

Causation in infectious disease epidemiology

The crab nebula illustrates the idea that we are all composed of elements which were created in the nuclear furnace of a supernova, and we have only known this within the last hundred years. Causation requires knowledge and is generally progressive. Aristotle identified four all kinds of cause. In case of a table the **Material cause** is the wood that the table is made from. The **Formal course** is the design, colour shape or appearance of the table. The **Efficient cause** is an agency that changes or moves to create the table, for example a carpenter. **Final cause** is the change or movement that is the reason for the table being made, in this case of dining. We will come back to the kinds of cause later in the talk.

Epidemiology is the study of patterns, causes and effects of disease conditions in defined populations. It is this cornerstone of public health, informing policy, evidence based medicine, interventions and prevention. The activities include documenting disease characteristics, examining disease aetiology, distribution and transmission, undertaking outbreak detection investigation and control and examining effectiveness of treatment including clinical trials. It also involves designing implementing and reviewing interventions. **Disease surveillance** began in the 17th-century with the establishment of bills of mortality. In London this was established through recording deaths within the parish and indicating the type of disease that people died from. The descriptions were based on a clinical cause of death, and many of the descriptions can be related to modern disease descriptions. Surveillance systems have evolved until now in the 21st-century we have range of different surveillance systems some of which are syndromic and others based on laboratory confirmed diagnoses.

John Snow is the father of epidemiology and in 1854 investigated a large outbreak of cholera in Soho in London. He examined where all the deaths had occurred and identified that the most likely source of infection was a water from a public pump. He famously removed the handle of the water pump to stop people using it and this is regarded as a classic example of intervention. Snow disproved the view that infection was spread by miasma through the atmosphere and identified other waterborne outbreaks that had occurred recently. He attributed the disease to a source (human faeces) and route of transmission (water from the Broad Street pump). Cholera is a disease that can occur in pandemics. The first pandemic was in 1817, and John Snow's investigation was during the third pandemic. The most recent pandemic, the seventh, started in Indonesia and Peru in 1961. Cholera is caused by *Vibrio cholerae*, a comma shaped bacteria, and can grow in coastal waters in association with algal blooms. It is thought that transmission of cholera around the world is facilitated by transport in cargo vessel ballast water and through infected people.

Louis Pasteur is the father of microbiology and worked on economic problems with fermentation, diseases of silkworms and a range of human and animal diseases. He established the evidence that spontaneous generation did not occur and that bacterial contamination derives from the environment. He was also involved in early attempts at vaccination and provided evidence of protective immunity.

Robert Koch and Friedrich Loeffler in 1883 developed four postulates for testing whether an organism could cause disease. 1. The microorganism must be found in all people suffering from the disease, but not in healthy people; 2. The microorganism must be isolated from a diseased person and grown in pure culture; 3. The cultured microorganism should cause disease when introduced into a healthy animal model; 4. The microorganism must be re-isolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent. These were extended in 1988 by Stanley Falkow to cover molecular issues relating to virulence.

The establishment of the cause of a disease was taken forward by Austin Bradford Hill in 1965 who established nine criteria that should be taken into account when considering the cause of a disease (analogy, biological gradient, coherence, consistency, experiment, plausibility, specificity, strength of association, temporality). The seasonality of infections can provide evidence, although association is not necessarily evidence of causation. The temporal occurrence of cases can result from different sorts of transmission. Two of the main analytical approaches to examining the epidemiology of infectious diseases are case-control and cohort studies. The two by two table is the basis of much of the analytical work and can involve multivariable analysis. An outbreak of Cryptosporidiosis in May 2012 will be examined, showing the range of investigations used and difficulties in the use of evidence.

Modern bacterial typing of *Salmonella* involves sequencing the whole genome sequencing and comparing to reference strains. The genetic detail allows isolates from foods to be linked to those from infected patients.

Guinea worm occurs in poor countries where water supplies are unprotected. The disease makes people temporarily unable to work, causing crop losses, social and financial problems. Infection confers little protective immunity- people in affected villages suffer regularly. The worm infects copepods (water fleas) that are swallowed in drinking water (the only way the infection can be transmitted). The worm grows in the leg and larvae are released into the water where they infect copepods. There is a dog reservoir. Diagnosis is easy (presence of an emerging worm). Interventions are effective, low cost, and simple to implement. Interventions include integrated community-based surveillance, immediate case reporting, regular zero case reporting, case containment, global and national databases. Interruption of transmission with case-containment measures (stopping people with a Guinea worm ulcer from entering water used for drinking water), improved water supply systems, filtering water fleas from drinking water, treating water sources with a chemical that kills water fleas (e.g. Abate), health education, certification and advocacy. An eradication campaign through the Carter Foundation, WHO, CDC, UNICEF was established in 1981. There were around 3.5 million infected people in 21 countries in 1986 while in 2017 there were 25 cases ; Chad (16); Ethiopia (3); South Sudan (6). Remaining cases are in areas of civil war.

In summarising the causes of infectious diseases the focus is naturally on the microbial cause, but other issues include personal differences, weather, water supply and waste water disposal, particular transmission routes, animal sources and environmental reservoirs, agriculture and the food industry and behavioural risks. The evolution of both pathogen and host are important. There are a range of other environments including the Public Environment, Socio-Political Environment, Institutional Environment, Research Environment, Public Health Environment, Technological Environment, Intervention Environment and Public Concern Environment. There are a variety of ways in which disease can be attributed to these factors.

Can we modify Bradford Hill Criteria or other approaches to causation for general use? The extension of Aristotle's causes may be possible, but causation in infectious diseases is predominantly a practical business that involves a reliable surveillance dataset, simple descriptive methods, statistically sophisticated analysis, modern genetic typing and a clear understanding of how to intervene to limit outbreaks and reduce the burden of disease in the future.

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