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Review of Terms Used in Modelling Influenza Infection

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Prepared for the
National Collaborating Centre
for Infectious Diseases
September 2014

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Introduction

This document provides a review of terms commonly used in modelling studies of influenza infection spread and control. The objective is to understand the similarities and discrepancies between definitions of the same terms used in different studies. Greater awareness of where divergence occurs and a more explicit approach to defining terms should help standardize terms used in different areas, including medical and infectious disease epidemiology, public health, and disease modelling. As a future goal, standardization of terms should reduce variation in study results produced by different research communities, and should improve the accessibility and policy-relevance of new knowledge for public health decision-makers.

For this review, we considered PubMed, Google Scholar, and Scopus as search engines for sources containing definitions of these terms, using each term as a keyword. The sources considered here include systematic reviews, peer-reviewed published articles, books, advisory health reports, and websites of public health agencies and organizations (e.g. World Health Organization, U.S. Centers for Disease Prevention and Control, Public Health Agency of Canada, European Center for Disease Control). The type of source was determined primarily based on the methods and materials used in the study. Although, by this method, types are not necessarily standard across all sources, they provide readers with a basic context of how and to what end each definition was used. Based on their use in modelling studies, terms were also classified in four main categories: (i) infection transmission; (ii) timelines of infection; (iii) epidemiological and clinical characteristics; and (iv) disease specific parameters. All definitions provided below have been reproduced verbatim, with the addition of a few editorial notations for clarity, signified by square brackets, e.g. [ ].

It is important to note that some of these definitions may be very specific to the context of the study from which they were derived and may not be generalizable to the context of influenza infection. Nevertheless, efforts were made to consider definitions in their original contexts as part of the analysis, and to reflect key conceptual elements in 'comments'. For each term, the comments identify common features across all definitions retrieved by the review and highlight areas where further clarity can be achieved. As well, the commentary explains the role or importance of certain concepts for modelling.

1. Infection Transmission

Close Contact

Definitions (*Source*)	**Type of source**
1. Close contacts were defined as individuals known to have been within 1 m, or had direct contact with respiratory secretions or faecal material of a patient with confirmed infection *(Li et al., 2014)*	*Epidemiology, data analysis, surveillance*
2. Close contact (<6 feet) *(de Perio et al., 2012)*	*Epidemiological, clinical, data analysis*
3. Close contact (less than one metre) *(Influenza team (ECDC), 2007)*	*Influenza transmission and control report, advisory policy and practice*
4. Published clinical observations suggest that influenza transmission usually occurs when the susceptible host and infectious source are within close proximity (less than two metres) *(Public Health Agency of Canada, 2011)*	*PHAC planning document for prevention and control of a pandemic in all healthcare settings*
5. Droplet and contact transmission are traditionally defined as requiring close contact to occur, whereas airborne transmission may occur over much larger distances. As such, transmission of natural infection is seen over long (greater than 1 m between source and susceptible individual) and shorter (less than 1 m between source and susceptible individual, such as during a casual conversation) distances, for those agents spread via the airborne route. *(Brankston, Gitterman, Hirji, Lemieux, & Gardam, 2007)*	*Systematic review of influenza transmission*

Comment

The term 'close contact' has been defined according to proximity to an infectious individual or an environment contaminated with an infectious agent. It is important to note that although infection usually occurs as a result of 'close contact' (Public Health Agency of Canada, 2011), it is not necessarily the case that every close contact will lead to infection. Two threshold measures of proximity relevant to influenza are quoted in the literature, that is, a distance within either one metre or six feet (approximately two metres) of an infectious individual or agent. The WHO recommendation for a distance of about 1 metre from individuals who show symptoms of influenza-like illness, such as coughing and sneezing, aims to minimize infection transmission. However, transmission of influenza virus, primarily in small-particle aerosols, has been reported for healthcare professionals within 1.8 metre of patients with influenza (Bischoff, Swett, Leng, & Peters, 2013), suggesting that influenza viruses could travel up to 6 feet. In most modelling studies, the measurements for 'close contact' are not explicitly included in the model structure, and this term is generally referred to as a proximity in which infection transmission can occur.

