 2018 took weeks to be identified, with dozens of suspected cases having already accumulated (44, 45).

Serological studies have received increasing enthusiasm for monitoring emerging pathogens of significance to humans (41, 46). The prevalence of antibodies indicating previous exposure may provide valuable information about the frequency of animal-human spillover events and the potential for person-to-person spread, overcoming reporting biases that favor detection of large outbreaks under traditional surveillance. Moreover, the low cost of multiplex assays makes integrated surveillance of multiple pathogens plausible. Although serosurveys have bolstered recent efforts to understand the geographic range and clinical spectrum of EBOV and Zika virus infections (47, 48), the enhancement of dengue hemorrhagic fever risk by prior exposure (49), and the role of immunologic history in influenza susceptibility and vaccine response (50), there remain few examples of public health programs undertaking serological studies for routine surveillance, at least in civilian populations (51).

Emerging data and analytics

Outside of laboratory-based surveillance, the increasing availability of passively collected "Big Data" on the health and behaviors of individuals has prompted enthusiasm about enhancing disease surveillance through alternative data streams. Initiatives such as the ProMED-mail network and HealthMap (52, 53) compile and disseminate news about outbreaks from media and other sources, aiming to trigger investigation by public health organizations. Data such as emergency department visits, medication sales, online search queries, and social media postings have also been suggested as real-time indicators of outbreak activity, although their integration into public health responses remains a subject of debate (54–56). The need to overcome reporting biases is a central challenge, because observations may be too nonspecific to distinguish between meaningful and spurious signals in settings with high technological capacity while also

being insensitive to even high-risk events in resource-poor settings (57, 58). Although nontraditional data sources have, in some applications, supported inferences about epidemic dynamics (59), limited information about cases from such sources remains a barrier. For instance, models fitted from news reports of recent measles and mumps outbreaks have yielded considerable underestimates of vaccine coverage (60–62), underscoring the importance of field investigations.

Forecasting the incidence of diseases has been a more successful application of these emerging data streams and data-analytic approaches. Although the acknowledged failure of Google Flu Trends—a prediction approach based on Internet search behavior—yielded important lessons about nonmechanistic forecasts, approaches based on machine learning and crowd-sourced human judgment have provided the most accurate within-season predictions of US influenza activity in recent comparisons (63–65). Given expanding interest in forecasting among researchers, funding agencies, and other stakeholders, there is a clear and compelling need to evaluate whether such forecasts can enhance the success and efficiency of public health response efforts.

UNDERSTANDING TRANSMISSION DYNAMICS

Model-data integration for emerging diseases

Mathematical modeling as a means to understanding infectious disease spread dates to studies by Sir Ronald Ross (8). Although the use of models to connect data such as age of infection to transmission dynamics of endemic infections has longstanding precedent (66, 67), assimilation of outbreak data for near-term assessments of control priorities is a comparatively recent phenomenon. Integration of modeling with the public health response to epidemics of bovine spongiform encephalopathy and foot-and-mouth disease in the United Kingdom and the severe acute respiratory syndrome epidemic (68–73) has led to expectations for near real-time modeling studies during major outbreaks. In recent experience, models of the spread of pandemic influenza A H1N1 (74), cholera (75), Middle East respiratory syndrome (76), EBOV (77, 78), Chikungunya virus (79), Zika virus (80, 81), yellow fever (82), and plague (83) have all been published within weeks of the respective outbreak notifications.

Although the circumstances of particular epidemics dictate what data may be available and pertinent, methods for fitting models to data have generally focused on exponential growth rates in cases (84) or the distribution of the serial interval (85). Methods based on the latter class of data offer the advantage of illustrating real-time changes in reproductive numbers (86); however, the requisite information from patient line lists is seldom available. Reliance instead on ecological data exposes models to numerous vulnerabilities, notably the inability to discern individual risk factors (and thus the population meaningfully at risk). These shortcomings may prevent models from predicting reductions in transmission before depletion of the susceptible population.

A challenge thus lies ahead in determining the role of models in outbreak response and the best practices for communicating modeling results. Although the ability of models to evaluate prophylactic strategies may be considered a benefit, recommendations

to act against remote future risks have sometimes triggered resistance among stakeholders (87). During the West African EBOV epidemic, for example, attention to worst-case model-based projections prompted some to question the reliability of the models (88), reflecting an important discrepancy between public understanding of modeling as a forecasting tool and the intended uses of models for scenario-based comparisons (89, 90). This use of modeling has been better understood in attempts to communicate the impact of interventions after the fact (91).

Microbial sequencing

The ease of sequencing pathogen genomes has afforded a new view into transmission during outbreaks. Use of sequence data to identify transmission clusters in the presence of unsure epidemiologic links dates to the early years of the human immunodeficiency virus and acquired immunodeficiency syndrome epidemic (92). In recent years, sequencing has aided efforts to track the sources of unexplained epidemics of cholera in Haiti (93) and EBOV in West Africa (94), and has shown increasing utility for reconstructing the geographic spread of pathogens (95, 96). A particular advantage of phylogenetic analysis is the possibility of estimating unobserved epidemiologic quantities, such as the reporting fraction (97) and reproductive numbers for subcritical transmission (98), which remain difficult to assess from traditional case-notification data.

Beyond reconstructing the demographic history of pathogen lineages, recent years have seen progress toward joint analysis of epidemiologic and sequencing data (99). Such "phylodynamic" approaches have shown particular relevance for emerging infections, including distinguishing the role of repeated introductions and subsequent local transmission (100–103). Whereas most applications have been tailored to specific data sets and assumptions, the development of generalized methods for joint inference of epidemiologic and phylogenetic parameters remains a priority (104) to support real-time analysis.

