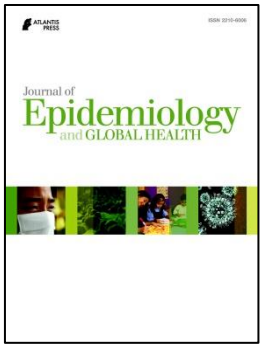

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REVIEW ARTICLE

Bradford Hill's criteria, emerging zoonoses, and One Health

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Abstract Zoonoses constitute more than 60% of infectious diseases and 75% of emerging infectious diseases. Inappropriate overemphasis of specialization of disciplines has ignored public health. Identifying the causes of disease and determining how exposures are related to outcomes in ''emerging zoonoses" affecting multiple species are considered to be the hallmarks of public health research and practice that compels the adoption of ''One Health". The interactions within and among populations of vertebrates in the causation and transmissions of emerging zoonotic diseases are inherently dynamic, interdependent, and systems based. Disease causality theories have moved from one or several agents causing disease in a single species, to one infectious agent causing disease in multiple species-emerging zoonoses. Identification of the causative pathogen components or structures, elucidating the mechanisms of species specificity, and understanding the natural conditions of emergence would facilitate better derivation of the causal mechanism. Good quality evidence on causation in emerging zoonoses affecting multiple species makes a strong recommendation under the One Health approach for disease prevention and control from diagnostic tests, treatment, antimicrobial resistance, preventive vaccines, and evidence informed health policies. In the tenets of One Health, alliances work best when the legitimate interests of the different partners combine to prevent and control emerging zoonoses.

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Contents

1. Introduction

Humans are members of the animal kingdom. Genetically, the human genome shows 99% similarity to great apes and 95% similarity to pigs. Therefore, humans can be considered as remodeled chimpanzee-like apes [1]. Although there is taxonomic relatedness among the species and other common features exist within the vertebrates of the animal kingdom, the crucial drivers of disease invasion and disease causal mechanisms of the infectious agents (zoonoses) are considered to be not straightforward.

A catalog reports that zoonoses constitute >60% of all known infectious diseases and 75% of emerging infectious diseases. Approximately 40% of fungi, 50% of bacteria, 70% of protozoa, 80% of viruses, and 95% of helminths that infect human beings are zoonotic. More than 50% of the recognized pathogens of human beings can infect other vertebrate hosts [2]. Only 100 of the 400 or so known emerging pathogens occur only as human pathogens [3]. Among the marine mammal pathogens, at least 49% are zoonotic, and 28% are emerging zoonoses [4].

This review neither attempts to reignite the debate between realism and pragmatism in causal theories, nor identifies deficiencies in Koch—Henle postulates or Sir Austin Bradford Hill's criteria, but aims to interpret the causation of emerging zoonoses in the fundamentals of One Health. Briefly, a cause of a disease is a factor, event, characteristic, or condition that affects its incidence; elimination of the cause would result in a change in disease incidence [5]. It has been continuously proven that inappropriate overemphasis of specialization of disciplines has ignored the large scale approaches to public health; identifying the causes of disease and determining how exposures are related to outcomes in ''emerging zoonoses''-assumed to be an established understanding of causal mechanisms in ''known zoonoses''-affecting multiple species are considered the hallmarks of public health research and practice. We believe that revisiting Bradford Hill's criteria on causation under One Health would strengthen public health research and policy for prevention and control of emerging zoonoses.

1.1. One Health and disease causal context in emerging zoonoses

People and animals have been in close contact since the domestication of animals, which has assisted in the swapping of diseases and their spread. The shared risks between humans and animals concerning zoonoses, compels the adoption of One Health among human and animal health professionals to identify and reduce such risks [6]. By definition, One Health is a multidisciplinary concept based on a systems approach, which amalgamates the ''collaborative effort of multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals and our environment'' [7]. Further, the One Health concept is a worldwide strategy that is expected to help protect and save millions of lives in our present and future generations [8].