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Exposure

Definitions (*Source*)	**Type of source**
1. Immediate proximity of infectious respiratory droplets or self-inoculation from contaminated hands after contact with infectious secretions on environmental surfaces *(Patrozou & Mermel, 2009)*	*Systematic review, viewpoint*
2. State of being in contact with an infected individual *(Ferguson, Mallett, Jackson, Roberts & Ward, 2003)*	*Modelling and epidemiology*
3. Exposure to an influenza virus occurs when a susceptible host comes into contact with an infected source or contaminated environment (e.g., inanimate/animate objects or via virus particles in the air). The three modes of potential respiratory pathogen exposure/transmission include contact, droplet, and airborne *(Public Health Agency of Canada, 2011)*	*PHAC planning document for prevention and control of a pandemic in all healthcare settings*
4. Presence within 6 ft of a patient, or having any direct droplet spray from a cough or sneeze without adequate personal protective equipment (*Poalillo, Geiling, & Jimenez, 2010)*	*Clinical and epidemiology, healthcare settings control practices*
5. Proximity and/or contact with a source of a disease agent in such a manner that effective transmission of the agent or harmful effects of the agent may occur. *(Porta, 2008)*	*Epidemiology reference dictionary*

Comment

Exposure appears to be defined according to proximity of an infectious person or an environment contaminated with the infectious agent. Any contact within a close proximity is referred to as exposure to infection. The literature on a measurable distance that specifies this proximity is rather scant, and what constitutes 'immediate proximity' to the infectious agent or contaminated environment requires further clarification. It is also worth noting that exposure is usually considered independently of the immune status (e.g., susceptibility or protection level) of the (exposed) individual in close proximity to an infectious person or contaminated environment. Consequently, it cannot be assumed that an individual who is exposed will become infected.

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2. Timelines of Infection

Latent Period [Exposed Period]

Definitions *(Source)*	**Type of source**
1. Time from infection to infectiousness *(Tuite et al., 2010)*	*Modelling, statistical data analysis, simulations, epidemiology*
2. The period between the moment of infection and the beginning of the infectious period *(Scalia Tomba, Svensson, Asikainen, & Giesecke, 2010)*	*Modelling, epidemiology*
3. The time between infection and becoming infectious *(Lessler, Reich, Brookmeyer et al., 2009)*	*Systematic review*
4. Representing the interval between exposure and infectiousness in an individual *(Moghadas et al., 2009)*	*Modelling, simulations and epidemiology*
5. Influenza transmission is often studied using the standard Susceptible–Exposed–Infectious–Removed (SEIR) model, where an infected individual is first latent (or exposed: infected but not infectious), then infectious, before being removed. *(Cori et al., 2012)*	*Epidemic modelling, statistical analysis*
6. The period of time beginning when an individual first harbors an agent and ending when that individual becomes infectious. *(Rvachev & Longini, 1985)*	*Modelling and epidemiology*
7. The period of time beginning when an individual first harbors an agent of disease and ending when that individual becomes infectious. *(Longini, Ackerman, & Elveback, 1978)*	*Modelling*
8. Exposed (infected but not yet infectious) stage *(Wallinga & Lipsitch, 2007)*	*Modelling, statistical analysis*
9. Exposed state refers to the period of time following transmission of infection during which the newly infected person cannot transmit the disease and symptoms are absent before developing clinical disease *(Mostaço-Guidolin, Bowman, Greer, Fisman, & Moghadas, 2012)*	*Modelling and epidemiology*
10. Time from infection to onset of infectiousness *(Lipsitch et al., 2003)*	*Modelling, epidemiology statistical analysis*
11. Time from infection to infectiousness *(Fine, 2003)*	*Epidemiology*
12. The time between initiation of infection and first shedding or excretion of the agent *(Porta, 2008)*	*Epidemiology reference dictionary*

Comment

Latent period and exposed period have been used interchangeably in many studies to define the time elapsed since exposure before a person becomes infectious. During this period, an infected individual is not infectious, and cannot transmit the disease. While there is general consensus on the definition of this term, some imprecision remains in denoting the end point of the period, as when some employ the term 'infectiousness' (a characteristic of disease) rather than the 'onset of infectiousness' (a point in time). Furthermore, the term 'exposed period' may be interpreted as a period of time during which exposure may take place. Several modelling studies have demonstrated the importance of the latent period for exploring intervention strategies, particularly for evaluating the impact of post-exposure prophylaxis (as a control measure offered following exposure and before the onset of symptoms) for prevention and mitigation of illness.

