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A Review of Simulation Modeling Approaches used for the Spread of Zoonotic Influenza Viruses in Animal and Human Populations

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Impact

- Overview of different methods for modeling the spread of zoonotic influenza are presented, including approaches and software applied in animals and humans.

- Summary of parameters required for modeling the spread of influenza viruses in animal and human populations are presented for ready reference.

- This review highlights the existence of significant gaps in the knowledge of influenza transmission dynamics in animals and at the animal-human interface. There is a need for more research on modeling disease spread at the animal-to-human interface.

Key words: Simulation models; modeling; zoonotic; influenza; parameters; software

Summary

Increasing incidences of emerging and re-emerging diseases that are mostly zoonotic (e.g. SARS, avian influenza H5N1, pandemic influenza) has led to the need for a multidisciplinary approach to tackling these threats to public and animal health. Accordingly, a global movement of "One-Health" or "One-Medicine" has been launched to foster collaborative efforts amongst animal and human health officials and researchers to address these problems. Historical evidence points to the fact that pandemics caused by influenza A viruses remain a major zoonotic threat to mankind. Recently a range of mathematical and computer simulation modeling methods and tools have increasingly been applied to improve our understanding of disease transmission dynamics, contingency planning and to support policy decisions on disease outbreak management. This review provides an overview of methods, approaches and software used for

modeling the spread of zoonotic influenza viruses in animals and humans, particularly those

related to the animal-human interface. Modeling parameters used in these studies are

summarized to provide references for future work. This review highlighted the limited

application of modeling research to influenza in animals and at the animal-human interface, in

marked contrast to the large volume of its research in human populations. Although, swine are

widely recognized as a potential host for generating novel influenza viruses, and that some of

these viruses, including pandemic influenza A/H1N1 2009, have been shown to be readily

transmissible between humans and swine, only one study was found related to the modeling of

influenza spread at the swine-human interface. Significant gaps in the knowledge of frequency of

novel viral strains evolution in pigs, farm-level natural history of influenza infection, incidences

of influenza transmission between farms and between swine and humans are clearly evident.

Therefore, there is a need to direct additional research to the study of influenza transmission

dynamics in animals and at the animal-human interface.

Introduction

Mathematical and computer simulation models are increasingly being used to characterize the

transmission dynamics of infectious diseases, to evaluate the effectiveness of various

intervention strategies and to guide policy decisions on disease outbreak management. Examples

include, the UK foot-and-mouth disease (FMD) outbreak in 2001(Ferguson et al., 2001b,

Ferguson et al., 2001a, Keeling et al., 2001, Morris et al., 2001), severe acute respiratory

syndrome (SARS) in 2003 (Gumel et al., 2004, Riley et al., 2003, Lipsitch et al., 2003, Lloyd-

Smith et al., 2003), and pandemic influenza (Ferguson et al., 2005, 2006, Flahault et al., 2006,

Germann et al., 2006, Gojovic et al., 2009, Halloran et al., 2008, Longini et al., 2004, Longini et

al., 2005, Flahault et al., 2009, Fraser et al., 2009, Yang et al., 2009). The application of disease

modeling has grown significantly since 2003 following the outbreaks of SARS and the highly

pathogenic avian influenza (HPAI) epidemics caused by the H5N1 virus in Asia (from its

perceived threat of generating a pandemic influenza strain) as highlighted by Lloyd-Smith et al.

(2009) and Keeling and Rohani (2008) and more recently after pH1N1 2009 outbreak. Models

have also become increasingly complex, evolving from simple deterministic compartmental

models (Arino et al., 2008, Brauer, 2008, Mills et al., 2004) to stochastic individual-based

models (Carpenter & Sattenspiel, 2009, Germann et al., 2006, Lee et al., 2009, Tsai et al., 2010,

Yang et al., 2009); with stochastic individual-based network models (Ajelli & Merler, 2008,

Chao et al., 2010, Davey et al., 2008) adding ever more realism through the use of computer

simulation.

The emergence of zoonotic diseases such as SARS and HPAI, caused by H5N1 and pH1N1

2009, together with the recognition that 58% of known human pathogens (Kwong et al., 2008)

and 60% of emerging infectious disease (Jones et al., 2008) are zoonotic diseases has heightened

research interest in zoonosis. Recognizing the need for a multidisciplinary approach in tackling

these emerging public health concerns, a global movement on "One-World / One-Health" was

initiated to foster and facilitate collaborative efforts amongst animal and human health

professionals (Harper et al., 2004). Historical evidence points to the fact that pandemics from

influenza A viruses still remains one of the major zoonotic threats to mankind, occurring over

intervals of one to four decades since pandemic influenza caused by H1N1 in 1918 (Zimmer &

Burke, 2009, Ma et al., 2009, Brown, 2000), with significant public health, livelihood and

economic consequences (Meltzer et al., 1999, Fiore et al., 2008). The pH1N1 2009 also rapidly

spread from humans to swine, with the first case reported on a swine farm in Alberta, Canada on

28 April 2009. This was linked to a carpenter employed in a swine barn, who was infected with the virus during his trip to Mexico (Howden et al., 2009, Office International des Epizooties (OIE), 2010). Subsequently, several other countries reported outbreaks in swine (20 countries as of 28 April 2010), while cases were also reported on two turkey farms in Chile and one in Canada (Office International des Epizooties (OIE), 2010). Human-to-swine transmission was suspected in almost all these outbreaks based on circumstantial evidence, with swine workers showing flu symptoms prior to outbreaks in swine (Office International des Epizooties (OIE), 2010). Furthermore, pH1N1 2009 virus transmission between pigs was demonstrated under experimental (Brookes et al., 2010, Itoh et al., 2009, Lange et al., 2009, Vincent et al., 2009) and observational studies (Pasma & Joseph, 2010, Lange et al., 2009, Howden et al., 2009). No back transmission from pigs to humans was reported except for one suspected case in Canada (Howden et al., 2009). However, this may be related to the lack of reporting systems for pH1N1 2009 humans cases acquired from pigs. This virus demonstrated the potential for the pandemic influenza viruses with swine influenza gene lineage to emerge and spread between humans and swine readily (Vincent et al., 2010). Recently, a novel swine-origin influenza A H3N2 variant virus (designated as A(H3N2)v) containing matrix gene derived from pH1N1 2009 virus was detected in humans in United States raising concern over pandemic potential of these viruses of swine origin (Lindstrom et al., 2012). It is therefore imperative to investigate epidemiological parameters influencing the transmission dynamics of pandemic influenza viruses at the swine-human interface. Similarly it is important to identify appropriate surveillance or early warning systems, and intervention strategies to respond effectively to future outbreaks. Computer simulation modeling is a useful tool for such studies. It would be of interest to know the extent of modeling research directed towards zoonotic influenza at the animal-human interface since it

presents a continuous threat to public health. In addition the role that birds and swine play in the generation of new viral strains and their transmission to humans. Therefore, this review consolidates the relevant literature on the modeling of influenza virus spread in animals (including birds) and humans. It provides an inventory of methods and approaches, including software/platforms used to model influenza viruses in animals and humans, with a particular emphasis on spread at the animal-human interface. Any differences and challenges that may exist for modeling spread of influenza between animals and humans simultaneously are also investigated. The review also identifies parameters required for modeling influenza spread between animals and humans. This should facilitate the modeling process under a range of conditions by providing parameters and methods that may be relevant under different emerging influenza epidemic or pandemic situations.

Materials and Methods

In this review, mathematical or computer simulation models refer to dynamic disease transmission models where force of infection varies with changes in the prevalence of infectious and susceptible individuals in a population over time. This differs from many statistical models where population status and parameter values remain fixed and are used to quantify association between outcome and explanatory variables (Vynnycky & White, 2010, Dohoo et al., 2009).

Search strategy

A standard search term was developed based on the review objectives to collect information on the following research questions: (a) what are the different approaches and types of mathematical

or computer simulation models used to model the spread of zoonotic influenza viruses in humans, animals or between animals and humans? (b) What modeling assumptions were used? (c) What were the parameters used in these studies? (d) What software or platforms have been used for modeling influenza between animals and humans simultaneously? The search term used across bibliographic databases was: ("mathematical model*" or "stochastic model*" or "deterministic model*" or "compartmental model*" or "epidemic model*" or "epidemiological model*" or "disease spread model*" or "simulation model*" or "transmission dynamic model*" or "agent-based model*" or "individual-based model*") and ("influenza" or "novel influenza" or "pandemic influenza" or "pandemic H1N1" or "novel H1N1" or H1N1 or H5N1 or "swine influenza" or "avian influenza" or "infectious diseases" or zoonosis or zoonoses or "zoonotic diseases"). Search fields were restricted to title and abstract while date of publication was used to exclude publications prior to 1990. Furthermore, search was limited to articles published in English. The searches were conducted on 9 February 2010 in the PubMed, CAB Abstract, ScienceDirect, and Agricola bibliographical databases. All articles retrieved from each of these four databases were imported into the bibliographic reference package, EndNote® version X2 (Thomson, Reuters, Carlsbad, CA) and duplicate articles were removed. Additional relevant articles not captured by the search term, particularly articles related to experimental or observational studies that provided relevant parameters, were retrieved based on the references contained in a number of key articles.

Screening of articles

Titles and abstracts were screened for their relevance by two reviewers. Articles deemed to be "irrelevant", such as those related to other infectious or to non-infectious diseases of animals,

humans, fish, or plants were removed. Articles were selected for review and data extraction if their abstract provided some details on mathematical or computer simulation models of influenza viruses in either animals, humans or both. Furthermore, if abstracts described the estimation of modeling parameters such as duration of disease states (incubation, latent, infectious, immune periods), contact parameters, transmission probabilities, the basic reproductive number (R_0) or generation intervals, these were also selected. Screening and selection of articles as to their relevance was reinforced using a predesigned data extraction template described below. To aid consistency in abstract screening, two reviewers pre-tested 15 articles and accepted or rejected articles were compared. Of these in only one case (Perlroth et al., 2010) did the reviewers come to a different conclusion on acceptance. On investigation it was seen that the confusion in this case was due to the fact that no guidance had been given for articles primarily focused on evaluating cost impacts of mitigation strategies. As this article also provided useful modeling parameters it was decided that it should be included. The screening criteria were further refined to provide guidance for similar cases.

Data extraction

A template was developed in Microsoft Excel® version 2007 to aid in the extraction and recording of relevant information and parameters from each selected article. Detailed information on study objectives, questions of interest, study type, model methods and approaches, software used, strain(s) of influenza virus(es), disease spread type (within or between species), population units, and type(s) of intervention evaluated, were recorded. In addition, modeled disease spread parameters were extracted according to strain of influenza viruses and unit of population (individual, household, herd or flock levels).

Inventory of model types and approaches

A summary of different modeling approaches was generated based on the research questions addressed in the selected studies. Research questions of interests were grouped into five categories, those aimed at: parameter estimation (coded as P), evaluation of the spread of the disease (S), evaluation of different types of intervention (I), method development (M), and the development of a modeling software/platform or tool (T). Many articles addressed a combination of these questions, in which case the relevant combinations of categories was recorded. The inventory of models in this review also included broad categorizations as to whether they were stochastic or deterministic, spatially explicit or not, and the type of contact structure modeled (homogeneous or heterogeneous mixing assumed or explicit contact network used).

For those unfamiliar with the range of modeling types and sometimes confusing terminology, a brief overview of some key approaches is provided below.

Deterministic model

A model in which a set of differential equations (DE) describes the flow of individuals from one disease state to another as determined by a fixed set of average parameters, and is therefore sometimes referred as an aggregate or mean-field model. This approach will produce the same predicted outcome given a set of predefined model parameters (Arino et al., 2008, Brauer, 2008, Nuño et al., 2008, Nuño et al., 2007a).

Stochastic model

Stochastic models incorporate elements of random processes into the system. The infection and transition of individuals from one state to another is determined probabilistically (Ajelli & Merler, 2008, Basta et al., 2009, Britton & Lindenstrand, 2009, Chao et al., 2010, Ferguson et al., 2005, Ferguson et al., 2006, Germann et al., 2006, Glass & Barnes, 2007, Gojovic et al., 2009, Halloran et al., 2008, Lee et al., 2009). Model parameters (e.g. disease state duration, contact frequency, or probability of transmission per contact) are specified in the form of probability distributions, and values are randomly selected from these distributions for each iteration. Accordingly, the predicted outcomes also vary by iteration. Therefore, stochastic models are typically run many times (e.g. 1000 iterations) to obtain a reasonable distribution of potential outcomes. The model types described below can be implemented in either a deterministic or stochastic manner.