In an integrated system, with regard to emerging zoonoses, One Health has the potential to result in improved effectiveness and efficiency of health-associated outcomes. Because disease causation is context dependent, the interactions within and among populations of vertebrates in the causation and transmission of emerging zoonotic diseases is inherently dynamic, interdependent, and systems based. Beyond the population dynamics, feedback among exposures and outcomes are integral to wider causal webs of the natural environment, and that generates context-dependent effects. Further, causal effects on individual and population levels are impacted by herd immunity and the threshold density of the cause. At an individual level, causal effects depend on the distribution of

population-level effects, although, population-level effects are not equivalent to the sum of individual-level effects [9].

1.2. Drivers of emerging zoonoses and transmission

Disease causality theories move from a one agent causing one disease (infectious diseases); one agent (silica, tobacco smoke) causing many diseases, and several agents or factors causing one disease (diabetes). All these relate to a single species. By contrast, this review is concerned about one infectious agent causing one disease in multiple species-emerging zoonoses.

The World Health Organization [10] defines emerging zoonosis as ''a zoonosis that is newly recognized or newly evolved, or that has occurred previously, but shows an increase in incidence or expansion in geographical, host or vector range". Important drivers (social, ecological, economic, epidemiological, and evolutionary) of zoonoses emergence and transmission are: (1) infectious dose; (2) the density of the host and vector population; (3) number of biological (microbial genetics, pathogenesis) and environmental characteristics (climate change, molecular ecology); (4) reassortment or recombination in multiple hosts, or pathogens that infect species that can harbor multiple closely related agents; (5) routes of transmission by more than one or by indirect contact; (6) anthropogenic practices (land use, travel, and intensified animal production systems); (7) antimicrobial use; (8) loss of biodiversity; and (9) breakdown of public health measures.

Furthermore, transmission of emerging zoonoses from one host to another is a product of two processes [11]: (1) contact rate, which is determined by host behavior, properties of the environment, interaction between hosts or between a host and the environment; and (2) infectivity, which is defined as the probability of infection given contact. This depends on the immune status of the host, virulence of the pathogen, host specificity, and stability of an infectious agent outside the host.

1.3. Necessary and sufficient causal mechanisms in zoonoses

In public health research, the most important emphasis is on the discovery of necessary or sufficient causes that are amenable to intervention. Briefly, a necessary cause (precondition, which is always associated with the outcome) in emerging zoonoses is the infectious agent and the outcome cannot occur without the causative agent. By contrast, a sufficient cause means complete causal mechanism, a minimal set of conditions and events that are sufficient for the outcome to occur [12]. Rabies virus is both a necessary (precondition) and sufficient (complete causal mechanism, minimal set of conditions) cause for rabies disease.

Among the 80% of the viruses that are zoonotic, a high proportion of negative-stranded RNA viruses and viruses with segmented genomes are emerging pathogens, with high mutability due to the absence of proofreading mechanisms. It has been concluded that the use of a conserved receptor is a necessary but not sufficient condition for a virus to have a broad host range encompassing different mammalian orders [13]. At the same time, receptor binding is a necessary (but not sufficient) condition to enable viral entry into a cell and successful replication [14].

In emerging zoonoses, some of the sufficient causes that operate are puzzling, such as why some viruses which are benign in their natural hosts induce a severe or lethal hyperinflammatory response in a new host (Ebola virus, Sin Nombre virus, Middle East respiratory syndrome coronavirus). Also, many zoonotic viruses that infect people cause no disease (simian foamy viruses [15]) or mild symptoms (Menangle virus [16]). Moreover, there are contributory causes which are neither necessary nor sufficient. In emerging zoonoses, identification of the causative pathogen components or structures, elucidating the mechanisms of species specificity, and understanding the natural conditions of emergence would facilitate better derivation of the causal mechanism.

1.4. Koch's postulates and Bradford Hill's criteria

Pragmatically, disease cause in zoonoses can be further explained as follows: given two or more populations (vertebrate species) of subjects that are sufficiently similar to the problem (zoonoses) under study, a disease cause is a set of mutually exclusive conditions by which these populations differ [17]. Conventionally, Koch's postulates and Bradford Hill's criteria are applied in explaining a cause.