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Incubation Period

Definitions *(Source)*	**Type of source**
1. Time from infection to onset of symptoms *(Tuite et al., 2010)*	*Modelling, statistical data analysis, simulations, epidemiology*
2. The time between infection and disease onset (the length of time between infection with a pathogen and the onset of symptoms) *(Reich, Lessler, Cummings, & Brookmeyer, 2009)*	*Statistical and data analysis*
3. (Time) from infection to symptoms *(Cowling, Fang, Riley, Malik Peiris, & Leung, 2009)*	*Statistical modelling, epidemiology*
4. Time from infection to the onset of symptoms *(Donnelly et al., 2011)*	*Statistical modelling, analysis, epidemiology*
5. Time between infection and symptoms *(Boëlle, Ansart, Cori, & Valleron, 2011)*	*Systematic review parameter estimation*
6. The time between infection and the onset of symptoms *(Lessler, Reich, Cummings et al., 2009)*	*Case study of school outbreak*
7. Time between infection and symptom onset *(Lessler, Reich, Brookmeyer et al., 2009)*	*Systematic review*
8. A combination of two stages: (i) a latent stage representing the interval between exposure and infectiousness in an individual; and (ii) an asymptomatic infectious stage, which represents the interval between the end of latency and the onset of clinical symptoms (referred to in this study as pre-symptomatic infection) *(Moghadas et al., 2009)*	*Modelling, simulations, epidemiology*
9. The period of time beginning when an individual first harbors an agent and ending when that individual begins to manifest symptoms of disease *(Rvachev & Longini, 1985)*	*Modelling, epidemiology*
10. The interval between exposure to an etiologic factor and the onset of symptoms or disease detection *(Armenian & Lilienfeld, 1983)*	*Review of incubation period, epidemiology*
11. The period of time beginning when an individual first harbors a disease agent and ending when that individual begins to experience symptoms of disease *(Longini et al., 1978)*	*Modelling*
12. Time from infection to clinical onset *(Fine, 2003)*	*Epidemiology*
13. The time interval between invasion by an infectious agent and appearance of the first sign or symptom of the disease in question *(Porta, 2008)*	*Epidemiology Reference Dictionary*

Comment

The incubation period is commonly used in epidemiological and modelling studies. These studies appear to have consensus on this term, referring to a time interval that starts from exposure of an individual and ends at the onset of clinical symptoms.

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Infectious Period

Definitions (*Source*)	**Type of source**
1. The infectious period or duration of infectiousness is defined as the time period during which contact with an (symptomatic or asymptomatic) infected host may lead to an infection *(Louz, Bergmans, Loos, & Hoeben, 2010)*	*Review of modelling studies*
2. The period of time when an infected individual can spread the agent to other individuals. This period begins at the end of the latent period and usually ends with recovery *(Rvachev & Longini, 1985)*	*Modelling and epidemiology*

Comment

While infectious period is one of the main terms used in influenza studies, the literature on its definition is rather scant. Most studies use or estimate this period with the assumption that it is well defined. Two studies have specifically defined the infectious period, and agree on the time interval during which an infected individual can transmit the infection. In modelling studies, recovery is considered as the end of the infectious period; however, it is important to note that in epidemiological and/or clinical contexts, recovery is commonly associated with the resolution of symptoms and may not necessarily coincide with the end of the infectious period. Notably, the likelihood of transmission is not dependent upon the illness status of the infected individual; they may be asymptomatic, pre-symptomatic, or symptomatic.

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3. Epidemiological and Clinical Characteristics

Protection

Definitions (*Source*)	**Type of source**
1. Full protection is defined as HI titre ≥ 40 to all three influenza antigens; partial protection is defined as HI titre ≥ 40 to one or more influenza antigens *(Anderson et al., 1999)*	*Clinical, seroconversion tests*
2. The average person will be exposed to the influenza virus many times over the course of his or her life and will thus build up a degree of immunity toward similar strains of the virus. This increased protection can be attained either through natural exposure or regular influenza vaccinations. This acquired immunity, however, will not help in the event of a novel or "pandemic" influenza strain. *(The Expert Panel of Influenza and Personal Protective Respiratory Equipment, 2007)*	*Expert panel assessment report on influenza transmission and personal protective equipment*
3. A subject is said to be seroprotected if the antibody level is above a certain cut-off level. This cut-off level for seroprotection is usually defined as the antibody level at which the probability of clinical protection is (assumed to be) 50% if exposed to infection. Seroprotection is not identical with clinical protection, but implies a moderate to high probability of clinical protection. If a subject is seroprotected, the probability of being clinically protected is at least 50% (i.e. moderate), but may be higher, depending on the antibody level. *(Nauta, Beyer, & Osterhaus, 2009)*	*Modelling, statistical analysis, antibody assay*
4. To protect, antibodies must be functional in the sense of neutralization or opsonophagocytosis. Correlates of protection after vaccination are sometimes absolute quantities but often are relative, such that most infections are prevented at a particular level of response but some will occur above that level because of a large challenge dose or deficient host factors. There may be >1 [more than one] correlate of protection for a disease, which we term "cocorrelates." Either effector or central memory may correlate with protection. *(Plotkin, 2008)*	*Clinical, immunological*
5. The proportion of subjects with post-vaccination HAI [hemagglutination-inhibition assay] antibody titers at >=2 cut-points (32 and 64, termed ''seroprotection'') *(Ohmit, Petrie, Cross, Johnson, & Monto, 2011)*	*Clinical and statistical analysis*
6. Based notably on the observations made in a seminal paper by Hobson et al. (Hobson, Curry, Beare & Ward-Gardner, 1972), a HI titre of 1:40 is generally accepted to be associated with a 50% reduction in the risk of illness in a susceptible population (Hannoun, Megas & Piercy, 2004), and can be referred to as the 50% protective titre (50% PT)... seroprotection rates (i.e. percentage of subjects with a HI titre above the 1:40 threshold for protection) *(Coudeville et al., 2010)*	*Review of clinical and immunological studies for data collection, statistical modelling*