Compartmental model

In a compartment model, individuals in the population are categorized into one or more subgroups (compartments) based on the similarity of certain characteristics, such as susceptibility to a particular infection, contact types and rates, and most importantly the individual's disease state (e.g. susceptible, infectious, and recovered which is why these are often referred to as "SIR" models). Infection process in the population is determined by the average behavior of the group, and individuals within each compartment are assumed to be homogenous and mixed perfectly. The flow of individuals from one compartment to another is determined by the sum of the individual's underlying probabilistic rate and the model tracks this on a collective basis during each time step of the simulation (Arinaminpathy & McLean, 2008, Arino et al.,

2008, Chowell et al., 2006a, Chowell et al., 2006b, Flahault et al., 2006, Hollingsworth et al., 2006, Nuño et al., 2007b, Tsai et al., 2010, Tuite et al., 2010b, Vardavas et al., 2007).

Agent-based / individual-based model

The disease transmission process in an agent-based or individual-based model is governed by the behavior of each individual. Rules governing disease transmission dynamics are defined at an individual level. Although the same disease states (susceptible / infectious / recovered) are used as in the compartmental model, they are only used to represent an individual's disease state at each time step of the simulation. The model keeps track of each individual (rather than the group of individuals) and adds up individuals in each disease state during each time-step of the simulation. Therefore, this type of model can capture heterogeneity of individual behavior (such as 'super-spreaders' - individuals who spread disease more readily than others as a result of a higher than average contact rate) and other sources of variation, which can have important impacts in terms of overall disease transmission dynamics. Incorporating such heterogeneity adds realism to the modeled process (Basta et al., 2009, Ferguson et al., 2006, Yang et al., 2009, Yasuda & Suzuki, 2009, Ferguson et al., 2005, Germann et al., 2006, Longini et al., 2005, Ohkusa & Sugawara, 2007).

Network model

Network models simulate disease spread in the population by explicitly taking into consideration the actual contact structures between individuals ('who is connected to whom'). Stochastic individual-based network models that simulate disease spread based on contact structures

between individuals are more complex, yet more realistic, providing more accurate predictions. However, the reliability of these models depends on the availability of contact information which is still rare in most situations (Carrat et al., 2006, Chao et al., 2010, Davey et al., 2008, Ajelli & Merler, 2008, Perlroth et al., 2010).

Gravity model

The gravity model can be used to model disease spread between different geographical locations (for example, from one province to another) by explicitly incorporating rates of movement of people which are influenced by the population sizes and distances between locations. Increased movement tends to occur with greater population size and more closely linked areas when compared to less densely populated areas that are farther apart. This approach was used to investigate influenza spread from a large city (point of introduction) to other provinces in Vietnam (Boni et al., 2009).

Metapopulation model

A metapopulation model consists of a collection of distinct subpopulations of the same species each having its own distinct dynamics, and yet being connected to other subpopulations through limited interactions. In this approach disease spread occurs through mobility or migration processes of individuals amongst subpopulations. These characteristics suggest that metapopulation modeling should provide a suitable approach for modeling the spread of pandemic influenza at global or regional levels via, for example, air travel (Balcan et al., 2009, Colizza et al., 2007, Cooper et al., 2006, Flahault et al., 2009).

Contact structure

Type and frequency of contacts between infectious and susceptible individuals is likely to play a crucial role in infectious disease transmission within a population, depending on the infectiousness and mode of transmission of the causative agent(s). Highly contagious diseases such as foot-and-mouth disease (FMD) can be transmitted over long distance through aerosol; similarly influenza or measles require less intimate contact than tuberculosis. In addition, the mixing pattern of hosts tends to play a crucial role in the way disease is transmitted. The modeling of transmission characteristics will therefore be heavily influenced by assumptions around the homogeneity or heterogeneity of mixing. Homogeneous mixing assumes that contact between different individuals occurs randomly with equal probability (e.g. each child is equally likely to make contact with any other child or adult and vice versa). Heterogeneous mixing assumes non-random mixing where some individuals or groups are more likely to be in contact with infected individuals than others (Brauer, 2008, Vynnycky & White, 2010). Furthermore, heterogeneous mixing can be assortative or disassortative. In assortative mixing, individuals belonging to the same subgroup make more contacts amongst themselves than with members of other subgroups (e.g. children are more likely to mix with other children than with adults). Disassortative mixing occurs when members of one subgroup mix more readily with members of a different subgroup than with members from within their own subgroup (e.g. sexual partners). Subgroups can be defined based on any characteristic (e.g. age group, gender, occupation, etc.) that is considered important in explaining differences in disease transmission and control. It has been noted that the assumption of homogeneous mixing, present in many models, is unrealistically simple in most situations (Brauer, 2008, Vynnycky & White, 2010).

Intervention strategies

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Approaches used for assessing different intervention strategies have been summarized by categorizing such strategies into the following groups: antiviral treatment, including prophylactic use (coded as A), vaccination prior to or during outbreak (V), school or day-care closure (S), and social distancing (D). This last category includes workplace closure, contact tracing, quarantine, isolation, cancellation of community and mass gathering, use of personal hygiene and protective equipment. In addition, movement control and depopulation of animals, including bird, are coded as (M), while air travel restrictions are coded as (T). A combination of these letters indicates that modeled assessment covered a combination of the respective intervention measures.

Modeling parameters

Parameters extracted have been summarized into three categories: (a) estimated values, where an article attempted to estimate parameters from empirical data taken from experimental, observational, or modeling studies; (b) referenced values, where values were taken from other articles; (c) assumed values, where values assumed for modeling purposes were based on either expert opinion or unpublished data sources. Furthermore, articles that estimated parameters with 95% confidence intervals are reported separately so as not to dilute them with values from other studies that only estimated mean, minimum and/or maximum values. Parameters were summarized as median and range (minimum and maximum values) of means, medians, minimum and maximum values from one or more articles. However, only summary estimates of means, minimum and maximum values are presented in the main text as very few median values were available for most parameters. A detailed summary of these estimates along with a list of articles and reference sources is provided in the Appendix of supplementary materials. Single values for a parameter (with no stated range) indicate that these were either extracted from a

single article or that the values were exactly the same when consolidated from two or more articles. If an article provided only a single value for a particular parameter then this was entered under the mean section. In the main text, parameters were summarized according to strain of influenza viruses. Studies that did not specify a particular virus strain but used general terms such as "novel influenza", "pandemic influenza" viruses, or "mutant form of avian influenza H5N1" have been grouped under "Novel influenza virus". In addition, studies that investigated a novel influenza virus but calibrated model parameters to a known influenza viral strain were also grouped under a novel influenza virus category. If studies described the agent as a seasonal influenza virus (without specifying a particular strain) or the term "general influenza virus" was used, they were grouped under influenza viruses. Detailed summary according to the specific strain or terms used for different influenza strain along with article list are presented in the Appendix of supplementary materials. All data processing and summary analyses were carried out using Stata version 11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP) after importing data from Microsoft Excel® version 2007.

Results and Discussion

Search strategy

A total of 721 unique articles were retrieved from PubMed, CAB Abstract, ScienceDirect and Agricola. Of these, 224 and 182 articles were excluded, through title and abstract screening respectively, as they were related to disease modeling and epidemiological studies of other infectious or non-infectious diseases of animals, humans, fishes, and plants, including one article related to computer viruses. Of the 315 articles reviewed, data were extracted from 133 articles. The remaining 182 articles were related to general reviews of models, general infectious disease

models, and an assessment of the economic impact of vaccine adjuvant from which no relevant parameters could be extracted. In addition, the references from 9 articles (Basta et al., 2009, Chao et al., 2010, Cowling et al., 2009, Milne et al., 2009, Tiensin et al., 2007, Tuite et al., 2009, Tuite et al., 2010a, van der Goot et al., 2005, van der Goot et al., 2007) considered to be important recent outputs in the area were individually reviewed and from these a further 18 articles were identified and added to the set for data extraction.

From a total of 151 articles from which data were extracted, 93 and 11 articles were related to simulation modeling studies in humans and birds respectively, while 5 articles reported models of zoonotic transmission. The remaining 42 articles (comprising 28 on humans, 10 on animals and 4 on birds) were routine statistical and experimental studies, from which modeling parameters were extracted.

Inventory of model types and approaches

It was apparent that different approaches were applied to model influenza for a variety of purposes. This may be because influenza is a commonly occurring disease that is readily amenable to modeling and also because it can often be the cause of large-scale pandemics. A summary of the different model types applied to influenza viruses in animals and humans addressing range of research questions is provided in Figure 1.

General trends in the application of different models

    Humans

Modeling to evaluate different intervention strategies dominated this literature. Of the 93 modeling studies dealing with influenza in human populations, 38 and 25 focused on the evaluation of intervention strategies alone or in combination with other questions of interest

respectively. Nine articles were solely aimed at parameter estimation (Chowell et al., 2006a, Chowell et al., 2007a, Chowell et al., 2008, Chowell et al., 2007b, Fraser et al., 2009, Lessler et al., 2007, Mills et al., 2004, Sertsou et al., 2006, Tuite et al., 2010b); while three articles addressed parameter estimation and an assessment of the spread of influenza viruses (Ajelli & Merler, 2008, Colizza et al., 2009, Massad et al., 2007). Four articles described methods or approaches related to influenza modeling (Addy et al., 1991, Fraser, 2007, Tsai et al., 2010, Aparicio & Pascual, 2007) and four others on these methods or approaches in combination with influenza spread or the development of software (Balcan et al., 2009, Brauer, 2008, Carpenter & Sattenspiel, 2009, Chao et al., 2010). These new methods and approaches included: extending stochastic models to allow for variable length of infectious period and heterogeneity in contact rates (Addy et al., 1991); models to estimate the R_0 of within and between household transmission of influenza virus (Fraser, 2007); to improve computational efficiency of large-scale spatial stochastic individual-based models through algorithm refinement including the use of an R_0 parameter rather than per contact transmission probability (Tsai et al., 2010); and the development of aggregate (system dynamic) models that capture the influence of contact network structures using basic reproductive ratios derived from the network structures (Aparicio & Pascual, 2007). Seven articles related solely to the spread of influenza (Boni et al., 2009, Flahault et al., 1994, Grais et al., 2003, Grais et al., 2004, Lavenu et al., 2004, Ohkusa & Sugawara, 2009, Rios-Doria & Chowell, 2009) and three focused on the development of modeling software (Eichner et al., 2007, Feighner et al., 2009, Hanley, 2006). A summary of the different models used for addressing various questions of interest is shown in Figure 1, while a detailed list of articles can be found in Table S1 of Appendix.

Some of the recent studies discussed the development of methods and approaches in combination with other questions as described below. Chao et al. (2010) developed the modeling platform FluTE for stochastic individual-based network models capable of simulating influenza spread across major metropolitan cities or even the entire population of the US, together with intervention measures. Lunelli et al. (2009) investigated the effects of incorporating contact matrices and spatial components (movements between geographic patches) into deterministic compartmental models and compared these with stochastic approaches. This was done to identify key elements of complexity to aid design decisions on achieving a balance between realism and computational efficiency. Deterministic models with heterogeneous mixing by partitioning populations into active and less active subgroups (Brauer, 2008, Larson, 2007) and a stochastic agent-based model for partitioning large-scale communities based on demographic, community features and daily activities (Das et al., 2008) were developed for assessing intervention strategies. Shaban et al. (2009) evaluated the effect of vaccination strategies at a household level during the early stage of an epidemic using a stochastic heterogeneous mixing compartmental model. An agent-based model to examine the effect of population movement and seasonal community structure on the transmission of influenza was developed by Carpenter and Sattenspiel (2009). Nigmatulina and Larson (2009) used a deterministic compartmental model with heterogeneous mixing to examine the inclusion of behavioral feedback to capture the changing behavior of people due to perceived threats during the epidemic phase on the modeled effect of non-pharmaceutical intervention. The role of memory and adaptation on decision-making around vaccination coverage based on two incentives (commitment and family incentive) was assessed by Vardavas et al. (2007) using a deterministic homogeneous mixing compartmental model. The effect of different mobility networks (long-range air travel versus

short-range commuting patterns) on the global and local spread of influenza epidemics was investigated using stochastic SEIR metapopulation models (Balcan et al., 2009).