EVALUATION OF INFECTIOUS DISEASE INTERVENTIONS

Efficacy evaluations in emergencies

The ability to rapidly develop and deploy countermeasures to mitigate the threat posed by emerging infections has received increasing recognition as a component of public health preparedness. However, outbreaks are difficult environments in which to evaluate interventions. During the West African EBOV epidemic, the feasibility of a new paradigm for development and evaluation of interventions in emergencies was demonstrated by accelerated vaccine safety, immunogenicity, and efficacy studies(105). The Coalition for Epidemic Preparedness Innovations was established in 2017, with an initial focus on vaccines against Nipah virus, Middle East respiratory syndrome coronavirus, and Lassa fever virus, in addition to adaptable vaccine platforms for novel threats (106).

Lessons learned in EBOV vaccine trials will have an influential bearing on evaluations during future emergencies. Despite efforts to accelerate evaluation of candidate vaccines, incidence had reached low levels by the time phase III efficacy trials were ready to begin, posing a threat to their statistical power: A planned trial

in Liberia was canceled due to declining transmission (107), and no cases of disease occurred in a second trial in Sierra Leone (108), preventing efficacy assessments. In a stepped-wedge trial in Guinea, clusters of primary and secondary contacts of EBOV disease cases were randomly assigned to immediate or delayed vaccination; no cases were reported among vaccine recipients during the trial (109) or in subsequent field deployments of the vaccine, supporting a conclusion of near 100% vaccine efficacy.

Debates surrounding design of these trials highlight methodological questions requiring additional attention. In the Guinean trial, a "ring" vaccination scheme helped maximize power by enrolling contacts of known cases (110). However, the choice of individual- or cluster-level randomization within rings was debated. Because members of a vaccinated cluster are exposed to direct protection through vaccination and indirect protection due to reduced transmission within their clusters (28), cluster-randomized trials have weaker statistical power than individually randomized trials of the same size (111). Moreover, the direct effect measured in individually randomized studies may be a preferred, transportable efficacy measure (112). Uses of simulation helped in planning vaccine trials tailored to the real-world circumstances of the EBOV outbreak (113) and enabled trialists to compare alternative designs in terms of ethical mandates (114). Simulation-guided design further presents the opportunity for applying adaptive trial methods (115) in the context of infectious disease outbreaks, where dynamic trends in incidence may highlight the benefits of such approaches.

Observational designs

In addition to efficacy trials for new interventions, observational studies are needed to assess licensed interventions against evolving and re-emerging pathogens. Most commonly applied in evaluations of influenza vaccines, test-negative designs have become popular in routine (116) and exploratory (117) studies of vaccine effectiveness. By measuring vaccine effectiveness from the exposure odds ratio of vaccination among individuals seeking care who test positive or negative for a pathogen of interest, this design seeks to overcome associations of health-care seeking with vaccination status (118). However, it is uncertain whether health-care seeking and other sources of confounding are appropriately controlled for, and whether measures accurately capture vaccine direct effects (119, 120). Uncertainty about the validity of estimates that routinely inform vaccine policy-making demonstrates the need for formal evaluations of such studies and strategies to reduce bias.

Time series analyses of public health surveillance data provide another approach to measuring the real-world impact of vaccination on disease incidence, with the advantage of identifying the overall effect of a vaccination program resulting from direct and indirect protection (28). Although the ecological nature of such designs permits the introduction of biases from changes in diagnostic practices or health-care seeking, such studies nonetheless have offered important insights where other approaches failed. Limited reductions in influenza-related deaths among elderly persons amid increases in influenza vaccine coverage during the 1990s provided an important indication that the "healthy vaccinee" effect accounted for astonishing and implausible protection against all-cause mortality among elderly influenza vaccine recipients in cohort and case-control studies (121–123). Newer methods continue to improve public health inferences obtained from time-series data. In a recent evaluation of invasive pneumococcal disease incidence, trends expected under continued use of 7-valent pneumococcal conjugate vaccine provided a counterfactual condition for measuring the impact of the switch to a 13-valent vaccine targeting emerging serotypes (124). Bayesian averaging of models encoding differing pre- and postvaccination trends and change points provides a generalized strategy for defining such counterfactual comparisons (125). Other signals of transmission intensity in surveillance data, such as age of infection and sub- or multiannual periodicity, may provide additional insights while reducing sensitivity to fluctuations in reporting effort (126, 127).

The re-emergence of pathogens against which vaccines are widely deployed, such as varicella, pertussis, and mumps in the United States, poses additional challenges for conducting vaccine effectiveness studies. Situational factors may undermine researchers' ability to establish the extent to which cases owe to primary or secondary vaccine failure in all or certain vaccine recipients, and whether emerging pathogen lineages are escaping vaccine-driven immune pressure. For instance, high compliance with vaccine schedules may limit variation in individuals' vaccination status and exposures, necessitating large samples to detect factors influencing vaccine performance (128). Because re-emergence most likely reflects the expansion of 1 or several pathogen clades, limited pathogen diversity may hinder the application of conventional approaches to identifying microbial determinants of vaccine escape (129, 130). Novel methods to distinguish null from vaccine-driven mutations in antigen-coding regions (102, 131) may streamline efforts to identify vaccine escape, while mathematical modeling provides a basis for comparing candidate hypotheses with observations (26, 27).

Vaccine safety

Because vaccine studies are typically powered for primary clinical endpoints, long-term observational studies are needed to monitor for rare vaccine-attributable adverse events. Such studies have been crucial to identifying safety concerns such as intussusception after rotavirus vaccination (132) and to refuting spurious links, such as autism onset after measles-mumps-rubella vaccination (133). However, unique challenges arise in vaccine safety studies; at the individual level, vaccination and adverse-event detection may be confounded due to health-care–seeking behavior, whereas at the population level, age-related confounding may occur when vaccine recommendations are based on the individual's age.

Ecological designs taking advantage of natural experiments have proven useful in numerous studies of vaccine safety (134, 135) but inconclusive for certain classes of rare events, including those that also result from the vaccine-targeted infection (136, 137). Recent years have seen growing interest in case-only methods offering the ability to reduce or rule out individual-level sources of confounding. Case-crossover methods are common among such approaches (138, 139) and resemble matched case-control studies by sampling "control" periods from the person-time contributed by case individuals before an adverse event. Self-controlled case-series methods similarly benefit from the use of cases as their own controls, following a cohort

logic in estimating the relative incidence of adverse events after vaccination within specified risk periods (140); with adequate sample size, researchers may be able to use such analyses to eliminate or greatly reduce potential time- or age-related confounding.