Comment

In clinical studies, protection is defined on the basis of level of antibody titres specific to the infectious pathogen. The degree of protection could vary widely from partial to full, depending on the level of antibody titers that result from exposure to natural infection or vaccination. In modelling and epidemiological contexts, protection is largely considered as reduced susceptibility to acquiring infection. However, in most modelling studies, particularly in those with deterministic systems, individuals are assumed to be either fully susceptible or fully protected. Studies that employ models with heterogeneous structure may be able to consider protection of individuals in a range that varies from partial to full, determined by the level of pre-existing immunity. This variation is an important consideration for modelling studies as it is useful to account for the effect of pre-existing immunity in the context of cross-protection (i.e., effective protection level conferred by prior vaccination or natural infection) against the specific strain in an epidemic scenario. Furthermore, the level of protection could have significant implications beyond infection prevention, including (potentially) reduced probability of developing symptomatic infection, severe illness, complications, or death. This reduced probability could measurably affect the modelling outcomes and estimates of parameters.

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Susceptibility

Definitions (*Source*)	**Type of source**
1. Antibody titer of less than 1:10 *(Gold et al., 1973)*	*Clinical, immune assay*
2. A 'susceptible host' is an individual not possessing sufficient immunity against a particular infectious agent to prevent contracting an infection when exposed to an infectious agent *(Public Health Agency of Canada, 2011)*	*PHAC planning document for prevention and control of a pandemic in all healthcare settings*
3. The susceptibility of a child is defined as the probability that, on fully effective contact with a maximally infectious child, the uninfected child will become infected *(Adalja, Crooke, & Hotchkiss, 2010)*	*Modelling and simulations*
4. Susceptible state consists of those individuals who can incur infection but (are) not yet infected *(Longini et al., 1978)*	*Modelling*
5. Vulnerability; lack of resistance to disease; the dynamic state of being more likely or liable to be harmed by a health determinant *(Porta, 2008)*	*Epidemiology reference dictionary*

Comment

In clinical settings, susceptibility refers to a low amount of antibody titres in an individual. In an epidemiological context, this term is used to define the state of an individual being at risk of acquiring infection due to inadequate immune protection. In modelling, susceptibility refers to a state of a person who can become infected. Since susceptibility and protection have varying levels, and are interrelated concepts, further clarification is required for the use of these terms depending on the context in which they are used. For example, the development of asymptomatic or clinical infection does not necessarily presuppose full susceptibility (or lack of any protection) for the infected individual at the time of exposure. Some studies with deterministic systems have considered a reduction factor for infection transmission in individuals with reduced susceptibility (or with partial protection). However, since this reduction factor depends on the level of susceptibility (or pre-existing immune protection), heterogeneous systems can more realistically represent this variability in infection transmission at the individual level.

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Infected / Infection

Definitions (*Source*)	**Type of source**
1. More than fourfold rise in pre- hemaglutination-inhibition antibody, or viral shedding (positive nasal wash cultures) at least 1 day after inoculation *(Carrat et al., 2008)*	*Systematic review of volunteer challenge studies*
2. Adsorption of red cells to infected cells is the basis for preliminary identification of influenza infection *(Knight, 1976)*	*Influenza text book*
3. More than fourfold increase in hemaglutination-inhibition antibody titer between serology at baseline and in serum during convalescence *(Halloran, Hayden, Yang, Longini, & Monto, 2007*	*Review of clinical trials for effects of antiviral drugs*
4. According to the World Health Organization, micro-neutralization titers >80 are indicative of infection but must be confirmed by a second serologic test because of the possibility of cross-reactivity *(Le et al., 2013)*	*Clinical methodology, identification of subclinical avian influenza*
5. Harboring an agent of disease *(Rvachev & Longini, 1985)*	*Modelling and epidemiology*
6. The infected state consists of those individuals in which the agent is multiplying, although they may not yet be infectious. *(Longini et al., 1978)*	*Modelling*
7. The entry and development or multiplication of an infectious agent in the body of man or animals *(Porta, 2008)*	*Epidemiology reference dictionary*

Comment

In several modelling studies, it is apparent that the terms 'infected' and 'infectious' have been used interchangeably, while these terms may indicate different clinical or epidemiological states of a person. In general, 'infected' has been defined in two ways: (i) an individual who is harboring an infectious agent, and may or may not be infectious; (ii) the amount of antibody-specific titre above a certain threshold due to stimulation of the adaptive immune system by the infectious pathogen. In epidemiological models, the former is generally used to define an infected individual, which is commonly assumed to be infectious in a deterministic modelling structure. In these models, exposure is also assumed to lead to infection; however, it is not necessarily the case that every exposure leads to infection. One of the advantages of probabilistic models, such as agent-based models, is their capacity to account for the probabilities associated with this type of event. The terms 'infected' and 'infectious' require further clarification in modelling studies.