In general, it is apparent that stochastic approaches have only recently been used to model influenza in humans. However, since the paper by Longini et al. (2004) this has been an increasingly important trend (Chao et al., 2010, Ferguson et al., 2005, Ferguson et al., 2006, Gojovic et al., 2009, Longini et al., 2005, Tsai et al., 2010, Basta et al., 2009, Lee et al., 2009, van den Dool et al., 2008, Wu et al., 2006, Yang et al., 2009, Yasuda & Suzuki, 2009). The numbers of stochastic models used to address different questions of interest and assess various intervention strategies are summarized in Figures 1 and 2, while a detailed list of articles can be found in Table S1. Stochastic approaches have some advantage over deterministic models, primarily through the incorporation of more flexible methods to represent variability and uncertainty. The introduction of a disease may or may not necessarily lead to epidemic outbreak under similar condition based on chance alone. This is particularly relevant in situations where numbers of infectious individuals and susceptible populations are small, when the infectious agent is not highly infectious, where spread occurs over smaller areas or where control measures are effectively implemented early in an outbreak (Britton & Lindenstrand, 2009, Keeling & Danon, 2009, Roberts et al., 2007, Lunelli et al., 2009). Furthermore, Britton & Lindenstrand (2009) demonstrated that the risk of a major outbreak is heavily dependent on the variability of the duration of the infectious period but not the latent period, whereas the initial growth rate of an influenza epidemic is greatly influenced by randomness in both periods. It is therefore likely that adopting a model which has limited capacity to capture stochastic behavior will, under these conditions, result in unrealistic predictions.

Most deterministic DE models simulated disease spread in continuous time-steps (Brauer, 2008, Eichner et al., 2007, Kim et al., 2010), while stochastic models simulated either in continuous (Hayden et al., 2000) or discrete time-steps, ranging from 1 to 4 time-steps per day (Ferguson et al., 2006, Tsai et al., 2010, van den Dool et al., 2008, Yang et al., 2009).

In general, most recent studies of pandemic influenza in humans have structured population by age, community (schools and daycare, workplace, households, etc.) and in some cases into high-risk and low-risk groups, using both deterministic and stochastic compartmental models (Brauer, 2008, Fraser et al., 2009, Lee et al., 2010, Milne et al., 2009, Ohkusa & Sugawara, 2009, Tuite et al., 2009, Gojovic et al., 2009). Deterministic models with heterogeneous mixing which stratified populations into different subgroups were considered a balanced approach, as they are more realistic than homogeneous mixing, while remaining more efficient than stochastic, individual-based models in terms of simulation time and complexity (Brauer, 2008, Eichner et al., 2007). More complex and realistic models used to simulate influenza spread and evaluate intervention strategies included stochastic individual-based models (22 of the 93 articles), network models (8 articles), or spatially explicit agent-based and network models (3 articles). Some examples of these models include: individual-based models (Carpenter & Sattenspiel, 2009, Chao et al., 2010, Lee et al., 2010, Perlroth et al., 2010, Yasuda & Suzuki, 2009, Basta et al., 2009, Tsai et al., 2010, Yang et al., 2009) , stochastic network models (Ajelli & Merler, 2008, Chao et al., 2010, Davey & Glass, 2008, Hsu & Shih, 2010, Perlroth et al., 2010), spatially explicit agent-based or network models (Ferguson et al., 2005, Halloran et al., 2008, Longini et al., 2005). The importance of incorporating spatial components in disease modeling were recognized both for evaluating spread and assessing the effect of control measures in humans (Colizza et al., 2009, Ferguson et al., 2005, Halloran et al., 2008, Lunelli et

al., 2009) and in birds (Le Menach et al., 2006, Savill et al., 2006, Sharkey et al., 2008) as disease tended to spread more within localized areas. These models were considered to better represent real world conditions by capturing individual level behavior, heterogeneity in contact structure and hence the ability to capture phenomena such as super-spreading. In addition, these modeling approaches allow more flexibility in assessment of targeted intervention measures (e.g. towards high-risk individuals or groups) and policy planning. While these models add more realism, they have disadvantages in terms of computational efficiency, requiring long hours of simulation to assess a plausible range of parameter values (particularly if population size is large). They also tend to require parameter specification at a fine level of resolution and detail (e.g. individual-level contact structures, individual-level or age specific transmission parameters, etc.). In addition, carrying out sensitivity analysis can be challenging since isolating influential parameters is difficult in the context of a large number of interacting parameters (Brauer, 2008, Gojovic et al., 2009). Therefore, it has been argued that simple deterministic compartmental models with heterogeneous mixing, which are also much easier to implement, represent a better alternative to these complex approaches for assessing disease management strategies during the early phase of an outbreak, particularly when little is known about model parameters (Brauer, 2008, Chowell et al., 2006b, Eichner et al., 2007, Nuño et al., 2007a). The qualitative results using simpler models for evaluating influenza control measures such as social distancing, antiviral treatment or vaccination (Nuño et al., 2007a) can be shown to be similar to those resulting from the creation of more complex models (Ferguson et al., 2005, Ferguson et al., 2006, Germann et al., 2006, Longini & Halloran, 2005, Longini et al., 2004, Longini et al., 2005). The choice of the most appropriate model: deterministic versus stochastic; compartmental versus individual-based; etc.; will depend on the nature of the agent or disease, the purpose of the

research, the availability of parameters and the time-frame within which guidance is required (Britton & Lindenstrand, 2009, Brauer, 2008, Nuño et al., 2007a). A complete list of articles that used each of these different types of modeling approaches is provided in Table S1.

Only a few studies have investigated the spread of influenza at the household level using either deterministic or stochastic heterogeneous mixing compartmental models (Fraser, 2007, Cauchemez et al., 2004, Shaban et al., 2009), or a stochastic individual-based model (Wu et al., 2006). These studies investigated the spread of influenza within and between households through contacts between infected and susceptible individuals locally (within household) and globally (between households). They also evaluated the effects of various intervention measures. This approach to modeling the spread of influenza at household level is analogous to disease spread at farm or herd level in animal populations, which often includes an assessment of similar intervention strategies (vaccination, quarantine, isolation, etc.). Modeling influenza spread at household and farm levels may be one approach for modeling the spread of influenza amongst and between animal and human populations that can effectively address different requirements in terms of model granularity.

Animals

There were 11 articles relating to studies that modeled influenza spread in birds. However, no papers reported the modeling of zoonotic influenza in swine or other animals (excluding one study of influenza viruses in equine populations (Garner et al., 2011), for which zoonotic importance is not yet known). Of the 11 avian articles, 6 assessed intervention strategies either alone or in combination with other questions of interests, 2 estimated parameters (van der Goot et al., 2003, Arinaminpathy & McLean, 2009), and 3 articles assessed the spread of avian influenza viruses (Bavinck et al., 2009, Bos et al., 2007, Guberti et al., 2007). Different types of

models were adopted to address these questions in bird populations as summarized in Figure 1 and Table S1. These included simple deterministic compartmental models (Bos et al., 2007, Elbakidze, 2008, Guberti et al., 2007, Iwami et al., 2009, Arinaminpathy & McLean, 2009), stochastic compartmental models (Bavinck et al., 2009, van der Goot et al., 2003, van der Goot et al., 2005), and a stochastic individual-based model (Savill et al., 2006). In addition, more complex models such as a deterministic network model (Aparicio & Pascual, 2007), a stochastic spatially explicit (Le Menach et al., 2006), and a stochastic spatially explicit network (Sharkey et al., 2008) model for avian influenza viruses H5N1 and H7N7 were also used.

Multispecies zoonotic models

A key focus of this review was to characterize the literature related to modeling for multi-species zoonotic influenza spread. This review could identify only five articles relating to such modeling studies (Arino et al., 2007, Iwami et al., 2007, Kim et al., 2010, Rao et al., 2009, Saenz et al., 2006). Of these, one focused on methods and platform development to model the spread of avian influenza (A/H5N1 virus) from wild migratory water birds to domestic birds and humans as a function of spatially overlapping population densities (derived from spherical geometry based on great-circle distances to elicit interactions amongst water birds, poultry and humans) using an SIR model with Markov processes. Specifically designed software called SEARUMS (Studying the Epidemiology of Avian Influenza Rapidly Using Modeling and Simulation) was developed to facilitate this modeling (Rao et al., 2009). Another study investigated the spread of low pathogenic avian influenza (with the assumption that the virus mutated to become a pandemic virus) from birds to human and assessed the effect of quarantine in both species using deterministic metapopulation modeling (Arino et al., 2007). Two studies used deterministic mathematical models to examine the mechanisms of spread of avian influenza from birds to

humans (Iwami et al., 2007, Kim et al., 2010). They examined at what Ro values and contact rates the disease would be maintained or undergo extinction in bird and human populations, assuming a mutant form of the AI virus capable of human to human transmission emerged. All these studies assumed there was no back-transmission of influenza virus from humans to birds.

Only one study investigated the spread of novel influenza virus between humans and swine species in a rural setting, using a simple deterministic model with homogenous mixing (Saenz et al., 2006). It investigated the amplifying effect on epidemic size of influenza spread in confined animal feeding operations (CAFO) and transmission back to humans through CAFO workers. It was assumed that transmission of the influenza virus between CAFO species and the general community occurred only through CAFO workers. This study showed that human influenza cases would increase by 42–86% assuming that swine workers comprised between 15–45% of a given community, while vaccination of 50% of the CAFO workers effectively nullified any amplification. Although this study provided preliminary insights into the effect of influenza spread between CAFO species and workers in a local setting, limitations inherent in deterministic homogenous mixing models, are likely to affect the ability of the model to capture the complexity of the human to animal and human to human interactions. In addition, other control strategies such as the effectiveness of biosecurity, contact reduction between sick CAFO workers and swine, and a reduction in transmission probability through personal hygiene measures need to be studied further.

Another study assessed the exposure risk of susceptible domestic species to pandemic influenza A/H1N1 2009 upon its successful introduction into various populations in Vietnam (Boni et al., 2009). This study investigated the spread of pH1N1 2009 in humans by developing an age-structured gravity model and tracked the number of livestock owners (rearing swine and

poultry) and non-livestock owners infected. From the number of livestock owners infected, they estimated the number of livestock exposed to the pandemic virus indirectly.

In terms of building a 'one-health' model to simulate spread of zoonotic influenza between animals and humans it is apparent that the most important differences relate to the unit of simulation as well as to the spatial and temporal scales involved. For humans, the unit of simulation is most often the individual. Individuals were assigned to spend differing amounts of time in various locations, such as at school, workplace or home, and disease spread was simulated in either continuous time-steps (Brauer, 2008, Duerr et al., 2007, Gani et al., 2005, Nuño et al., 2007b) or using two to four time-steps per day (Ajelli & Merler, 2008, Basta et al., 2009, Carrat et al., 2006, Ferguson et al., 2006, van den Dool et al., 2008). In animal populations the unit of simulation was mostly the farm, typically modeled in time-steps of one day (Bavinck et al., 2009, Guberti et al., 2007, Le Menach et al., 2006). Despite these differences, it seems feasible to simulate the spread of influenza between human and animal populations by adopting a relatively simple approach which models at the household level. The household level model can be justified on the basis that it is pragmatic to implement most intervention measures such as antiviral drugs, vaccination, quarantine or isolation at the household level.

Modeling software/platforms

The main purpose of this section is to provide an inventory of the software used for modeling rather than to describe features of each of these tools, which is beyond the scope of this review. Only 13 articles specified the modeling software or platform used; details are given in Table 1. Four modeling software were described fully for modeling influenza in humans. FluTe is a stochastic individual-based modeling platform capable of simulating large-scale spread of

influenza and evaluation of intervention measures against pandemic influenza across major metropolitan areas or the continental US (Chao et al., 2010). InfluSim is a simple deterministic DE SEIR model that captures heterogeneous mixing (Eichner et al., 2007), while EpiFlex is a stochastic individual-based model which can simulate other diseases such as HIV and smallpox in addition to influenza (Hanley, 2006). Pandemic Influenza Policy Model (PIPM) is an agent-based model specifically designed for military settings (Feighner et al., 2009). All these modeling platforms can handle populations partitioned by demographic and clinical parameters and are available freely. Other modeling platforms mentioned in the literature were AnyLogic (two articles), Berkely Madonna, MATLAB, and RePAST (Recursive Porous Agent Simulation Toolkit), all of which are generic modeling platforms. Finally, GLEaM (Global Epidemic and Mobility Modeler), a stochastic metapopulation modeling platform for simulating large-scale spread of influenza viruses, was noted in one article (Balcan et al., 2009).