Antimicrobial drugs

In response to the growing threat posed by antimicrobial resistance, the World Health Organization and national governments have prioritized bringing novel antimicrobial drugs to market (141). These plans will necessitate phase III trials in which the efficacy of new therapeutic agents is addressed and possibly phase IV studies, in which the optimal use of new and existing drugs, either singly or in combination, can be determined. Whereas patients traditionally have been enrolled in antimicrobial treatment studies on the basis of target bacterial species infections or clinical syndromes, it is uncertain within what strata such trials may yield transportable inferences. Rather than merely the infecting pathogen's baseline resistance or susceptibility phenotype, strata may be defined by factors such as pathogen lineage, mutational barriers to resistance development (142), and presence of horizontally transferable resistance elements in cocolonizing agents or environmental sources (143). Stratification based on interpatient and even intrapatient tumor heterogeneity is an emerging feature of cancer therapy trials and may provide a template for such designs (144).

In addition to clinical endpoints, carriage of susceptible and resistant bacteria, including commensal agents not purposefully targeted by treatment, can inform the impact of treatment on resistance selection in targeted and bystander species (145). Whereas between-group differences in the absolute prevalence of colonization with resistant organisms (146) are tested for routinely, stratified measurements (see the reports of Shrag et al. (147) and Feikin et al. (148), for example) of the effect of treatment on acquisition and clearance of susceptible and resistant pathogens are more informative of the underlying biology (149) and may detect signals of selection masked by simpler between-group comparisons (150, 151).

Studies are also needed to address optimal deployment of new and existing antimicrobial drugs in clinical practice. The tradeoff between maximizing a drug's impact and minimizing resistance selection has led policymakers to ration certain new drugs as last-resort treatments. However, in recent experience, such decisions have ignited ethical debates (152). Coupling mathematical modeling with field-based studies has proven useful for understanding the effectiveness of antimicrobial use policies, as highlighted in recent evaluations of the risk of resistance under population-wide access of the tuberculosis drug bedaquiline (153, 154) and antimicrobial cycling to limit resistance selection in hospital settings (155, 156).

ETIOLOGIC UNDERSTANDING

Whereas certain efforts we have discussed have been made to identify novel microorganisms able to cause human infection (40, 157), most epidemics caused by emerging pathogens have been recognized first by clusters of anomalous syndromes—such as cardiopulmonary syndrome caused by New World hantaviruses, severe acute respiratory syndrome caused by a coronavirus,

and congenital abnormalities caused by Zika virus —before the role or even existence of the etiologic microorganism had been characterized. The problem of ascribing a clinical syndrome to an etiologic agent is among the oldest in epidemiology, dating at least to the 19th century, when Robert Koch laid out criteria for such inference (i.e., Koch's, or more correctly, Henle-Koch's, postulates (158)). However, these postulates have long been recognized as inadequate, particularly for illnesses caused by viruses, and thus of largely historical interest (159); for instance, the notion that a pathogen should be absent from healthy individuals is incompatible with the prominence of carriage and asymptomatic infection in the natural history of numerous pathogens. A growing appreciation of the complexity of the human microbiome, and the likelihood that intricate mixtures of microorganisms at diverse body sites may be either the cause or consequence of both detrimental and beneficial physiological states, has further highlighted the difficulty of linking a given health outcome to infection by a single microorganism.

The now-recognized critically important role of persistent infection and the inflammation it can produce in diverse cancers and possibly other chronic diseases has further diminished the relevance of Koch's postulates and the age-old distinction between infectious and chronic diseases, as illustrated in the well-known example of human papillomavirus causing cervical, anal, and oral cancers (160). The best causal understanding of such relationships has come from randomized trials demonstrating that infection-preventing interventions are efficacious against downstream chronic illness, such as peptic ulcers due to *Helicobacter pylori* and chronic wheeze due to respiratory syncytial virus (161, 162). Natural experiments following the same intuition have provided additional evidence of such relationships, such as measles-induced immunosuppression (163), malnutrition and stunting due to enteric infection (164), and complex or chronic otitis media due to tissue damage from acute early-life disease (165). Such relationships have proven difficult to probe in the absence of a randomized or natural experiment, because of the likelihood that confounding factors influence individuals' risk for initial infection as well as chronic sequelae. New paradigms for ascribing an etiologic role to microorganisms and resulting host responses are clearly needed and may prove important in efforts to quantify the health impacts of infectious disease interventions.

SUMMARY

The recognition in the 1970s and 1980s that infectious diseases were not, in fact, disappearing as important causes of morbidity and mortality in human populations has been followed by renewed interest in these conditions, especially in the emergence or re-emergence of diverse infectious diseases and in the role of infection in various chronic diseases. At the same time, advances in epidemiologic and statistical methods, together with the growing availability of data from diverse sources, have provided new tools and approaches for studying infectious diseases. The infectious disease epidemiologists of the future will need a solid grounding in the biology of infection and the host immune response, as well as training in the increasingly sophisticated approaches to causal inference; the manipulation and analysis of large-scale data sets, including pathogen genome sequences; and

mathematical modeling, together with the behavioral and social determinants of health. Integration of these elements into epidemiology training programs (e.g., through coursework in Bayesian statistics and phylogenetics) represents an increasingly important consideration for academic departments.