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Asymptomatic Infection

Definitions (*Source*)	**Type of source**
1. Never symptomatic, but clear viral shedding on multiple days *(Woods et al., 2013)*	*Clinical and epidemiological*
2. [Transmission from] people who are infected but never develop symptoms *(Influenza team (ECDC), 2007)*	*Influenza transmission and control report, advisory policy and practice*
3. Individuals with either no or only mild clinical symptoms and who would typically not display health seeking behaviour but would continue normal behavioural patterns in terms of workplace, school and family contacts *(Ferguson, Mallett, Jackson, Roberts & Ward, 2003)*	*Modelling and epidemiology*
4. After the latent period, exposed individuals either develop clinical disease or undergo an asymptomatic phase without showing symptoms for the entire course of infection *(Alexander et al., 2007)*	*Modelling and epidemiology*
5. An exposed individual may become infectious after the latent period and shed virus without showing clinical symptoms; this is referred to as asymptomatic infection *(Moghadas, Bowman, Rost, Fisman, & Wu, 2009)*	*Modelling and epidemiology*
6. A person or animal harboring a specific infectious agent in the absence of discernible clinical disease and serves as a potential source of infection. The carrier state may occur in an individual with an infection that is inapparent throughout its course (known as a healthy or asymptomatic carrier) *(Porta, 2008)*	*Epidemiology reference dictionary*

Comment

Asymptomatic infection has commonly been referred to as a stage of illness during which infection transmission can occur. Asymptomatic individuals are infectious and shed virus, although perhaps at lower levels than symptomatic individuals. Most studies consider asymptomatic infection to be a stage of illness without any signs of clinical symptoms. However, some studies (Ferguson et al, 2003) have included individuals with mild clinical symptoms (who do not seek care) within the definition of asymptomatic infection. In an epidemiological context, mild clinical symptoms may be considered as symptomatic infection regardless of behavioural patterns in seeking care. Distinguishing between symptomatic and asymptomatic infections is important in modelling the spread of influenza infection, which could potentially influence model-based recommendations for control strategies (Laskowski et al., 2014; Moghadas et al., 2008). In modelling studies aimed at estimating clinical attack rate, this distinction is imperative.

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Pre-symptomatic Infection

Definitions *(Source)*	**Type of source**
1. Transmission from people who will become sick with influenza before they develop symptoms *(Influenza team (ECDC), 2007)*	*Influenza transmission and control report, advisory policy and practice*
2. Asymptomatic infectious stage, which represents the interval between the end of latency and the onset of clinical symptoms (referred to in this study as pre-symptomatic infection) *(Moghadas, Bowman, Röst, Fisman, & Wu, 2009)*	*Modelling and epidemiology*
3. (A period) during which transmission can occur before symptoms appear *(Alexander et al., 2007)*	*Modelling and epidemiology*
4. (A period) during which the disease can be transmitted but clinical symptoms are absent *(Laskowski et al., 2013)*	*Modelling and epidemiology*
5. From initiation of disease to the first appearance of symptoms and/or signs. *(Porta, 2008)*	*Epidemiology reference dictionary*

Comment

Although pre-symptomatic infection has generally been considered as part of another stage of illness (i.e., incubation period), several studies have explicitly considered this to be a distinct stage of illness. This term is commonly referred to as a stage of illness preceding symptomatic infection when infection transmission is possible, but clinical symptoms are absent. The distinction between pre-symptomatic and asymptomatic infection in modelling studies may be important in evaluating the effect of intervention strategies. For example, post-exposure prophylaxis may be initiated during pre-symptomatic infection, and converted to antiviral treatment after the onset of symptoms. However, individuals with asymptomatic infection may continue with post-exposure prophylaxis without being offered antiviral treatment due to the absence of symptoms.