Intervention strategies

Humans

In general, the intervention strategies evaluated against pandemic influenza included: antiviral drugs for both prophylaxis and treatment of cases; vaccination; school, daycare and work place closure; personal hygiene; and other social distancing measures such as quarantine, isolation and travel restriction. These measures were evaluated either singly or in combination. A total of 63 articles evaluated different intervention strategies to control influenza in humans. The intervention evaluated most frequently was vaccination, either alone (14 articles) or in combination with other intervention measures (22 articles). This was followed by antivirals, either alone (6 articles) or in combination (30 articles). Eight articles evaluated social distancing

measures, including one which specifically evaluated different strategies of school closure, such as isolating only sick students, closing individual schools or whole school system closures (Lee et al., 2009). Four articles evaluated travel bans solely and five more studied travel ban in combination with other interventions as a means of controlling an influenza pandemic. This included three that specifically evaluated the effect of air travel restrictions in mitigating a pandemic. They observed that unless air travels restriction were imposed in approximately 100% of the affected countries, there would be no effect on influenza spread, even though these measures delayed the peak of the influenza epidemic to varying degrees (Cooper et al., 2006, Hollingsworth et al., 2006, Wood et al., 2007). One article studied the effect of travel restriction between neighboring communities during a pandemic with similar results (Nigmatulina & Larson, 2009). The various types of models applied in the evaluation of these intervention measures are summarized in Figure 2. The two articles that assessed the effect of targeted antiviral prophylaxis and quarantine on containing a pandemic at source of origin, taking southeast Asia as the example case, were also the most highly cited references in the case of pandemic influenza modeling in human population (Ferguson et al., 2005, Longini et al., 2004).

All interventions using prophylactic antiviral treatment, vaccination or social distancing (such as quarantine and isolation) were evaluated based on the assumption that these measures were implemented at household, school or health care settings (An der Heiden et al., 2009, Lee et al., 2010, Longini et al., 2004, Longini et al., 2005, Shaban et al., 2009, van den Dool et al., 2008, Vardavas et al., 2007, Wu et al., 2006). It was difficult to compare the results of these studies as they evaluated the intervention measures under varying assumptions and population settings. However, all of these measures produced a positive effect on the containment of any influenza pandemic when implemented either singly or in combination with others.

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The effects of these interventions were assessed by parameterizing the models through percentage reduction in contact rates (in the cases of social distancing measures such as school or workplace closure, or quarantine measures, etc.) and reduction in susceptibility to infection and infectivity or duration of infectiousness (in the cases of antiviral treatment and vaccination). Parameters used in assessing these intervention measures are described in the "modeling parameters" section below. In general, the outcome of these models were assessed in terms of clinical attack rates, secondary attack rates, hospitalization rates, case fatality rates, duration of epidemic, and day to epidemic peak.

Birds

Five articles investigated intervention strategies for influenza in birds. They included movement control, quarantine, isolation, depopulation (Elbakidze, 2008, Le Menach et al., 2006, Sharkey et al., 2008), and vaccination (Iwami et al., 2009, Savill et al., 2006) against avian influenza A/H5N1 and H7N7. Outcomes of these models were assessed in terms of R_0 values, size of epidemic (number of infected premises), numbers depopulated and duration of epidemic.

Multispecies zoonotic models

Two articles evaluated the effect of intervention measures on zoonotic spread. One considered the effect of vaccinating certain high-risk populations (50% of CAFO workers) against a novel influenza virus (Saenz et al., 2006), while the other examined the effect of quarantine measures on the spread of low pathogenic avian influenza in birds and humans (Arino et al., 2007).

Modeling parameters

Parameters used in models related to the natural history of influenza viruses, contact and

transmission parameters, as well as intervention measures are summarized in Table 2 to 11.

Detailed lists of references from which these parameters were extracted are presented in Tables

S3 to S6.

Natural history

Parameters associated with natural history of influenza infection include those used to model:

incubation, latency, subclinical (asymptomatic infectious), clinically infectious, and immune

periods. These parameters are presented according to influenza strains reported in the literature

for humans in Table 2(a) to 2(b), and for birds and swine in Table 3(a) and 3(b). In addition,

percentages of pre-existing immunity used in some of these studies for humans are presented

under the natural history of influenza section in Table 2(b).

Parameters relating to disease state duration for different influenza viruses in humans were

similar. Apparently modeling studies conducted after 2005 and prior to the pH1N1 2009

outbreaks (Basta et al., 2009, Carpenter & Sattenspiel, 2009, Colizza et al., 2007, Duerr et al.,

2007, Flahault et al., 2006, Fraser, 2007, Gojovic et al., 2009, Halloran et al., 2008) mainly

adopted the parameters (disease states durations, transmission parameters, contact frequencies

and probabilities) specified in Ferguson et al. (2006, 2005), German et al. (2006), Longini et al.

(2004, 2005) and Mills et al. (2004). Articles published after the outbreaks of pH1N1 2009 (Lee

et al., 2010, Perlroth et al., 2010, Tuite et al., 2010a, Tuite et al., 2010b, Yang et al., 2009)

tended to use parameters from Boëlle et al. (2009), Fraser et al. (2009) , and Pourbohloul et al.

(2009). Distributional characteristics of parameters used for the natural history of influenza

infection in humans and birds are presented in Table 4. The most commonly used distributions

for incubation and latency period in human studies was a mean of 1.9 days with empirical

distribution of 1 day (30%), 2 days (50%) and 3 days (20%) (Tsai et al., 2010, Chao et al., 2010,

Colizza et al., 2007, Germann et al., 2006, Ohkusa & Sugawara, 2007, Longini et al., 2004,

Longini et al., 2005), and the clinically infectious period with a mean of 4.1 with empirical

distribution of 3 days (30%), 4 days (40%), 5 days (20%) and 6 days (10%) (Weycker et al.,

2005, Germann et al., 2006, Halloran et al., 2002, Ohkusa & Sugawara, 2009, Tsai et al., 2010,

Longini et al., 2004, Longini et al., 2005). No study estimated the duration of disease state

parameters for any influenza virus at the household level in humans (which would be required if

spread of influenza were to be modeled at the household level). None of the articles included in

this review provided information on distributions related to the natural history of influenza

infection in swine.

     Contact parameters

Daily contact frequencies for different age groups, household sizes, student groups, risk

behaviors (highly active or less active subgroups of a population), and different community

structures are summarized in Table 5. Parameters relating to contact frequencies used for

modeling in human populations were either derived from small pilot surveys (Lee et al., 2009,

Longini et al., 2005, Yang et al., 2009, Yasuda & Suzuki, 2009) or from a large-scale survey

carried out in eight European countries (Hens et al., 2009, Mossong et al., 2008). These contact

frequencies were defined as adequate contact (sufficient to transmit influenza virus between

infectious and susceptible individuals) of a physical nature such as skin-to-skin contact, kiss or

handshake, or a two-way conversation consisting of three or more words. Although, the latter

two articles used the same survey data, there were minor differences in the way contact

frequencies were estimated, in particular, number of contacts at works were included in the article by Hens et al. (2009). A number of recently published articles (Chao et al., 2010, Medlock & Meyers, 2009, Tuite et al., 2009, Tuite et al., 2010a) used the contact frequencies estimated by Mossong et al. (2008). Estimates of daily contact frequencies used in other articles are summarized separately in Table 5. Both direct and indirect contact rates between poultry or poultry farms, extracted from two articles (Elbakidze, 2008, Sharkey et al., 2008), are also summarized in Table 5.

Transmission parameters

Transmission parameters in disease spread models use either R_0 in combination with a generation interval, or a transmission coefficient derived by multiplying contact frequency and transmission probability per contact and duration of relevant disease states. Some models used a single value of β defined as the per capita rate at which two individuals come into effective contact (i.e. adequate contact that will lead to infection if one is infectious and other is susceptible) (Vynnycky & White, 2010). Not all adequate contact will be effective (e.g. an adequate contact between infectious individual and immune individual will not be effective contact). Transmission probability per adequate contact (including contact frequencies) or transmission coefficient/contact rates (without requiring knowledge of contact frequency) were all estimated by calibrating these to match the attack rates (proportion of newly infected individuals in a exposed population) or R_0 values of past influenza pandemics (pandemic influenza A/H1N1 1918-1919, influenza A/H2N2 1957-58, and influenza A/H3N2 1968-1969). Transmission probabilities were estimated using varying units of contact frequency, such as frequency per day (Chao et al., 2010, Longini et al., 2005), frequency per hour (Gojovic et al., 2009), contact duration expressed in minutes per day (Lee et al., 2009), or as a probability per simulation time-

step (Viboud et al., 2004). The transmission probabilities presented in Table 6 are a summary of all these estimates. Transmission probabilities for within-flock bird to bird and per dangerous contact through trucks picking up birds for slaughterhouse are also presented in Table 6.

Similarly transmission coefficients/rates were expressed in units of continuous time, per-day or certain hours/day. Transmission coefficients/rates which were expressed in terms of daily or 8 to 12 hourly intervals were summarized together, whereas those expressed in continuous time unit from seconds to hourly intervals were summarized separately and are presented in Table 7. Assumed values of transmission coefficient/rates for between-species transmission of influenza are also presented in the same table. Since these transmission probabilities and coefficients were calibrated under different disease spread scenarios and other assumptions, they are intended only to provide readers with an overview of the ranges of values used. In addition, all these parameters were summarized over all contact types. For more detailed information relating to specific contact patterns and transmission probabilities, readers may refer the original articles.

Estimates of mean R_0 values, with and without 95% confidence intervals, for different influenza viruses in in different human populations are presented in Tables 8(a) and 8(b) respectively. Reproductive numbers based either on references from other literature or assumed within the reported models in human population are also presented in Table 8(b). Chowell et al. (2006a) and (2007a) have estimated ranges of R_0 values for pandemic influenza A/H1N1 1918 based on different datasets collected around spring and autumn waves of outbreaks in Geneva, Switzerland. Autumn outbreaks had significantly higher R_0 values than spring waves. They also estimated R_0 values based on a different set of outbreak data from San Francisco, California, and by applying different modeling methods with some differences in the estimates. Estimates of R_0 values for the most recent pH1N1 2009 virus were reported in Pourbohloul et al., (2009), Tuite et

al., (2010b) and using four different approaches by Boëlle et al., (2009). The estimates from the

first two studies were significantly lower compared with those of Boëlle et al., (2009). In

general, R_0 values for all pandemic influenza outbreaks ranged from 1.1 to 4.0. Two articles

estimated R_0 values for influenza spread at the household level (Fraser, 2007, Shaban et al.,

2009). The effect of household size on the basic reproductive number was evaluated by taking

examples of small and large household size distributions for populations in Sweden and

Tanzania respectively (Shaban et al., (2009). This study found that the R_0 for between-household

spread was much higher in populations with larger family size ($R_0 = 6$) than in those with smaller

family size ($R_0 = 2$).

Basic reproductive numbers estimated with 95% CI for different influenza viruses in birds at

individual and flock levels are presented in Table 9(a). Summary of R_0 estimated (without 95%

CI), referenced and assumed at the individual, flock and village levels in the literature are

summarized in Table 9(b). Different R_0 values assumed for different species in modeling

zoonotic transmission of novel influenza virus between human and swine or birds are also

presented in Table 9(b).

Summary estimates of generation intervals or serial intervals (time from onset of primary

case to a secondary case (Vynnycky & White, 2010)) are presented in Table 10. Generation

intervals are estimated by adding the averages of incubation or latency period and infectious

period stated in the models.