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REFERENCES

1. Panum PL. Observations made during the epidemic of measles on the Faroe Islands in the year 1846. In: *The Challenge of Epidemiology: Issues and Selected Readings*. New York, NY: Pan American Health Organization; 1988:37–41.
2. Snow J. *On the Mode of Communication of Cholera*. London, United Kingdom: John Churchill; 1855.
3. XXXIII. The experimental production of plague epidemics among animals. *J Hyg (Lond)*. 1910; 10(3):315–334.
4. Budd W. Typhoid fever: its nature, mode of spreading, and prevention. *Am J Public Health (N Y)*. 1918;8(8):610–612.
5. Ross R. *The Prevention of Malaria*. London, United Kingdom: John Murray; 1911.
6. Reed W, Caroll J, Agramonte A, et al. The etiology of yellow fever—a preliminary note. *Public Health Pap Rep*. 1900;26: 37–53.
7. Kuh D, Ben-Shlomo Y, Lynch J, et al. Life course epidemiology. *J Epidemiol Community Health*. 2003;57(10): 778–783.
8. Ross R. Some *a priori* pathometric equations. *Br Med J*. 1915;1(2830):546–547.
9. Kermack WO, McKendrick AG. A contribution to the mathematical theory of epidemics. *Proc R Soc Lond A Math Phys Sci*. 1927;115(772):700–721.
10. Greenwood M. On the statistical measure of infectiousness. *J Hyg (Lond)*. 1931;31(3):336–351.
11. Epidemics and crowd-diseases: measles. By Major Greenwood, 1935. *Rev Infect Dis*. 1988;10(2):492–499.
12. Cox DR. Regression models and life-tables. In: *Breakthroughs in Statistics*. New York, NY: Springer; 1992:527–541.
13. The controlled therapeutic trial. *Br Med J*. 1948;2(4582):791–792.
14. Box GEP, Cox DR. An analysis of transformations. *J R Stat Soc Series B Stat Methodol*. 1964;26(2):211–252.
15. Morse SS. Factors in the emergence of infectious diseases. *Emerg Infect Dis*. 1995;1(1):7–15.
16. Stanaway JD, Shepard DS, Undurraga EA, et al. The global burden of dengue: an analysis from the Global Burden of Disease Study 2013. *Lancet Infect Dis*. 2016;16(6):712–723.
17. Ali M, Nelson AR, Lopez AL, et al. Updated global burden of cholera in endemic countries. *PLoS Negl Trop Dis*. 2015;9(6): e0003832.
18. Cohen KA, Abeel T, Manson McGuire A, et al. Evolution of extensively drug-resistant tuberculosis over four decades: whole genome sequencing and dating analysis of *Mycobacterium tuberculosis* isolates from KwaZulu-Natal. *PLoS Med*. 2015;12(9):e1001880.
19. Klemm EJ, Shakoor S, Page AJ, et al. Emergence of an extensively drug-resistant *Salmonella enterica* serovar *Typhi* clone harboring a promiscuous plasmid encoding resistance to fluoroquinolones and third-generation cephalosporins. *MBio*. 2018;9(1):e00105–e00118.
20. Ashley EA, Dhorda M, Fairhurst RM, et al. Spread of artemisinin resistance in *Plasmodium falciparum* malaria. *N Engl J Med*. 2014;371(5):411–423.
21. Fifer H, Natarajan U, Jones L, et al. Failure of dual antimicrobial therapy in treatment of gonorrhea. *N Engl J Med*. 2016;374(25):2504–2506.
22. Mitjà O, Godornes C, Houinei W, et al. Re-emergence of yaws after single mass azithromycin treatment followed by targeted treatment: a longitudinal study. *Lancet*. 2018; 391(10130):1599–1607.
23. Musicha P, Cornick JE, Bar-Zeev N, et al. Trends in antimicrobial resistance in bloodstream infection isolates at a large urban hospital in Malawi (1998–2016): a surveillance study. *Lancet Infect Dis*. 2017;17(10):1042–1052.
24. Filia A, Bella A, Del Manso M, et al. Ongoing outbreak with well over 4,000 measles cases in Italy from January to end August 2017—what is making elimination so difficult? *Euro Surveill*. 2017;22(37):30614.
25. Barrett AD. Yellow fever in Angola and beyond—the problem of vaccine supply and demand. *N Engl J Med*. 2016; 375(4):301–303.
26. Lewnard JA, Grad YH. Vaccine waning and mumps re-emergence in the United States. *Sci Transl Med*. 2018; 10(433):eaao5945.
27. Domenech de Cellès M, Magpantay FMG, King AA, et al. The impact of past vaccination coverage and immunity on pertussis resurgence. *Sci Transl Med*. 2018;10(434):eaaj1748.
28. Halloran ME, Haber M, Longini IM, Jr, et al. Direct and indirect effects in vaccine efficacy and effectiveness. *Am J Epidemiol*. 1991;133(4):323–331.
29. Anderson RM, May RM. Population biology of infectious diseases: Part I. *Nature*. 1979;280(5721):361–367.
30. May RM, Anderson RM. Population biology of infectious diseases: Part II. *Nature*. 1979;280(5722):455–461.
31. Heesterbeek H, Anderson RM, Andreasen V, et al. Modeling infectious disease dynamics in the complex landscape of global health. *Science*. 2015;347(6227):aaa4339.
32. Bouckaert R, Heled J, Kühnert D, et al. BEAST 2: a software platform for Bayesian evolutionary analysis. *PLoS Comput Biol*. 2014;10(4):e1003537.
33. Kao RR, Haydon DT, Lycett SJ, et al. Supersize me: how whole-genome sequencing and big data are transforming epidemiology. *Trends Microbiol*. 2014;22(5):282–291.
34. Langmuir AD. The surveillance of communicable diseases of national importance. *N Engl J Med*. 1963;268:182–192.
35. Doyle TJ, Glynn MK, Groseclose SL. Completeness of notifiable infectious disease reporting in the United States: an analytical literature review. *Am J Epidemiol*. 2002;155(9):866–874.
36. Tappero JW, Cassell CH, Bunnell RE, et al. US Centers for Disease Control and Prevention and its partners' contributions to global health security. *Emerg Infect Dis*. 2017;23(13).
37. Whitney CG, Pilishvili T, Farley MM, et al. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. *Lancet*. 2006;368(9546):1495–1502.
38. US Agency for International Development. Emerging Pandemic Threats Program. https://www.usaid.gov/ept2. Accessed July 30, 2018.