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Infectiousness

Definitions (*Source*)	**Type of source**
1. A characteristic of a disease that concerns the relative ease with which it is transmitted to other hosts. A droplet spread disease, for instance, is more infectious than one spread by direct contact. The characteristics of the portals of exit and entry are thus also determinants of infectiousness, as are the agent characteristics of ability to survive away from the host and of infectivity *(Last, 2001; Porta, 2008)*	*Epidemiology reference dictionary*
2. Influenza infectiousness is usually equated to the presence of virus shedding *(Carrat et al., 2008)*	*Systematic review of volunteer challenge studies*
3. Infectiousness has been inferred based on the presence of influenza in the upper respiratory tract rather than from transmission experiments. Although asymptomatic individuals may shed influenza virus, studies have not determined if such people effectively transmit influenza *(Patrozou & Mermel, 2009)*	*Systematic review, viewpoint*
4. Infectiousness is defined as the probability that a contact between a fully infectious child and a fully susceptible child will result in transmission of the virus to the susceptible child *(Adalja et al., 2010)*	*Modelling*
5. A characteristic of the disease agent that embodies capability to enter, survive and multiply in the host. A measure of infectivity is the secondary attack rate. *(Morris & Jackson, 2005)*	*Epidemiological report on control of avian influenza*

Comment

There are apparent discrepancies in the use of 'infectiousness' in different contexts. In clinical and most epidemiological studies, it is referred to as a characteristic of the disease, which is subject to the identification of an infectious pathogen or its shedding (transmission). In some modelling studies, this is referred to as the presence of symptoms, or even probability of pathogen transmission, a concept that is also referred to as 'transmissibility'. It may also be useful to distinguish 'infectiousness' (a continuous characteristic) from 'infectious' (binary characteristic), although no such distinction was found in the literature. Consistency in use of this terminology between modelling and clinical/epidemiological studies is currently not established.

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4. Disease Specific Parameters

Generation Time

Definitions *(Source)*	**Type of source**
1. Average delay from a person's being infected to that individual's infecting other people *(Carrat et al., 2008)*	*Systematic review of volunteer challenge studies*
2. Average time between the infection of an infector [infected individual] and the infection of their infectees [secondary cases], calculated on a per infector basis *(Cowling et al., 2009)*	*Statistical modelling, epidemiology*
3. Time from the moment one person becomes infected until that person infects another person. The actual time (although usually unobservable) between the moments of infection *(Scalia Tomba et al., 2010)*	*Modelling, statistical analysis*
4. Time interval between the date of infection of one case and that of its infector *(Boëlle et al., 2011)*	*Systematics review parameter estimation*
5. The time between successive onsets of symptoms in a chain of transmission *(Lessler, Reich, & Cummings, 2009)*	*Case study of school outbreak*
6. The mean serial interval or generation time is the average time between new infection and transmission to another susceptible *(Longini et al., 2005)*	*Modelling and epidemiology*
7. Serial interval or generation time is the average interval from infection of one individual to when their contacts are infected *(Ferguson et al., 2005)*	*Modelling and epidemiology*
8. The mean generation interval, defined as the mean duration between time of infection of a secondary infectee and the time of infection of its primary infector (sometimes this is called the serial interval or generation time) *(Wallinga & Lipsitch, 2007)*	*Modelling, statistical analysis*
9. The interval between receipt of infection by the host and the latter's maximal infectivity. This applies to both clinical cases and inapparent [asymptomatic] infections. With person-to-person transmission of infection, the interval between cases is determined by the generation time *(Porta, 2008)*	*Epidemiology reference dictionary*

Comment

Generation time has been a source of much debate, mostly in modelling and epidemiological studies. There are different perspectives on its definition, usefulness, and approaches to estimate it. In several studies, generation time is used to determine the time interval between the onset of infectivity (ability to infect others) in the first infectious case in the epidemic and the onset of infectivity in the first secondary case infected by the first case. Since this time interval is used to estimate other epidemiologic parameters, the identification of the first infectious case in the epidemic is of critical importance (but not necessarily possible). Other studies have only used this interval for the two successive (one caused by the other) infections, and a subset of these studies suggests that generation time should be an average of all intervals for the successive infections throughout the epidemic. Clearly, as the epidemic spreads, herd immunity increases and may pass a certain threshold that decelerates the rate of infection spread. This would lead to an increase in the time interval between infectivity of two successive infections, and therefore inflate the estimate of generation time. There is also no general consensus on statistical methods to calculate this time interval, and different studies suggest different methods to reduce bias. A number of studies have also used generation time and serial interval (to be defined below) interchangeably. Although one may be used as a close approximation for the other, they conceptually refer to two different time intervals.