Parameters for intervention measures

Parameters used for assessing different intervention strategies in human and bird populations are

presented in Table 11. The estimated of efficacy of antiviral treatment ranged from 61–90%

(Cooper et al., 2003, Hayden & Aoki, 1999), whereas efficacy values used for modeling ranged

from 28–100%. Reduction in infectivity by infected person through treatment used for modeling ranged from 28–100%, and for susceptibility through prophylactic treatment from 25–100%. The antiviral coverage rate, treatment duration including compliance rate are provided in the same table. The estimated vaccine efficacy for influenza in human ranged from 19–68% (Hayden et al., 2004, Vu et al., 2002). However, its values used (referenced or assumed values) in the models ranged from, 5–100%. Reduction in infectiousness by infected person due to vaccination used in the models ranged from 20–100% with a delay to immunity from no delay to 15–42 days. The vaccination coverage evaluated ranged from 18–100% in humans.

Assessment of school and day-care closure were modeled through contact reduction ranging from 30–100% with the closure period ranging from 7–300 days. The delay to school closure from the first case ranged from without any delay to 7–56 days. The values used for reduction in contacts as a result of quarantine or isolation in human populations ranged from 40-100% while the duration of quarantine or isolation periods ranged from 1–21 days. A quarantine period of 21–31 days with 100% effectiveness was assumed for infected bird flocks (Sharkey et al., 2008).

It was apparent that there is adequate information on disease states and transmission parameters to model spread of influenza viruses in human population, including the recently emerged pH1N1 2009 virus. While some data exist for influenza viruses in birds, very little information on parameters other than disease state duration (Brookes et al., 2010, Pasma & Joseph, 2010, Vincent et al., 2010) exists for swine influenza viruses (including the pH1N1 2009 virus) for the review period considered; despite the fact that many outbreaks in swine have been reported from a range of countries (Office International des Epizooties (OIE), 2010).

Conclusion

This study has provided a synopsis of the different methods and approaches applied to modeling the spread of zoonotic influenza in humans and animal populations, including a summary of important modeling parameters. It was apparent that the majority of recent influenza modeling studies applied to human populations had been motivated by the perceived threat of the emergence of a mutant strain of the avian influenza A/H5N1 and pH1N1 2009 viruses. However, only four studies modeled the transmission dynamic of influenza spread between birds and humans, and one study modeled its spread at swine-humans interface. In spite of the recognized role of swine as a potential mixing host for different influenza viruses (particularly avian and human influenza viruses) in generating novel viruses through reassortment, and considering the fact that the pH1N1 2009 virus is known to readily transmit between swine and humans, modeling research at the animal-human interface has been relatively sparse. Significant gaps in the knowledge of parameters such as frequency of evolution of novel viral strains in pigs, farm-level natural history of influenza infection in swine, incidences of its transmission between farms, and between pigs and humans are clearly evident. Given the potential benefits of simulation studies not only for understanding the transmission dynamics of zoonotic influenza but also in investigating various scenarios for contingency planning and developing sound early warning systems, it seems clear that priority must be given to research at the animal-human interface. This is imperative bearing in mind the continued threat posed by the repeated emergence of pandemic influenza viruses and the potential role animals may play in generating novel influenza viruses. It was also evident that there are adequate numbers of both generic and specific software (both for commercial and free) available for modeling influenza spread in human and animal populations using methods ranging from a simple deterministic to a more complex and realistic network-based models.

Conflict of interest

Declared none.

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Supporting information

Appendix: Methods, intervention strategies and parameters estimated or used for modeling spread of zoonotic influenza in human and animal populations:

Table S1. List of articles that used different methods for modeling the spread of zoonotic influenza viruses in human and animal populations to address various research questions

Table S2. List of articles that used different modeling methods for assessing various intervention strategies against zoonotic influenza in human and animal populations

Table S3. Summary of natural history parameters of influenza infections in humans along with list of articles and references

Table S4. Summary of natural history parameters of influenza infection in animals along with list of articles and references

Table S5. Summary of natural history parameters of avian influenza infection in birds along with list of articles and references

Table S6. Distributions of natural history parameters of influenza infection in human and bird populations along with list of articles and references

Table S7. Summary of daily contact frequencies in human and animal populations along with list of articles and references

Table S8. Summary of transmission probability per contact of influenza infection in human and bird populations along with list of articles and references

Table S9. Summary of transmission coefficients/rates of influenza infection in human and animal populations along with list of articles and references

Table S10. Summary of R0 and generation intervals of influenza infection in human and animal populations along with list of articles and references

Table S11. Summary of intervention parameters used for modeling influenza infection in human and bird populations along with list of articles and references.
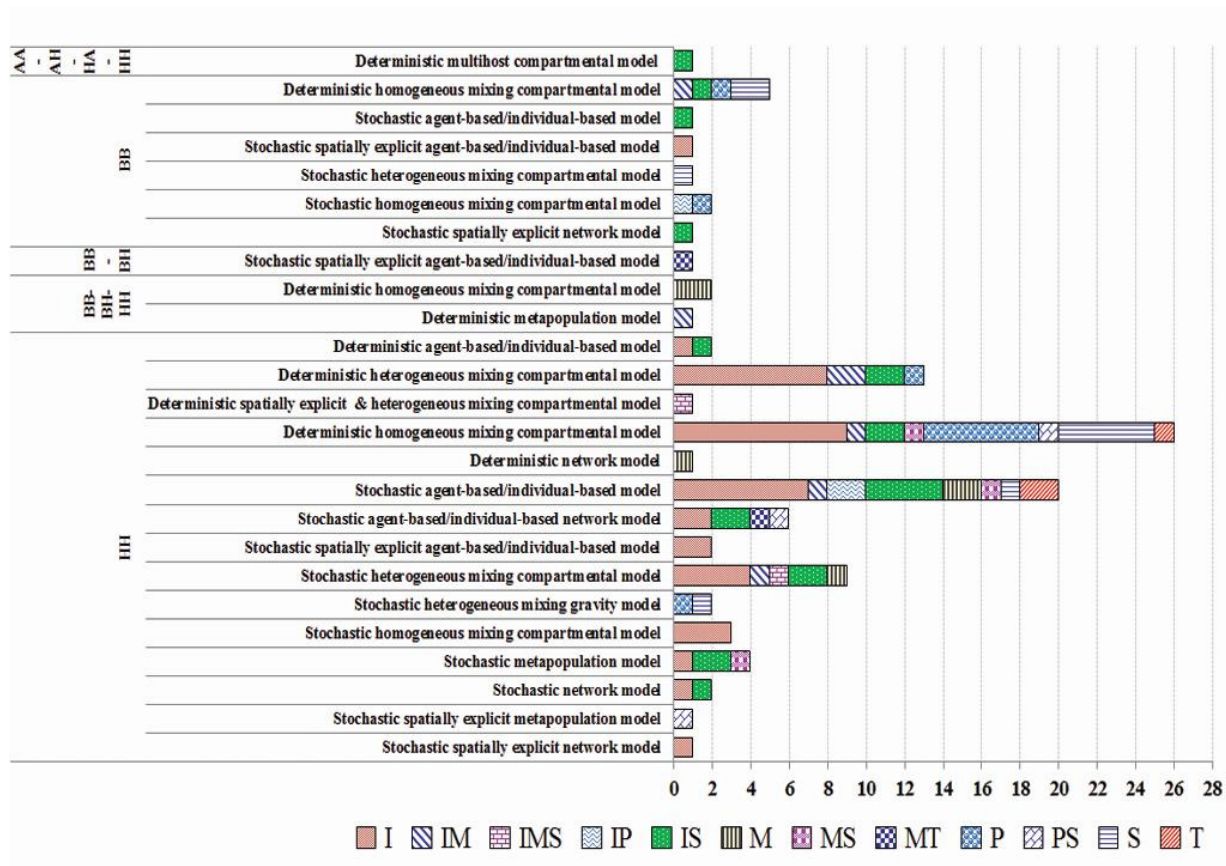
Abbreviations: (a) AA-AH-HA-HH = spread within and between swine and human simultaneously; (b) BB = spread between bird species; (c) BB -BH = spread within bird species and birds to humans; (d) BB-BH-HH = spread between birds, birds to humans and humans to humans; e) HH = spread between humans. No distinction of spread is made between individual, household, herd/flock or village levels. Legends: (i) P = estimate parameters; (ii) S = evaluate spread; (iii) I = evaluate intervention strategies; (iv) M = describe new modeling methods and approaches; (v) T = develop modeling platform or tool. A combination of these letters indicates combination of research questions of interests.

Figure 1. Different model types used for modelling spread of influenza viruses in human and animal populations to address various research questions.
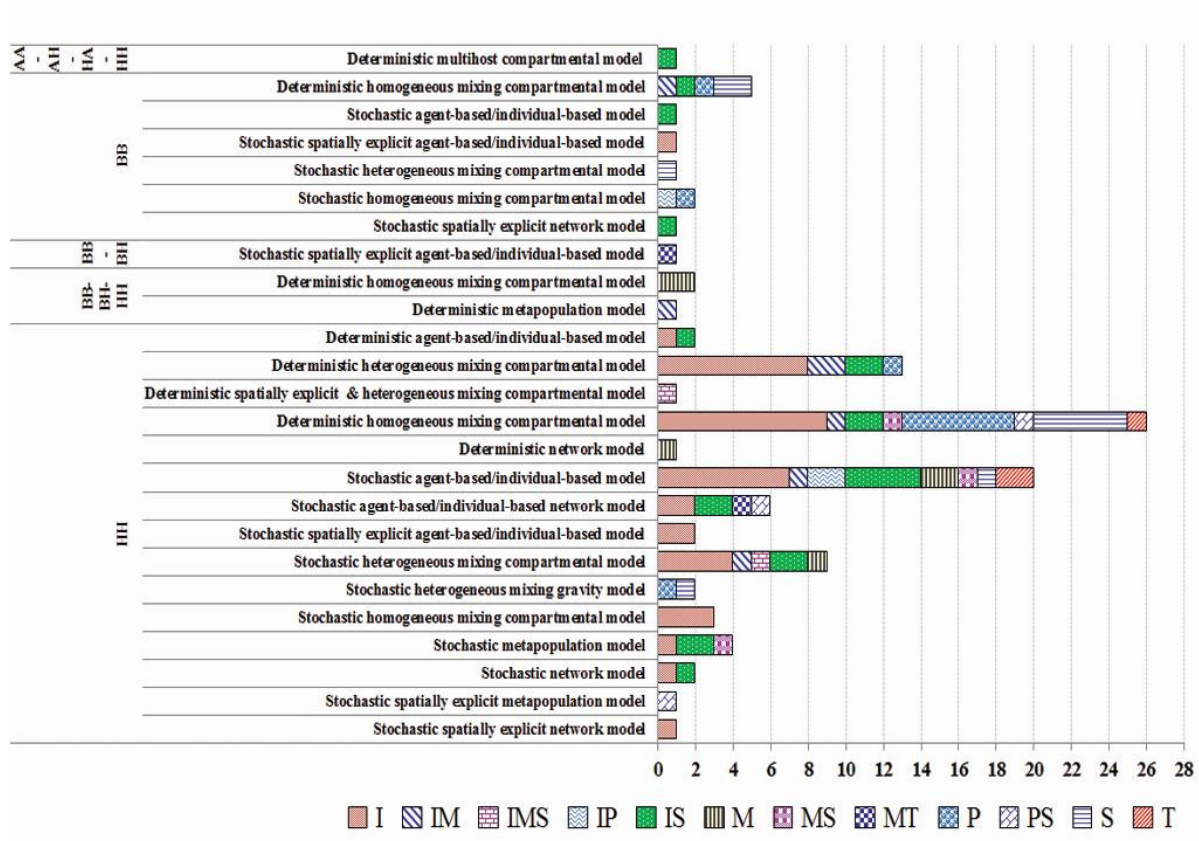
Abbreviations: (a) AA-AH-HA-HH = spread within and between swine and human simultaneously; (b) BB = spread between bird species; (c) BB - BH = spread within bird species and birds to humans; (d) BB-BH-HH = spread between birds, birds to humans and humans to humans; e) HH = spread between humans. No distinction of spread is made between individual, household, herd/flock or village levels.

Legend: (a) A = antiviral for either or both prophylactic and treatment; (b) D = include workplace closure, contact tracing, quarantine, isolation, cancellation of community and mass gathering, use of personal hygiene and protective equipment; (c) M = movement control and depopulation in animals (including birds); (d) S = specifically school and daycare closure; (e) T = air travel restriction; (f) V = vaccination prior to outbreak or during the outbreak. Combinations of letters indicate combination of these measures.