Koch's postulates were developed in the 19th century to establish causation. Currently, a number of infectious agents-prion disease-are accepted as the cause of disease, despite their not fulfilling all of Koch's postulates. However, severe acquired respiratory syndrome fulfilled the postulates.

Bradford Hill's criteria are considered to determine causation. All of Hill's criteria have not stood the test of time. Nevertheless, they are still recognized as the starting point of many new causal explanations for emerging zoonoses. On the contrary, Bradford Hill's criteria cannot be used to dismiss the assumption of a causal relation. The most recent description of Bradford Hill's causality criteria, given by Rothman and Greenland [18] lists the following nine causality criteria which are applied to emerging zoonoses: (1) strength of the association: the stronger the association, the more likely that the association is causal and a weak association would be easier to imagine as an unmeasured confounder. However, a strong association is neither necessary nor sufficient for a cause and a weak association is neither necessary nor sufficient for the absence of causality. (2) Consistency: if more studies find similar results, the more likely it is that the association is causal. Nonetheless, lack of consistency does not rule out a causal association since some effects are produced under unusual circumstances. (3) Specificity: a specific exposure exerts a specific effect. (4) Temporality: the causal exposure should precede the disease in time and this is an inarguable criterion. (5) Biological gradient or dose response: associations of trend with increasing levels of exposure are more likely but not necessarily causal. (6) Plausibility: depends on the current knowledge of the etiology of the disease. The causal inference must be made from not only epidemiology, but also with inputs from toxicology, pharmacology, basic biology, and other sciences. (7) Coherence: refers to other observed biological effects, possibly relevant in the etiologic pathway, that makes a causal association more likely, for instance, histological changes in the target organ. (8) Experimental evidence: to Hill, experimental evidence meant a reduction in the disease rates after the causal agent has been eliminated. (9) Analogy: if a similar agent exerts similar effects, it is more likely that the association is causal.

Bradford Hill described the above listed nine criteria as viewpoints or perspectives. However, he considered the criteria as ambivalent, and pondered if any other way of explaining the cause and effect exists. In addition, Poole [19] stated that there are no universal and objective causal criteria and are yet to be identified. Therefore, considering the drivers of emerging zoonoses, population level effects and construing a cause of a disease as a factor, event, characteristic or condition that affects its incidence [5], the following supportive criteria or viewpoints to strengthen the causal explanation of emerging zoonoses may be considered: (1) outbreak: sudden increase in incidence of unknown disease; (2) species specificity: humans and type of animal species affected; (3) basic reproduction number ($R0$): measured to discern the speed of travel (transmission) of the pathogen; and (4) virulence of the pathogen: measured by case fatality rate.

Determining a cause in emerging zoonoses requires characterizing the outbreak, identifying the new disease in nonhost species, describing the transmission patterns, and measuring the case fatality rates. These viewpoints may aid Hill's criteria in the emerging disease causal contexts.

2. Conclusion

Causal inference is a distinct step in disease prevention and control, and this is not unproblematic. There is no single accepted method to establish a causal relationship between an infective agent and its corresponding infectious disease. The two main purposes of epidemiological evidence are to provide a sound understanding on causation and to recommend the basis for intervention. Both of these are dependent on causal status of the observed associations [20]. Currently, we have 70 human vaccines licensed for 30 microbes and this number is expected to rise. Public health authorities traditionally respond to emerging zoonoses by identifying disease in humans and then identifying the cause among animals, or at best, by identifying risk factors related to human infection from animals.

Specific geographical regions or interfaces between people, wildlife, livestock, and the environment have been identified as the origins of recent emerging zoonoses, e.g., Ebola viral disease, and thus are the targets for intense surveillance. Analysis of previous emergence events has led to a better understanding of the causes (drivers) of emergence. Predicting pandemics needs a better understanding of the dynamics of pathogen transmission, ecology, and evolution. These advances in causation in One Health can provide valuable insights into pathogen ecology and can inform zoonotic disease-control programs, evidence-based policies and practices. In the tenets of One Health, alliances work best when the legitimate interests of the different partners combine to prevent and control emerging zoonoses.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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