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Serial Interval

Definitions *(Source)*	**Type of source**
1. Average time from onset of infectiousness in a case to the onset of infectiousness in a person infected by that case *(Tuite et al., 2010)*	*Modelling, statistical data analysis, simulations, epidemiology*
2. Clinical-onset serial interval of human influenza infection is the time between onset of symptoms in an index case and a secondary case; The serial interval is the sum of 2 distinct phases of the natural history of influenza infection, namely, the infectious period (from exposure to infection) and the incubation period (from infection to symptoms) *(Cowling et al., 2009)*	*Statistical modelling, epidemiology*
3. Time between two similar, well-defined, observable events, such as appearance of symptoms. *(Scalia Tomba et al., 2010)*	*Epidemic modelling*
4. The duration of time between the onset of symptoms of an index individual and the onset of symptoms of an infected contact *(Donnelly et al., 2011)*	*Statistical modelling, analysis, epidemiology*
5. Time between symptoms onset in primary case and secondary case *(Boëlle et al., 2011)*	*Systematics review parameter estimation*
6. The time between infections in consecutive generations *(White et al., 2009)*	*Statistical analysis, parameter estimation*
7. The interval between the onset of symptoms in a case patient and the onset of symptoms in the household contacts who were infected by that patient *(Cauchemez et al., 2009)*	*Clinical, epidemiology, parameter estimation*
8. Time between successive cases in a chain of transmission *(Cannell, Zasloff, Garland, Scragg, & Giovannucci, 2008)*	*Epidemiology*
9. The mean serial interval or generation time is the average time between new infection and transmission to another susceptible *(Longini et al., 2005)*	*Modelling, epidemiology*
10. Serial interval or generation time is the average interval from infection of one individual to when their contacts are infected *(Ferguson et al., 2005)*	*Modelling, epidemiology*
11. The mean generation interval, defined as the mean duration between time of infection of a secondary infectee and the time of infection of its primary infector (sometimes this is called the serial interval or generation time) *(Wallinga & Lipsitch, 2007)*	*Modelling, statistical analysis*
12. The time from the onset of symptoms in an index case to the onset of symptoms in a subsequent case infected by the index patient *(Fine, 2003)*	*Epidemiology*
13. The interval between receipt of infection by the host and the latter's maximal infectivity. This applies to both clinical cases and inapparent infections. *(Porta, 2008)*	*Epidemiology reference dictionary*

Comment

In general, most epidemiological studies refer to the serial interval as the average time between the onset of symptoms in an index case and the onset of symptoms in a secondary case infected by the index case. This time interval depends on the observable events (i.e., symptoms onset). Several modelling studies have used the same interpretation for both the serial interval and generation time; however, generation time depends on unobservable events (i.e., onset of infectivity: ability to infect others), and in the case of influenza, infectivity may begin before the onset of symptoms. There is clearly a need for further clarification of these terms, and their usefulness in modelling and epidemiological studies with disease-specific context.

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Transmissibility

Definitions *(Source)*	**Type of source**
1. Susceptibility of the population multiplied by the infectivity of the disease multiplied by the average number of contacts an individual has per day *(Tracht, Del Valle, & Hyman, 2010)*	*Modelling, epidemiology*
2. In the absence of control measures, this number is termed basic reproduction number (R_0) and defines the intrinsic transmissibility of an infectious agent *(Grundmann & Hellriegel, 2006)*	*Modelling, epidemiology*
3. An important index of transmissibility for a communicable disease is the basic reproduction number (R_0) which represents the number of secondary infections generated by a single infected case in an entirely susceptible population *(Mostaço-Guidolin et al., 2012)*	*Modelling, epidemiology*

Comment

In modelling studies, this term is quantified by the reproduction number (discussed below) for a communicable disease. However, a definition of transmissibility could consider the ability of a pathogen to be transmitted independent of the number of secondary cases of infection calculated for the reproduction number. It is worth noting that transmissibility is different from infectivity, which is defined (Porta, 2008) as the characteristic of the disease agent that embodies capability to enter, survive, and multiply in the host.