Figure 2. Different model types used for assessing various intervention strategies against influenza in human and animal populations.
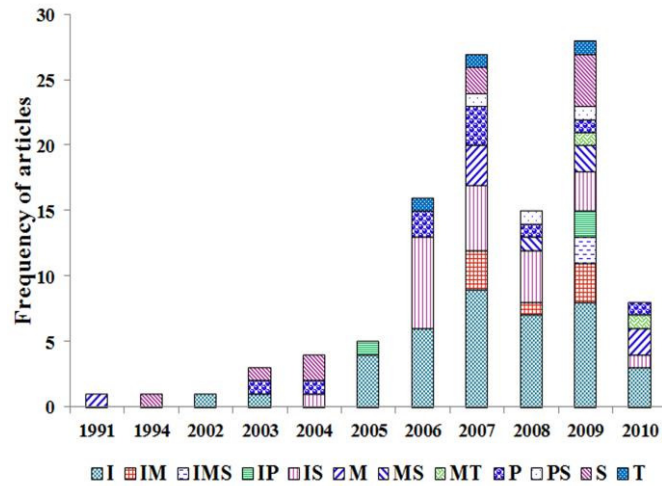
Legend key: (i) P = estimate parameters; (ii) S = evaluate spread; (iii) I = evaluate intervention strategies; (iv) M = describe new modeling methods and approaches; (v) T = develop modeling platform or tool. A combination of these letters indicates combination of research questions of interests.

Figure 3. Temporal trend in the research questions of interest for modeling influenza viruses in human and animal populations.
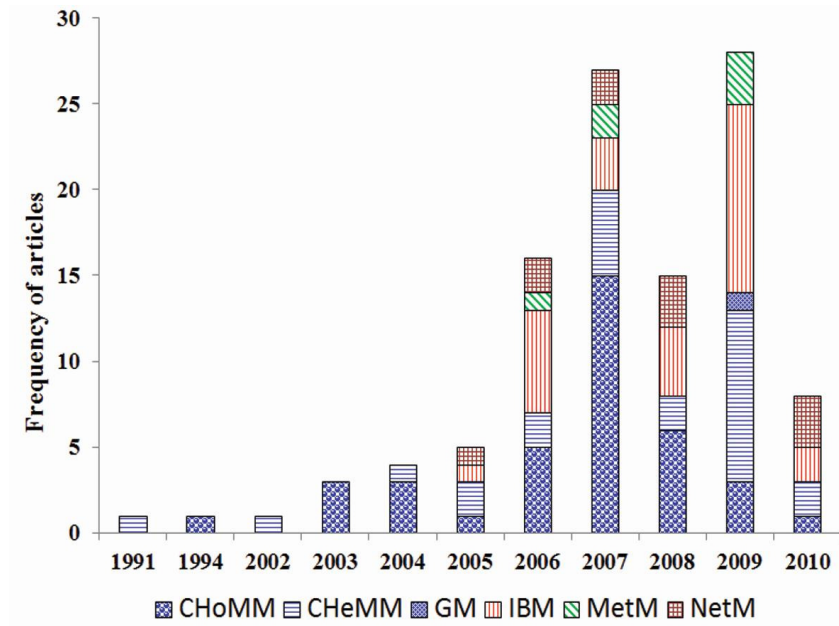
Legend key: (i) CHoMM = Compartmental homogeneous mixing models; (ii) CHeMM = Compartmental heterogeneous mixing models; (iii)IBM = Individual-based/agent-based model; (iv) M etM= Metapopulation models; (v) NetM = Network models.

Figure 4. Temporal trend in the application of modeling methods for research on influenza viruses in human and animal populations.

Table 1. Inventory of modeling software/platforms either specifically developed and/or used for influenza spread in human and animal populations.

Platform	Description	Agent	Question of interest	Spread type	Article
1. AnyLogic	General modelling platforms that supports all three major modelling approaches; system dynamics, discrete event simulation, agent-based modelling and hybrid of any of these models	Pandemic influenza A/H1N1 2009 (articles 1 & 2) Novel influenza virus (article 3)	I (all articles)	Human-human (all articles)	(1. Tuite et al., 2009, 2. Tuite et al., 2010a) (3. Epstein et al., 2007)
2. Berkeley Madonna	General modelling platform	Pandemic influenza A/H1N1 2009	P	Human-human	(Fraser et al., 2009)
3. EpiFlex	Stochastic individual-based modelling platform	Influenza viruses	T	Human-human	(Hanley, 2006)
4. FluTE	Stochastic individual-based network model	Pandemic influenza A/H2N2 1957-1958 and A/H1N1 2009	MT	Human-human	(Chao et al., 2010)
5. GLEaM model (Metapopulation stochastic model on global scale)	Stochastic metapopulation modelling platform for modelling large-scale spread of influenza viruses	Pandemic influenza viruses	MS	Human-human	(Balcan et al., 2009)
6. InfluSim	Deterministic homogeneous mixing compartmental model	Influenza virus in general	T	Human-human	(Duerr et al., 2007, Eichner et al., 2007)
7. MATLAB	General modelling platform	Pandemic influenza A/H1N1 1918-1919	P	Human-human	(Chowell et al., 2007b)
8. PIPM (Pandemic Influenza Policy Model)	Stochastic agent-based/individual-based model	Pandemic influenza viruses	T	Human-human	(Feighner et al., 2009)
9. RePAST (Recursive Porous Agent Simulation Toolkit)	Stochastic agent-based general modelling platform	Pandemic influenza A/H1N1 1918-1919	MS	Human-human	(Carpenter & Sattenspiel, 2009)
10. SEARUMS (Studying the Epidemiology of Avian Influenza Rapidly Using Modelling and Simulation)	Stochastic agent-based spatially explicit model	Avian influenza A/H5N1	MT	Bird-bird and bird-human	(Rao et al., 2009)

Abbreviations: (i) P=parameter estimation; (ii) S=evaluate spread; (iii) I=evaluate different intervention strategies; (iv) M=describe new modeling methods and approaches; (v) T= development of modelling software/platforms (T). Combination of these letters indicates combination of research questions of interests.

Table 2(a). Disease states durations of influenza viruses infection in humans estimated with 95% confidence intervals (CI) either from experimental, observational or modeling studies.

Disease states	Agent	Mean (95% CI) in days	References
a) Incubation period	1. Pandemic influenza A/H1N1 2009	4.3 (2.6–6.6)	(Tuite et al., 2010b)
b) Latent period	1. Pandemic influenza A/H1N1 2009	2.6 (2.4–3.1)	(Tuite et al., 2010b)
c) Subclinical infectious period	1(a). Pandemic influenza A/H1N1 1918 (Spring wave)	2.9 (2.8–3.1)	(Chowell et al., 2006)
	1(b). Pandemic influenza A/H1N1 1918 (Autumn wave)	2.2 (1.9–2.7)	(Chowell et al., 2006)
d) Clinical infectious period	1(a). Pandemic influenza A/H1N1 1918 (Spring wave)	1.2 (1.1–1.3)	(Chowell et al., 2006)
	1(b). Pandemic influenza A/H1N1 1918 (Autumn wave)	2.6 (2.43–2.8)	(Chowell et al., 2006)
	2. Pandemic influenza A/H1N1 2009	3.4 (2.1–4.7)	(Tuite et al., 2010b)
	3. Seasonal influenza A/H1N1	4.5 (3.7–5.3)	(Carrat et al., 2008)
	4. Seasonal influenza A/H3N2	5.1 (4.5–5.8)	(Carrat et al., 2008)
	5. Influenza viruses	4.8 (4.3–5.3)	(Carrat et al., 2008)

Table 2(b). Summary of disease states durations of influenza viruses' infection in humans estimated without 95% CI, referenced or assumed for modeling.

Disease states	Agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
1. Incubation period				
a) Estimated values	1. Pandemic influenza A/H1N1 2009	2.0	1.0 (1.0–2.0)	-
	2. Seasonal influenza A/H1N1	-	1.0	-
	3. Seasonal influenza virus A/H3N2	2.0	1.0	3.0
b) Referenced values	1. Pandemic influenza A/H1N1 1918	1.0	-	-
	2. Pandemic influenza A/H1N1 2009	2.0 (1.5–3.0)	1.0	5.0
	3. Seasonal influenza virus A/ H1N1	-	1.0	4.0
	4. Seasonal influenza virus A/H3N2	-	1.0	3.5 (3.0–4.0)
	5. Influenza viruses	2.4 (1.9–2.9)	1.0	3.0 (3.0–4.0)
	6. Novel influenza viruses	1.9 (1.0–2.0)	1.0	3.0
c) Assumed values	1. Pandemic influenza A/H1N1 2009	-	1.0	3.0
	2. Novel influenza viruses	2.0	-	-
2. Latent period				
a) Estimated values	1. Influenza viruses	1.0	-	-
b) Referenced values	1. Pandemic influenza A/H1N1 1918	1.9 (1.0–3.5)	1.2 (0.8–1.5)	1.7 (1.5–1.9)
	2. Pandemic influenza A/H1N1 2009	1.5 (1.0–3.5)	0.9 (0.7–1.0)	4.0 (2.0–5.0)
	3. Pandemic influenza A/H2N2 1957	1.9	-	-
	4. Seasonal influenza A/H1N1	1.9	1.0	3.0
	5. Seasonal influenza A/H3N2	1.9	1.0	3.0
	6. Influenza viruses	1.9 (0.6–2.1)	1.0	3.0 (2.0–3.0)
	7. Novel influenza viruses	1.5 (0.5–2.0)	1.0 (1.0–1.2)	2.0
c) Assumed values	1. Pandemic influenza A/H1N1 2009	2.0	1.0	3.0

Disease states	Agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
	2. Influenza viruses	1.0	-	-
	3. Novel influenza viruses	2.3 (1.5–3.0)	-	-
3. Subclinical infectious period				
a) Estimated values	1. Pandemic influenza A/H1N1 1918	-	-	-
b) Referenced values	1. Pandemic influenza A/H1N1 2009	1.0 (0.5–2.5)	-	2.0
	2. Influenza viruses	3.0 (0.5–4.1)	-	-
	3. Novel influenza viruses	1.0 (0.3–4.1)	0.5	0.7
c) Assumed values	1. Novel influenza viruses	0.5	-	-
4. Clinical infectious period				
a) Estimated values	1. Pandemic influenza A/H1N1 1918	1.8 (1.7–3.0)	1.7 (1.6–1.7)	1.9 (1.8–1.9)
	2. Pandemic influenza A/H1N1 2009	5.6	1.0	10.0 (8.0–12.0)
	3. Seasonal influenza A/H3N2	3.8	3.1	4.6
b) Referenced values	1. Pandemic influenza A/ H1N1 1918	4.6 (4.1–5.0)	2.6 (1.5–3.3)	4.15 (2.9–10)
	2. Pandemic influenza A/H1N1 2009	3.8 (2.5–7.0)	3.8 (1.9–4.0)	5.5 (2.9–10)
	3. Pandemic influenza A/H2N2 1957	4.1	-	-
	4. Seasonal influenza A/H1N1	4.1	2.0	8.0
	5. Seasonal influenza A/H3N2	4.1(3.8–4.1)	2.0	8.0
	6. Influenza viruses	4.1 (1.4–7.0)	3.0 (2.0–3.0)	6.0 (6.0–10.0)
	7. Novel influenza viruses	4.0 (1.0–7.0)	3.3 (2.5–5.0)	7.0 (4.1–12.0)
c) Assumed values	1. Pandemic influenza A/H1N1 2009	5.0 (3.0–5.0)	3.0	7.0
	2. Pandemic influenza A/H2N2 1957	-	3.8	5.3
	3. Pandemic influenza A/H3N2 1968	3.0	-	-
	4. Influenza viruses	3.0	-	-
	5. Novel influenza viruses	4.0	2.0	3.0
5. Immunity period	1. Novel influenza viruses	-	365	-
6. Pre-existing immunity (%)				
a) Estimated values	1. Pandemic influenza A/H1N1 2009	-	4.0	34.0
b) Referenced values	1. Pandemic influenza A/H1N1 1918	50.0	10.0	20.0
	2. Pandemic influenza A/H1N1 2009	34.0 (5.0–50.0)	30.0	50.0 (15.0–70.0)
	3. Seasonal influenza A/H3N2	-	-	27.0
	4. Influenza viruses	-	-	30.0
	5. Novel influenza viruses	30.0	-	63.5 (27.0–100.0)
c) Assumed values	1. Influenza viruses	-	-	62.5 (50.0–75.0)
	2. Novel influenza viruses	25.0	-	-

Note: (a) Estimated values are those estimated from empirical data of experimental or observational studies; (b) Referenced values refer to those values taken from other articles; (c) Assumed values are values *assumed based on expert's opinion and other unpublished sources. All values are reported in days. Summary estimated are media*ns (ranges) of means, minimum and maximum values of two or more articles. Those with single value represented value from either a single article or were of exactly the same value if consolidated from two or more articles.