39. Paez-Espino D, Eloe-Fadrosh EA, Pavlopoulos GA, et al. Uncovering Earth's virome. *Nature*. 2016;536(7617): 425–430.
40. Carroll D, Daszak P, Wolfe ND, et al. The Global Virome Project. *Science*. 2018;359(6378):872–874.
41. Holmes EC, Rambaut A, Andersen KG. Pandemics: spend on surveillance, not prediction. *Nature*. 2018;558(7709): 180–182.
42. Jones KE, Patel NG, Levy MA, et al. Global trends in emerging infectious diseases. *Nature*. 2008;451(7181): 990–993.
43. Gardy JL, Loman NJ. Towards a genomics-informed, real-time, global pathogen surveillance system. *Nat Rev Genet*. 2018;19:9–20.
44. Lewnard JA. Ebola virus disease: 11,323 deaths later, how far have we come? *Lancet*. 2018;392(10143):189–190.
45. World Health Organization Regional Office for Africa. Ebola virus disease, Democratic Republic of the Congo: External situation report 9. http://apps.who.int/iris/bitstream/handle/10665/275330/SITREP_EVD_DRC_20181004-eng.pdf?ua=1. Accessed October 8, 2018.
46. Metcalf CJ, Farrar J, Cutts FT, et al. Use of serological surveys to generate key insights into the changing global landscape of infectious disease. *Lancet*. 2016;388(10045): 728–730.
47. Crozier I. Mapping a filoviral serologic footprint in the Democratic Republic of the Congo: who goes there? *J Infect Dis*. 2018;217(4):513–515.
48. Wikan N, Smith DR. Zika virus: history of a newly emerging arbovirus. *Lancet Infect Dis*. 2016;16(7):e119–e126.
49. Katzelnick LC, Gresh L, Halloran ME, et al. Antibody-dependent enhancement of severe dengue disease in humans. *Science*. 2017;358(6365):929–932.
50. Cobey S, Hensley SE. Immune history and influenza virus susceptibility. *Curr Opin Virol*. 2017;22:105–111.
51. Perdue CL, Cost AA, Rubertone MV, et al. Description and utilization of the United States department of defense serum repository: a review of published studies, 1985–2012. *PLoS One*. 2015;10(2):e0114857.
52. Yu VL, Madoff LC. ProMED-mail: an early warning system for emerging diseases. *Clin Infect Dis*. 2004;39(2):227–232.
53. Brownstein JS, Freifeld CC, Reis BY, et al. Surveillance Sans Frontières: internet-based emerging infectious disease intelligence and the HealthMap project. *PLoS Med*. 2008; 5(7):e151.
54. Brownstein JS, Freifeld CC, Madoff LC. Digital disease detection—harnessing the Web for public health surveillance. *N Engl J Med*. 2009;360(21):2153–2155, 2157.
55. Heffernan R, Mostashari F, Das D, et al. Syndromic surveillance in public health practice, New York City. *Emerg Infect Dis*. 2004;10(5):858–864.
56. Reingold A. If syndromic surveillance is the answer, what is the question? *Biosecur Bioterror*. 2003;1(2):77–81.
57. Centers for Disease Control and Prevention (CDC). Increased antiviral medication sales before the 2005–06 influenza season—New York City. *MMWR Morb Mortal Wkly Rep*. 2006;55(10):277–279.
58. Buckee CO, Cardenas MIE, Corpuz J, et al. Productive disruption: opportunities and challenges for innovation in infectious disease surveillance. *BMJ Glob Health*. 2018;3(1): e000538.
59. Chunara R, Andrews JR, Brownstein JS. Social and news media enable estimation of epidemiological patterns early in the 2010 Haitian cholera outbreak. *Am J Trop Med Hyg*. 2012;86(1):39–45.
60. Leung R, Munoz M. Vaccination compliance and the US measles epidemic. *JAMA Pediatr*. 2015;169(9):876–877.
61. Majumder MS, Cohn EL, Mekaru SR, et al. Substandard vaccination compliance and the 2015 measles outbreak. *JAMA Pediatr*. 2015;169(5):494–495.
62. Majumder MS, Nguyen CM, Cohn EL, et al. Vaccine compliance and the 2016 Arkansas mumps outbreak. *Lancet Infect Dis*. 2017;17(4):361–362.
63. Lazer D, Kennedy R, King G, et al. Big data. The parable of Google Flu: traps in big data analysis. *Science*. 2014; 343(6176):1203–1205.
64. Brooks LC, Farrow DC, Hyun S, et al. Flexible modeling of epidemics with an Empirical Bayes framework. *PLoS Comput Biol*. 2015;11(8):e1004382.
65. Farrow DC, Brooks LC, Hyun S, et al. A human judgment approach to epidemiological forecasting. *PLoS Comput Biol*. 2017;13(3):e1005248.
66. Fales WT. The age distribution of whooping cough, measles, chicken pox, scarlet fever, and diphtheria in various areas in the United States. *Am J Epidemiol*. 1928;8(5):759–799.
67. Muench H. Derivation of rates from summation data by the catalytic curve. *J Am Stat Assoc*. 1934;29(185):25–38.
68. Ferguson NM, Donnelly CA, Anderson RM. The foot-and-mouth epidemic in Great Britain: pattern of spread and impact of interventions. *Science*. 2001;292(5519):1155–1160.
69. Woolhouse M, Chase-Topping M, Haydon D, et al. Epidemiology. Foot-and-mouth disease under control in the UK. *Nature*. 2001;411(6835):258–259.
70. Ferguson NM, Donnelly CA, Anderson RM. Transmission intensity and impact of control policies on the foot and mouth epidemic in Great Britain. *Nature*. 2001;413(6855): 542–548.
71. Anderson RM, Donnelly CA, Ferguson NM, et al. Transmission dynamics and epidemiology of BSE in British cattle. *Nature*. 1996;382(6594):779–788.
72. Lipsitch M, Cohen T, Cooper B, et al. Transmission dynamics and control of severe acute respiratory syndrome. *Science*. 2003;300(5627):1966–1970.
73. Riley S, Fraser C, Donnelly CA, et al. Transmission dynamics of the etiological agent of SARS in Hong Kong: impact of public health interventions. *Science*. 2003;300(5627): 1961–1966.
74. Fraser C, Donnelly CA, Cauchemez S, et al. Pandemic potential of a strain of influenza A (H1N1): early findings. *Science*. 2009;324(5934):1557–1561.
75. Tuite AR, Tien J, Eisenberg M, et al. Cholera epidemic in Haiti, 2010: using a transmission model to explain spatial spread of disease and identify optimal control interventions. *Ann Intern Med*. 2011;154(9):593–601.
76. Breban R, Riou J, Fontanet A. Interhuman transmissibility of Middle East respiratory syndrome coronavirus: estimation of pandemic risk. *Lancet*. 2013;382(9893):694–699.
77. Nishiura H, Chowell G. Early transmission dynamics of Ebola virus disease (EVD), West Africa, March to August 2014. *Euro Surveill*. 2014;19(36):20894.
78. Barry A, Ahuka-Mundeke S, Ali Ahmed Y, et al. Outbreak of Ebola virus disease in the Democratic Republic of the Congo, April–May, 2018: an epidemiological study. *Lancet*. 2018; 392(10143):213–221.
79. Cauchemez S, Ledrans M, Poletto C, et al. Local and regional spread of chikungunya fever in the Americas. *Euro Surveill*. 2014;19(28):20854.
80. Lessler J, Chaisson LH, Kucirka LM, et al. Assessing the global threat from Zika virus. *Science*. 2016;353(6300): aaf8160.