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Reproduction Number

Definitions *(Source)*	**Type of source**
1. The average number of new cases created by a single primary case in a susceptible population *(Tuite et al., 2010)*	*Modelling, statistical data analysis, simulations, epidemiology*
2. A reproduction number may be calculated at any time during an outbreak, a value larger than 1 corresponding to epidemic spread of the disease. In practice, additional qualifiers are often used when reporting a reproduction number: 'initial' in the beginning of an epidemic; 'basic' when the whole population is initially susceptible to the disease –R is in this case denoted R_0; 'effective' when the natural course of the outbreak is altered, for example, by interventions. *(Boëlle et al., 2011)*	*Systematic review, parameter estimation*
3. The average number of secondary cases per typical case in an otherwise susceptible population *(White et al., 2009)*	*Statistical analysis, parameter estimation*
4. Estimation of the average number of new cases of influenza produced by each infectious case in a fully susceptible population *(Cannell et al., 2008)*	*Epidemiology*
5. The mean number of secondary cases of infection transmitted by a single primary case in a susceptible population *(Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza et al., 2010)*	*Review, clinical, epidemiology*
6. The average number of secondary infections caused by a single typical infectious individual in a completely susceptible population *(Longini et al., 2005)*	*Modelling, epidemiology*
7. The average number of secondary infections caused by a single typical infected individual among a completely susceptible population *(Germann, Kadau, Longini, & Macken, 2006)*	*Modelling, epidemiology*
8. Average number of new infections generated by a single infected case introduced into an entirely susceptible population *(Moghadas et al., 2009)*	*Modelling, epidemiology*
9. Quantifies the transmissibility of any pathogen, which is defined as the average number of secondary cases generated by a typical primary case in an entirely susceptible population *(Ferguson et al., 2005)*	*Modelling, epidemiology*
10. Represents the number of secondary infections generated by a single infected case in an entirely susceptible population *(Mostaço-Guidolin et al., 2012)*	*Modelling, epidemiology*
11. Defined as the number of secondary infections that arise from a typical primary case in a completely susceptible population. *(Wallinga & Lipsitch, 2007)*	*Modelling, statistical analysis*
12. The expected number of secondary infectious cases generated by an average infectious case in an entirely susceptible population *(Lipsitch et al., 2003)*	*Modelling, epidemiology, statistical analysis*
13. The average number of transmissions per case *(Fine, 2003)*	*Epidemiology*

Comment

The reproduction number has a long history dating back over a century (Ross, 1911) when the prevention of malaria in India was under investigation by Sir R. Ross. This is a well-defined concept in epidemiology, and used widely in modelling, referring to the average number of secondary infections generated by a single infectious case during the entire course of infection in a fully susceptible population. Models provide a systematic way of formulating the reproduction number (commonly denoted by R_0) and characterizing important factors in disease transmission and control by examining their effects on R_0. The simplest epidemiological models (Anderson & May, 1991) yield the expression $R_0 = \beta S_0 / \alpha$, where β is the transmission rate of infection in an entirely susceptible population of size S_0, and α is the recovery rate of infected individuals (i.e., $1/\alpha$ represent the infectious period). The principal aim of public health measures is to reduce R_0 below 1 in order to make disease control feasible. This provides the criterion for improving control strategies, such as immunization that reduces S_0 (susceptibility of the population), or quarantine/isolation that lowers β (the incidence of infection).

Two areas where consensus and clarity on R_0 are lacking may warrant further consideration. First, although in modelling the calculation of R_0 is based on the assumption that the population at risk is fully susceptible to the invading pathogen, in practice, this assumption may not be fulfilled. This is particularly true for pandemic influenza for which some individuals have pre-existing cross-reactive immunity (i.e., due to prior exposure to similar strains of virus), which can reduce susceptibility and, in turn, reduce R_0. Therefore, even in the absence of interventions, the extent of susceptibility and its influence on R_0 remains a source of debate. Second, in some studies, the terms reproduction number and transmissibility of disease have been used interchangeably. However, clarification is needed where transmissibility is defined as the ability of the infectious pathogen to spread between individuals in the population and not necessarily the number of secondary infections.

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Conclusion

From this review, it is clear that many terms related to influenza infection are often poorly defined, mis-defined, or in many research articles not defined at all. The causes of this could be many-fold, including an assumption made by authors that particular terms are well-defined or well-understood, where no consensus exists. As well, definitions of some terms have drifted over time as our understanding of influenza has evolved, and our terms do not yet reflect current knowledge. In order to improve consistency in definition and use of influenza-related terms, we recommend that researchers and authors define these terms either in the context in which they are used in the document, or in a glossary section. This will help knowledge users and policymakers to better understand the research outcomes and their applicability to policy and practice, particularly for making informed decisions that requires knowledge and scientific evidence from multiple disciplines involving influenza research.

Read more about modelling and influenza

This document, and its companion piece (*A Logical Modelling Framework for Influenza Infection*), lay the groundwork for developing a common language and framework for modelling influenza. The larger goal is to encourage collaboration among modellers, infectious disease epidemiologists and public health planners, and to increase the use of modelling for decision-making on influenza.

You may be interested in other publications issued by NCCID and its partners, as part of a suite of knowledge products related to the prevention and control of influenza. The collaborative Influenza & Influenza-like Illness Project has leveraged the expertise of six National Collaborating Centres on Public Health to address recognized knowledge gaps and needs of public health and primary care professionals who work in influenza prevention. Questions remain about estimates of the burden of influenza, surveillance methods, the effectiveness of vaccination and other prevention strategies, and equitable delivery of services. Documents within the series address these and other issues.

Learn more about the 'influenza project' at www.nccid.ca/influenza.

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