These definitions applies to subsequent tables from Table 3 to Table 11

Table 3(a). Disease states durations of influenza viruses in birds estimated with 95% confidence interval (CI) either from experimental, observational or modeling studies.

Disease states	Agent	Mean (95% CI) in days	References
a) Clinical infectious period	1. Highly pathogenic avian influenza A/H5N2	6.8 (4.9–8.7)	(van der Goot et al., 2003)
	2. Low pathogenic avian influenza A/H5N2	4.3 (2.6–5.9)	(van der Goot et al., 2003)
	3. Highly pathogenic avian influenza A/H7N7	6.3 (3.9–8.7)	(van der Goot et al., 2005)

Table 3(b). Summary of disease states durations of influenza viruses infections in swine and birds estimated (without 95% CI), referenced or assumed for modeling.

Species and disease states	Agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
A. Swine				
1. Incubation period				
a) Estimated values	1. Pandemic influenza A/H1N1 2009	-	1.0 (1.0–2.0)	2.5 (1.0–3.0)
2. Latent period				
a) Estimated values	1. Pandemic influenza A/H1N1 2009	-	1.0	2.0 (2.0–5.0)
	2. Swine influenza H1N1 virus	-	-	3.0
3. Clinical infectious period				
a) Estimated values	1(a). Pandemic influenza A/H1N1 2009 (Individual level)	-	7.0 (3–7.0)	8.0 (5.0–15.0)
	1(b). Pandemic influenza A/H1N1 2009 (Herd level)	-	10.0	31 (20.0–42.0)
	2. Swine influenza A/H1N1	-	3.0	5.0
b) Referenced values	1. Novel influenza virus	7.0	-	-
4. Immunity period				
a) Estimated values	1. Swine influenza A /H1N1	-	365.0	692.5 (545.0–840.0)
B. Birds				
1. Incubation period				
a) Referenced values	1(a). Avian influenza A/H5N1 (Individual level)	5.0	-	-
	1(b). Avian influenza A/H7N1 (Individual level)	-	-	6.0
	2. Avian influenza A/H7N7	-	-	3.0
b) Assumed values	1. Avian influenza A/H7N1	-	2.0	-
	2. Avian influenza A/H7N7	-	1.0	-
2. Latent period				
b) Referenced values	1. Avian influenza A/H5N1	1.75 (1.5–2.0)	1.0	2.0
	2. Avian influenza A/H7N7	2.0	-	-
c) Assumed values	1. Avian influenza A/H7N7	2.0	-	-
3. Subclinical infectious period				
b) Referenced values	1. Avian influenza A/H5N1	1.0	-	-
	2. Avian influenza A/H7N7	4.0	-	6.0
4. Clinical infectious period				
b) Referenced values	1(b). Avian influenza A/H5N1 (Flock level)	10.0	-	-
	2(a). Avian influenza A/H7N7 (Individual level)	6.3	1.0	6.0

	2(b). Avian influenza A/H7N7 (Flock level)	13.8	4.0	12.0
	3. Avian influenza virus	14.0	-	-
c) Assumed values	1. Avian influenza A/H5N1 (Village level)	7.0	-	-

Table 4. Distributions used for duration of disease states of influenza viruses' infection in human and bird populations estimated from experimental, observational studies, referenced from other articles, or assumed for modeling

Species and disease states	Agent	Distribution
A. Human		
1. Incubation period		
a) Estimated values	1. Pandemic influenza A/H1N1 2009	Log-normal with mean duration of 4.3 (95% CI 2.6–6.6) days
b) Referenced/assumed values	1. Pandemic influenza A/H1N1 2009	Uniform; exponential
	2. Seasonal influenza viruses	Normal; Weibull distribution (offset = 0.5, shape 2.21, scale = variable)
	3. Novel influenza viruses	Mean of 1.9 days with probability distribution of 1 day (30%); 2 days (50%); 3 days (20%); Exponential distribution.
2. Latent period		
a) Estimated values	1. Novel influenza viruses	Weibull distribution (2.24, 1.11) with offset value of 0.5 day;
b) Referenced/assumed values	1. Pandemic influenza A/H1N1 2009	Exponential (mean = 0.5 and offset = 0.75 = 0.5+0.75 = 1.25 days)
	2. Seasonal influenza viruses	Exponential (mean = 0.5 and offset = 0.75 = 0.5+0.75 = 1.25 days)
	3. Novel influenza viruses	Mean of 1.9 days with probability distribution of 1 day (30%) 2 days (50%) and 3 days (20%); exponential; gamma; Weibull with offset value of 0.5
4. Clinical infectious period		
b) Referenced/assumed values	1. Pandemic influenza A/ H1N1 1918	Exponential
	2. Pandemic influenza A/H1N1 2009	Exponential; gamma; uniform; Log-normal with mean duration of 9.3 (95% CI 2.6–24.2) days
	3. Novel influenza viruses	Mean of 4.1 days with empirical distribution of 3 days (30%); 4 days (40%); 5 days (20%); 6 days (10%); exponential; log-normal
B. Bird		
1. Latent period		
b) Referenced/assumed values	1. Avian influenza A/H5N1	48+ binomial(48, 0.25)*
2. Subclinical infectious period		
b) Referenced/assumed values	1. Avian influenza A/H5N1	24+ binomial(24, 0.25)*
3. Clinical infectious period		
b) Referenced/assumed values	1. Avian influenza A/H5N1	Binomial(96, 0.05)*

*Unit in hours

Table 5. Summary estimates of daily contact frequencies in human and bird populations estimated either from survey, referenced from other articles or assumed for modeling

Species	Contacts category	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
A. Human-human	**A. Age**			
a) Estimated values	<5	10.21 (7.65)	-	-
	5-9	14.81 (10.09)	-	-
	10–14	18.69 (13.4)	-	-
	15–19	19.93 (21.14)	-	-
	20–29	17.18 (25.72)	-	-
	30–39	17.83 (21.68)	-	-
	40–49	17.51 (23.29)	-	-
	50–59	15.96 (20.84)	-	-
	60–69	10.51 (14.47)	-	-
	70+	7.71 (10.97)	-	-
	B. Household			
	Household size 1	11.23 (18.26)	-	-
	Household size 2	13.32 (17.89)	-	-
	Household size 3	14.67 (16.44)	-	-
	Household size 4	17.71 (17.67)	-	-
	Household size 5	19.49 (29.12)	-	-
	Household size 6+	19.3 (13.14)	-	-
	C. Students			
	Students -classmates	38.4	-	-
	Students –non-classmates	14.8	-	-
b) Referenced values	**A. Activity based**			
	1. Low activity	2.0	-	-
	2. Medium activity	10.0	-	-
	3. High activity	50.0	-	-
	B. Age group			
	1. Children (0–11 years)	14.0 (3.0–24.0)	-	-
	2. Teen (12–18 years)	4.0 (3.0–4.0)	-	-
	3. Adult (19–64 years)	6.0 (3.0–13.0)	-	-
	4. Senior (65+ years)	4.0 (3.0– 5.0)	-	-
	C. Occupational/community structure			
	1. Community in general	16.0 (1.0–32.0)	5.0 (5.0–14.0)	27.0 (24.0–50.0)
	2. Health care worker with coworkers	2.0 (2.0–8.0)	-	-
	3. Health care worker with patients	30.0	-	-
	4. Student with classmates	14.0 (14.0–15.0)	-	-
	5. Student with non-classmates	15.0	-	-

Species	Contacts category	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
c) Assumed values	**A. Age group**			
	1. Children (0-11 years)	6.0	-	-
	B. Community structure			
	1. Community in general	1.0 (1.0–2.0)	-	1.0
B. Bird-bird				
a) Estimated values	1. Maximum farms visited by feed lorry/trip	-	-	6.0
b) Referenced values	1. Flock to flock contact rate/day	-	0.2	0.3
c) Assumed values	1. Inter-company contact /day	3.0	-	-
	2. Maximum farms visited by slaughter lorry/day	-	-	4.0

Table 6. Summary estimates of transmission probability per contact of influenza viruses in humans and birds estimated, referenced, or assumed for modeling

Species and transmission parameter	Agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
A. Human-human (all contact types combined)				
a) Estimated/calibrated values	1. Pandemic influenza A/H1N1 1918	0.51		-
	2. Influenza viruses	0.24	0.39	0.78
	3. Novel influenza viruses	0.24 (0.1–0.024)	-	-
b) Referenced values	1. Pandemic influenza A/H1N1 2009	0.0435 (0.00255–0.6)	-	-
	2. Influenza viruses		0.2503 (0.0006–0.5)	0.0012
	3. Novel influenza viruses		0.55 (0.5–0.6)	0.7
B. Bird-bird				
c) Assumed values	1. Avian influenza A/H5N1(within flock/day)	0.5	-	-
	2. Avian influenza A/H5N1(per dangerous slaughterhouse contact)	0.25	-	-

Table 7. Summary estimates of transmission coefficients/rates of influenza viruses in humans, birds, and swine estimated, referenced or assumed for modeling

Species and transmission parameter	Agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
I. Discrete time (daily)				
A. Human-human				
a) Estimated values	1. Pandemic influenza A/H1N1 2009	0.060192 (0.0095–0.060192)	0.00001	0.6
	2. Influenza viruses	-	0.000005	0.08
	3. Novel influenza viruses	0.00058	0.00029	0.00102
b) Referenced values	1. Pandemic influenza A/ H2N2 1957	0.0125 (0.00001–0.08)	-	-
c) Assumed values	1. Novel influenza viruses	-	0.58	0.64
B. Bird-Bird				
a) Estimated values	1. Avian influenza A/H5N1 (bird level)	2.66	2.01	2.55
	2. Avian influenza A/H5N1 (flock level)	0.66	0.5	0.87
	3. Avian influenza A/H5N2 (bird level)	0.24	0.12	0.45
	4. Avian influenza A/H7N7 (bird level)	33.0	-	
	5. Avian influenza viruses	0.22	-	0.42
C. Zoonotic spread	1. Novel influenza virus			
c) Assumed values	a) Bird-human	0.012	-	-
	b) Human-human	0.03	-	-
II. Continuous time				
A. Human-human				
a) Estimated values	1. Pandemic influenza A/H1N1 2009	-	0.00001	0.0125
	2. Influenza viruses	0.581	0.199	0.425
b) Referenced values	1. Novel influenza virus	0.00017	-	-
B. Zoonotic spread				
1. Between bird-human	1. Novel influenza virus			
c) Assumed values	a) Bird-bird	0.15 (0.1–0.2)	-	-
	b) Human-human	0.0006	0.0015	0.0025 (0.002–0.003)
2. Animal-human	1. Novel influenza virus			
c) Assumed values	a) Swine-swine	0.2857	-	-
	b) Swine-human	0.00123	-	-
	c) Human-human	0.3	-	-
	d) Human-swine	0.122851	-	-

Table 8(a). Estimated basic reproduction numbers (Ro) with 95% confidence interval (CI) of influenza viruses in human population estimated either from experimental, observational or modeling studies