81. Ferguson NM, Cucunubá ZM, Dorigatti I, et al. Countering the Zika epidemic in Latin America. *Science*. 2016; 353(6297):353–354.

82. Wu JT, Peak CM, Leung GM, et al. Fractional dosing of yellow fever vaccine to extend supply: a modelling study. *Lancet*. 2016;388(10062):2904–2911.

83. Tsuzuki S, Lee H, Miura F, et al. Dynamics of the pneumonic plague epidemic in Madagascar, August to October 2017. *Eurosurveill*. 2017;22(46).

84. King AA, Domenech de Cellès M, Magpantay FM, et al. Avoidable errors in the modelling of outbreaks of emerging pathogens, with special reference to Ebola. *Proc Biol Sci*. 2015;282(1806):20150347.

85. Wallinga J, Lipsitch M. How generation intervals shape the relationship between growth rates and reproductive numbers. *Proc Biol Sci*. 2007;274(1609):599–604.

86. Wallinga J, Teunis P. Different epidemic curves for severe acute respiratory syndrome reveal similar impacts of control measures. *Am J Epidemiol*. 2004;160(6):509–516.

87. Eddy RG. Vets asked valuable questions about foot-and-mouth measures. *Nature*. 2001;412(6846):477.

88. Butler D. Models overestimate Ebola cases. *Nature*. 2014; 515(7525):18.

89. Lofgren ET, Halloran ME, Rivers CM, et al. Opinion: mathematical models: a key tool for outbreak response. *Proc Natl Acad Sci U S A*. 2014;111(51):18095–18096.

90. Rivers C. Ebola: models do more than forecast. *Nature*. 2014; 515(7528):492.

91. Kucharski AJ, Camacho A, Flasche S, et al. Measuring the impact of Ebola control measures in Sierra Leone. *Proc Natl Acad Sci U S A*. 2015;112(46):14366–14371.

92. Ou CY, Ciesielski CA, Myers G, et al. Molecular epidemiology of HIV transmission in a dental practice. *Science*. 1992;256(5060):1165–1171.

93. Chin CS, Sorenson J, Harris JB, et al. The origin of the Haitian cholera outbreak strain. *N Engl J Med*. 2011;364: 33–42.

94. Gire SK, Goba A, Andersen KG, et al. Genomic surveillance elucidates Ebola virus origin and transmission during the 2014 outbreak. *Science*. 2014;345(6202):1369–1372.

95. Dudas G, Carvalho LM, Bedford T, et al. Virus genomes reveal factors that spread and sustained the Ebola epidemic. *Nature*. 2017;544(7650):309–315.

96. Metsky HC, Matranga CB, Wohl S, et al. Zika virus evolution and spread in the Americas. *Nature*. 2017;546(7658): 411–415.

97. Scarpino SV, Iamarino A, Wells C, et al. Epidemiological and viral genomic sequence analysis of the 2014 Ebola outbreak reveals clustered transmission. *Clin Infect Dis*. 2015;60(7): 1079–1082.

98. Dudas G, Carvalho LM, Rambaut A, et al. MERS-CoV spillover at the camel-human interface. *ELife*. 2018;7:e31257.

99. Li LM, Grassly NC, Fraser C. Genomic analysis of emerging pathogens: methods, application and future trends. *Genome Biol*. 2014;15(11):541.

100. Grubaugh ND, Ladner JT, Kraemer MUG, et al. Genomic epidemiology reveals multiple introductions of Zika virus into the United States. *Nature*. 2017;546(7658):401–405.

101. Faria NR, Kraemer MUG, Hill SC, et al. Genomic and epidemiological monitoring of yellow fever virus transmission potential. *Science*. 2018;361(6405):894–899.

102. Wohl S, Metsky HC, Schaffner SF, et al. Co-circulating mumps lineages at multiple geographic scales [published online ahead of print June 12, 2018]. *bioRxiv*. 2018. (doi: 10. 1101/343897). Accessed 28 November, 2018.