Agent	Mean (95% CI)	Reference
1(a). Pandemic influenza A/H1N1 1918 (using first 10 days data of spring wave of Geneva)	1.6 (1.5–1.7)	(Chowell et al., 2007a)
1(b). Pandemic influenza A/H1N1 1918 (using first 10 days data of autumn wave of Geneva)	3.1 (2.8–1.7)	(Chowell et al., 2007a)
1(c). Pandemic influenza A/H1N1 1918 (using non-hospitalized and asymptomatic cases of 1st phase/spring wave in Geneva)	1.5 (1.5–1.5)	(Chowell et al., 2006)
1(d). Pandemic influenza A/H1N1 1918 (using non-hospitalized and asymptomatic cases of 2nd phase/autumn wave of Geneva)	3.8 (3.6–3.9)	(Chowell et al., 2006)
1(e). Pandemic influenza A/H1N1 1918 (using early exponential growth phase of autumn wave daily case notification data of San Francisco, California)	3.0 (2.7–3.3)	(Chowell et al., 2007b)
1(f). Pandemic influenza A/H1N1 1918 (using deterministic SIR compartmental model of daily case notification data of autumn wave in San Francisco, California)	2.4 (2.2–2.6)	(Chowell et al., 2007b)
1(g). Pandemic influenza A/H1N1 1918 (using complex SEIR model of daily case notification data of autumn wave in San Francisco, California)	2.2 (1.6–2.1)	(Chowell et al., 2007b)
1(h). Pandemic influenza A/H1N1 1918 (using SIR Bayesian approach of daily case notification data of autumn wave in San Francisco, California)	2.1 (1.1–3.0)	(Chowell et al., 2007b)
1(i). Pandemic influenza A/H1N1 1918	2.0 (1.7–2.3)*	(Mills et al., 2004)
2(a). Pandemic influenza A/H1N1 2009	1.3 (1.3–1.4)	(Tuite et al., 2010b)
2(b). Pandemic influenza A/H1N1 2009	1.4 (1.4–1.5)	(Pourbohloul et al., 2009)
2(c). Pandemic influenza A/H1N1 2009 (using intrinsic growth rate and generation interval obtained from households study)	2.2 (2.1–2.4)	(Boëlle et al., 2009)
2(d). Pandemic influenza A/H1N1 2009 (using intrinsic growth rate and generation interval obtained from viral excretion of experimental influenza infection study)	2.6 (2.4–2.8)	(Boëlle et al., 2009)
2(e). Pandemic influenza A/H1N1 2009 (using intrinsic growth rate and generation interval obtained from hypothetical distribution from Elveback et al., (1976)	3.1 (2.9–3.5)	(Boëlle et al., 2009)
2(f). Pandemic influenza A/H1N1 2009 (using real time estimation of averaging the number of secondary cases across all possible chains of transmissions of epidemic curve)	3.2 (2.1–4.0)*	(Boëlle et al., 2009)
3. Seasonal influenza A/H1N1	1.2 (0.8–1.7)*	(Chen & Liao, 2010)
4. Seasonal influenza A/H3N2	1.4 (0.9–2.2)*	(Chen & Liao, 2010)
5. Seasonal influenza viruses	1.3 (1.2–1.4)	(Chowell et al., 2008)

* Median and its 95% CI values instead of mean

Table 8(b). Summary estimates of basic reproductive number (Ro) of influenza viruses in human, bird and swine populations estimated, referenced or assumed for modeling

Species and transmission parameter	Agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
A. Human-human				
a) Estimated values	1. Pandemic influenza A/H1N1 1918	2.2 (1.8–2.7)	1.3 (1.2–2.8)	2.2 (1.2–3.1)
	2. Pandemic influenza A/H1N1 2009	1.5	1.34 (1.1–2.3)	1.9 (1.3–2.9)
	3. Pandemic influenza A/H3N2 1968	-	1.2	3.0
	4. Seasonal influenza A/H1N1	1.1	-	1.4
	5. Seasonal influenza A/H3N2	1.5 (1.4–1.7)	1.4 (1.3–1.5)	1.7 (1.6–1.8)
	6. Influenza viruses (between households)	3.9 (2.0–6.0)	-	-
	7. Novel influenza viruses	2.1	1.5	1.8
b) Referenced values	1. Pandemic influenza A/H1N1 2009	1.5 (1.3–1.8)	1.3 (1.2–1.6)	2.0 (1.3–2.2)
	2. Pandemic influenza A/H2N2 1957	1.7 (1.7–1.7)	-	-
	3(a). Influenza viruses (individual level)	2.1 (1.7–2.5)	1.4 (1.3–1.6)	2.4 (1.4–2.73)
	3(b). Influenza viruses (between households)	1.2	-	-
	4. Novel influenza viruses	1.9 (1.4–3.1)	1.4 (0.3–1.9)	2.4 (1.4–3.3)
c) Assumed values	1. Pandemic influenza A/H1N1 2009	1.7	1.4	2.4
	2. Pandemic influenza A/H3N2 1968	-	1.5	3.5
	3. Influenza viruses	2.0	1.5	3.0
	4. Novel influenza viruses	1.9	1.3	2.3 (1.7–3.5)
B. Bird-bird				
a) Estimated values	1(a). Avian influenza A/H5N1 (within flock)	-	25.0	66.0
	1(b). Avian influenza A/H5N1 (between villages)	2.5 (2.2–2.7)	2.0	2.1
	2(b). Avian influenza A/H7N1 (between farms)	-	0.6	1.8
	3(a). Avian influenza A/H7N7 (within flock)	-	1.3	-
	3(b). Avian influenza A/H7N7 (between farms)	3.3 (1.3–5.2)	3.6 (3.1–4.0)	6.7 (6.5–6.9)
b) Referenced values	1. Avian influenza A/H5N1 (within flock)	-	25.0	66.0
	2. Avian influenza A/H7N7 (between farms)	-	0.8	6.5
C. Zoonotic spread articles				
c) Assumed values	1. Novel influenza virus			
	a) Human-human	1.0	2.0 (0.6–3.5)	4.1 (1.1–7.1)
	b) Swine-swine	2.0	-	-
	c) Bird-bird	1.1	0.4 (0.1–0.8)	1.8 (1.1–2.5)

Table 9(a). Estimated basic reproduction numbers (Ro) with 95% confidence intervals estimated either from experimental, observational or modeling studies in birds

Agent	Mean (95% CI)	Reference
1(a). Highly pathogenic avian influenza A/H5N1 (within-flock using 1 day infectious period)	2.3 (2.0–2.6)	(Tiensin et al., 2007)
1(b). Highly pathogenic avian influenza A/H5N1 (within-flock using 4 days infectious period)	2.6 (2.0–3.5)	(Tiensin et al., 2007)
2. Highly pathogenic avian influenza A/ H5N2 (between flock level)	1.0 (0.0–2.4)	(van der Goot et al., 2003)
3. Low pathogenic avian influenza A/LPAI H5N2 (between flock level)	1.0 (0.0–2.3)	(van der Goot et al., 2003)

Table 9(b). Summary estimates of basic reproductive number (Ro) of influenza viruses in bird and swine populations including zoonotic transmissions estimated, referenced or assumed for modeling

Transmission parameter	Spread in species and agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
A. Bird-bird				
a) Estimated values	1(a). Avian influenza A/H5N1 (within flock)	-	25.0	66.0
	1(b). Avian influenza A/H5N1 (between villages)	2.5 (2.2–2.7)	2.0	2.1
	2(b). Avian influenza A/H7N1 (between farms)	-	0.6	1.8
	3(a). Avian influenza A/H7N7 (within flock)	-	1.3	-
	3(b). Avian influenza A/H7N7 (between farms)	3.3 (1.3–5.2)	3.6 (3.1–4.0)	6.7 (6.5–6.9)
b) Referenced values	1. Avian influenza A/H5N1 (within flock)	-	25.0	66.0
	2. Avian influenza A/H7N7 (between farms)	-	0.8	6.5
C. Zoonotic spread				
c) Assumed values	1. Novel influenza virus			
	a) Human-human	1.0	2.0 (0.6–3.5)	4.1 (1.1–7.1)
	b) Swine-swine	2.0	-	-
	c) Bird-bird	1.1	0.4 (0.1–0.8)	1.8 (1.1–2.5)

Table 10. Summary estimates of generation interval of different influenza viruses in human estimated, referenced or assumed for modeling

Transmission parameter	Type of spread and agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
a) Estimated values	1. Pandemic influenza A/H1N1 1918	2.6	-	-
	2. Pandemic influenza A/H1N1 2009	3.5	2.6 (2.2–4.0)	3.2 (2.6–5)
	3. Seasonal influenza A/H1N1	2.1 (1.9–2.3)	1.6 (1.5–1.6)	3.8
	4. Seasonal influenza A/H3N2	3.1	2.2	4.0
	5. Influenza viruses	3.5 (3.4–3.6)	2.9	4.3
	6. Novel influenza viruses	2.4	1.0	3.9
b) Referenced values	1. Pandemic influenza A/ H1N1 1918	6.0	2.8 (2.6–3.0)	5.0 (4.0–6.0)
	2. Pandemic influenza A/H1N1 2009	3.0 (1.9–4.6)	1.6 (1–6.6)	5.0 (2.7–7.4)
	3. Seasonal influenza A/H3N2	2.4	-	-
	4. Influenza viruses	2.8 (2.8–2.9)	-	-
	5. Novel influenza viruses	2.9 (2.6–3.4)	2.6 (2.1–3.0)	3.0 (2.7–3.8)

		Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
c) Assumed values	1. Pandemic influenza A/H3N2 1968	3.9 (3.5–4.2)	-	-
	2. Novel influenza viruses	2.6	2.8	4.0

Table 11. Summary estimates of intervention parameters estimated, referenced or assumed for modeling influenza viruses in human and bird populations

Intervention type	Parameter	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
A. Human				
1. Vaccination				
a) Estimated values	1. Vaccine efficacy (%)	-	38.75 (19.0–58.5)	57.5 (47.0–68.0)
b) Referenced values	1. Vaccine efficacy (%)	-	40.0 (20.0–70.0)	73.0 (30.0–100)
	2. Reduction in infectiousness (%)	-	30.0 (20.0–50.0)	70.0 (40.0–90.0)
	3. Vaccine immune delay (days)	-	7.0	42.0
	4. Vaccination coverage (%)	60.0 (50.0–60.0)	25.5 (18.0–26.0)	87.5 (69.0–100.0)
c) Assumed values	1. Vaccine efficacy (%)	-	30.0 (5.0–50.0)	70.0 (30.0–100)
	2. Reduction in infectiousness (%)	-	50.0 (30.0–50.0)	80.0 (40.0–100)
	3. Vaccine immune delay (days)	-	15.0 (0.0–15.0)	14.0 (0.0–14.0)
	4. Vaccination coverage (%)	50.0 (30.0–50.0)	20.0 (0.0–50.0)	75.0 (7.0–100)
2. Antiviral treatment (AV)				
a) Estimated values	1. AV efficacy	-	70.0	75.5 (61.0–90.0)
b) Referenced values	1. AV efficacy (%)	-	30.0 (28.0–30.0)	70.0 (30.0–100)
	2. Reduction in infectiousness (%)	-	30.0	60.0 (28.0–80.0)
	3. Reduction in susceptibility (%)	-	30.0 (25.0–30.0)	30.0 (30.0–90.0)
	4. AV coverage (%)	-	50.0 (0.0–60.0)	90.0 (50.0–100)
	5. AV treatment duration (day)	-	10.0 (5.0–10.0)	10.0 (5.0–10.0)
	6. AV use compliance (%)	-	48.0 (5.0–90.0)	90.0
c) Assumed values	1. AV efficacy (%)	-	50.0	30.0 (30.0–100)
	2. Reduction in infectiousness (%)	-	-	62.0 (30.0–100)
	3. Reduction in susceptibility (%)	-	-	30 (30.0–100)
	4. AV coverage (%)	-	50.0 (2.0–80.0)	100 (6.0–100)
	5. AV treatment duration (day)	-	7.5 (5.0–10.0)	5.0
	6. AV use compliance (%)	-	5.0	100 (80.0–100)
3. School closure				
c) Assumed values	1. School closure contact reduction (%)	75.0 (50.0–80.0)	31.5 (30.0–33.0)	25.0 (7.0–300.0)
	2. School closure duration (days)	14.0 (7.0 – 28.0)	7.0 (7.0–60.0)	7.0 (0.0–56.0)
	3. School closure delay (days)	-	0.0–14.0	
4. Quarantine				
c) Assumed values	1. Quarantine contact reduction (%)	50.0	55.0 (40.0–60.0)	85.0 (30.0–100)
	2. Quarantine period (days)	10.0 (2.0–10.0)	1.0	7.0 (3.0–21.0)
B. Birds				
1. Quarantine				
c) Assumed values	1. Quarantine period (days)	21.0–31.0	-	-

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