103. Stoesser N, Giess A, Batty EM, et al. Genome sequencing of an extended series of NDM-producing *Klebsiella pneumoniae* isolates from neonatal infections in a Nepali hospital characterizes the extent of community- versus hospital-associated transmission in an endemic setting. *Antimicrob Agents Chemother*. 2014;58(12):7347–7357.

104. Klinkenberg D, Backer JA, Didelot X, et al. Simultaneous inference of phylogenetic and transmission trees in infectious disease outbreaks. *PLoS Comput Biol*. 2017;13(5):e1005495.

105. Røttingen JA, Gouglas D, Feinberg M, et al. New vaccines against epidemic infectious diseases. *N Engl J Med*. 2017; 376(7):610–613.

106. Brende B, Farrar J, Gashumba D, et al. CEPI—a new global R&D organisation for epidemic preparedness and response. *Lancet*. 2017;389(10066):233–235.

107. Kennedy SB, Bolay F, Kieh M, et al. Phase 2 placebo-controlled trial of two vaccines to prevent Ebola in Liberia. *N Engl J Med*. 2017;377(15):1438–1447.

108. Widdowson MA, Schrag SJ, Carter RJ, et al. Implementing an Ebola vaccine study—Sierra Leone. *MMWR Suppl*. 2016; 65(3):98–106.

109. Henao-Restrepo AM, Camacho A, Longini IM, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). *Lancet*. 2017;389(10068):505–518.

110. Camacho A, Carroll MW, Dean NE, et al. The ring vaccination trial: a novel cluster randomised controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola. *BMJ*. 2015;351: h3740.

111. Bellan SE, Pulliam JR, Pearson CA, et al. Statistical power and validity of Ebola vaccine trials in Sierra Leone: a simulation study of trial design and analysis. *Lancet Infect Dis*. 2015;15(6):703–710.

112. Kahn R, Rid A, Smith PG, et al. Choices in vaccine trial design for epidemics of emerging infections. *PLoS Med*. 2018;15(8):e1002632.

113. Camacho A, Eggo RM, Goeyvaerts N, et al. Real-time dynamic modelling for the design of a cluster-randomized phase 3 Ebola vaccine trial in Sierra Leone. *Vaccine*. 2017; 35(4):544–551.

114. Halloran ME, Auranen K, Baird S, et al. Simulations for designing and interpreting intervention trials in infectious diseases. *BMC Med*. 2017;15:223.

115. Berry SM, Carlin BP, Jack Lee J, et al. *Bayesian Adaptive Methods for Clinical Trials*. Boca Raton, FL: CRC Press; 2010.

116. Jackson ML, Chung JR, Jackson LA, et al. Influenza vaccine effectiveness in the United States during the 2015–2016 season. *N Engl J Med*. 2017;377(6):534–543.

117. Petousis-Harris H, Paynter J, Morgan J, et al. Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study. *Lancet*. 2017;390(10102):1603–1610.

118. Foppa IM, Haber M, Ferdinands JM, et al. The case test-negative design for studies of the effectiveness of influenza vaccine. *Vaccine*. 2013;31(30):3104–3109.

119. Sullivan SG, Tchetgen Tchetgen EJ, Cowling BJ. Theoretical basis of the test-negative study design for assessment of influenza vaccine effectiveness. *Am J Epidemiol*. 2016; 184(5):345–353.

120. Lewnard JA, Tedijanto C, Cowling BJ, et al. Measurement of vaccine direct effects under the test-negative design. *Am J Epidemiol*. 2018;187(12):2686–2697.

121. Gross PA, Hermogenes AW, Sacks HS, et al. The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. *Ann Intern Med*. 1995;123(7): 518–527.

122. Simonsen L, Reichert TA, Viboud C. Impact of influenza vaccination on seasonal mortality in the US elderly population. *Arch Intern Med*. 2005;165(3):265–272.

123. Rizzo C, Viboud C, Montomoli E, et al. Influenza-related mortality in the Italian elderly: no decline associated with increasing vaccination coverage. *Vaccine*. 2006;24(42–43): 6468–6475.

124. Moore MR, Link-Gelles R, Schaffner W, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. *Lancet Infect Dis*. 2015;15(3):301–309.

125. Kürüm E, Warren JL, Schuck-Paim C, et al. Bayesian model averaging with change points to assess the impact of vaccination and public health interventions. *Epidemiology*. 2017;28(6):889–897.

126. Grenfell BT, Anderson RM. The estimation of age-related rates of infection from case notifications and serological data. *J Hyg (Lond)*. 1985;95(2):419–436.

127. Earn DJ, Rohani P, Bolker BM, et al. A simple model for complex dynamical transitions in epidemics. *Science*. 2000; 287(5453):667–670.

128. Chaves SS, Gargiullo P, Zhang JX, et al. Loss of vaccine-induced immunity to varicella over time. *N Engl J Med*. 2007; 356(11):1121–1129.

129. Gilbert P, Self S, Rao M, et al. Sieve analysis: methods for assessing from vaccine trial data how vaccine efficacy varies with genotypic and phenotypic pathogen variation. *J Clin Epidemiol*. 2001;54(1):68–85.

130. Power RA, Parkhill J, de Oliveira T. Microbial genome-wide association studies: lessons from human GWAS. *Nat Rev Genet*. 2017;18:41–50.

131. Sealey KL, Harris SR, Fry NK, et al. Genomic analysis of isolates from the United Kingdom 2012 pertussis outbreak reveals that vaccine antigen genes are unusually fast evolving. *J Infect Dis*. 2015;212(2):294–301.

132. Murphy TV, Gargiullo PM, Massoudi MS, et al. Intussusception among infants given an oral rotavirus vaccine. *N Engl J Med*. 2001;344(8):564–572.

133. Taylor B, Miller E, Farrington CP, et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. *Lancet*. 1999;353(9169):2026–2029.

134. Dourado I, Cunha S, Teixeira MG, et al. Outbreak of aseptic meningitis associated with mass vaccination with a urabe-containing measles-mumps-rubella vaccine: implications for immunization programs. *Am J Epidemiol*. 2000;151(5): 524–530.

135. Shields WD, Nielsen C, Buch D, et al. Relationship of pertussis immunization to the onset of neurologic disorders: a retrospective epidemiologic study. *J Pediatr*. 1988;113(5): 801–805.

136. Choe YJ, Bae GR, Lee DH. No association between influenza A(H1N1)pdm09 vaccination and narcolepsy in South Korea: an ecological study. *Vaccine*. 2012;30(52):7439–7442.

137. Han F, Lin L, Warby SC, et al. Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. *Ann Neurol*. 2011;70(3):410–417.

138. Hambidge SJ, Glanz JM, France EK, et al. Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old. *JAMA*. 2006;296(16):1990–1997.

139. Ki M, Park T, Yi SG, et al. Risk analysis of aseptic meningitis after measles-mumps-rubella vaccination in Korean children by using a case-crossover design. *Am J Epidemiol*. 2003; 157(2):158–165.

140. Farrington CP. Relative incidence estimation from case series for vaccine safety evaluation. *Biometrics*. 1995;51(1): 228–235.

141. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis*. 2018;18(3):318–327.

142. Levin BR, Perrot V, Walker N. Compensatory mutations, antibiotic resistance and the population genetics of adaptive evolution in bacteria. *Genetics*. 2000;154(3):985–997.

143. Martínez JL. Antibiotics and antibiotic resistance genes in natural environments. *Science*. 2008;321(5887):365–367.

144. Siu LL, Conley BA, Boerner S, et al. Next-generation sequencing to guide clinical trials. *Clin Cancer Res*. 2015; 21(20):4536–4544.

145. Tedijanto C, Olesen S, Grad Y, et al. Estimating the proportion of bystander selection for antibiotic resistance among potentially pathogenic bacterial flora. *bioRxiv*. 2018. (doi: 10.1101/288704). Accessed 28 November, 2018.

146. Lipsitch M. Measuring and interpreting associations between antibiotic use and penicillin resistance in *Streptococcus pneumoniae*. *Clin Infect Dis*. 2001;32(7):1044–1054.

147. Schrag SJ, Peña C, Fernández J, et al. Effect of short-course, high-dose amoxicillin therapy on resistant pneumococcal carriage: a randomized trial. *JAMA*. 2001;286(1):49–56.

148. Feikin DR, Dowell SF, Nwanyanwu OC, et al. Increased carriage of trimethoprim/sulfamethoxazole-resistant *Streptococcus pneumoniae* in Malawian children after treatment for malaria with sulfadoxine/pyrimethamine. *J Infect Dis*. 2000;181(4):1501–1505.

149. Lipsitch M, Colijn C, Cohen T, et al. No coexistence for free: neutral null models for multistrain pathogens. *Epidemics*. 2009;1(1):2–13.

150. Lewnard JA, Tähtinen PA, Laine MK, et al. Impact of antimicrobial treatment for acute otitis media on carriage dynamics of penicillin-susceptible and penicillin-nonsusceptible *Streptococcus pneumoniae*. *J Infect Dis*. 2018;218(9):1356–1366.

151. Tähtinen PA, Laine MK, Huovinen P, et al. A placebo-controlled trial of antimicrobial treatment for acute otitis media. *N Engl J Med*. 2011;364(2):116–126.

152. Lessem E, Cox H, Daniels C, et al. Access to new medications for the treatment of drug-resistant tuberculosis: patient, provider and community perspectives. *Int J Infect Dis*. 2015; 32:56–60.

153. Kunkel A, Cobelens FG, Cohen T. Tradeoffs in introduction policies for the anti-tuberculosis drug bedaquiline: a model-based analysis. *PLoS Med*. 2016;13(10):e1002142.

154. Kunkel A, Furin J, Cohen T. Population implications of the use of bedaquiline in people with extensively drug-resistant tuberculosis: are fears of resistance justified? *Lancet Infect Dis*. 2017;17(12):e429–e433.

155. Bergstrom CT, Lo M, Lipsitch M. Ecological theory suggests that antimicrobial cycling will not reduce antimicrobial resistance in hospitals. *Proc Natl Acad Sci U S A*. 2004; 101(36):13285–13290.

156. van Duijn PJ, Verbrugghe W, Jorens PG, et al. The effects of antibiotic cycling and mixing on antibiotic resistance in intensive care units: a cluster-randomised crossover trial. *Lancet Infect Dis*. 2018;18(4):401–409.

157. Kuiken T, Leighton FA, Fouchier RA, et al. Public health. Pathogen surveillance in animals. *Science*. 2005;309(5741): 1680–1681.

158. Evans AS. Causation and disease: a chronological journey. The Thomas Parran Lecture. 1978. *Am J Epidemiol*. 1978; 108(4):249–258.

159. Fredericks DN, Relman DA. Sequence-based identification of microbial pathogens: a reconsideration of Koch's postulates. *Clin Microbiol Rev*. 1996;9(1):18–33.

160. Muñoz N, Castellsagué X, de González AB, et al. HPV in the etiology of human cancer. *Vaccine*. 2006;24(suppl 3): S1–S10.

161. Graham DY, Lew GM, Klein PD, et al. Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. A randomized, controlled study. *Ann Intern Med*. 1992;116(9):705–708.

162. Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med*. 2013;368(19):1791–1799.

163. Mina MJ, Metcalf CJ, de Swart RL, et al. Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality. *Science*. 2015;348(6235):694–699.

164. MAL-ED Network Investigators. The MAL-ED study: a multinational and multidisciplinary approach to understand the relationship between enteric pathogens, malnutrition, gut physiology, physical growth, cognitive development, and immune responses in infants and children up to 2 years of age in resource-poor environments. *Clin Infect Dis*. 2014;59(suppl 4):S193–S206.

165. Dagan R, Pelton S, Bakaletz L, et al. Prevention of early episodes of otitis media by pneumococcal vaccines might reduce progression to complex disease. *Lancet Infect Dis*. 2016;16(4):480–492.