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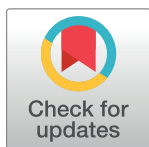▶ **To cite this version:**

Influenza interaction with cocirculating pathogens and its impact on surveillance, pathogenesis, and epidemic profile: A key role for mathematical modelling

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Abstract

Evidence is mounting that influenza virus interacts with other pathogens colonising or infecting the human respiratory tract. Taking into account interactions with other pathogens may be critical to determining the real influenza burden and the full impact of public health policies targeting influenza. This is particularly true for mathematical modelling studies, which have become critical in public health decision-making. Yet models usually focus on influenza virus acquisition and infection alone, thereby making broad oversimplifications of pathogen ecology. Herein, we report evidence of influenza virus interactions with bacteria and viruses and systematically review the modelling studies that have incorporated interactions.

Despite the many studies examining possible associations between influenza and *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Neisseria meningitidis*, respiratory syncytial virus (RSV), human rhinoviruses, human parainfluenza viruses, etc., very few mathematical models have integrated other pathogens alongside influenza. The notable exception is the pneumococcus–influenza interaction, for which several recent modelling studies demonstrate the power of dynamic modelling as an approach to test biological hypotheses on interaction mechanisms and estimate the strength of those interactions.

We explore how different interference mechanisms may lead to unexpected incidence trends and possible misinterpretation, and we illustrate the impact of interactions on public health surveillance using simple transmission models. We demonstrate that the development of multipathogen models is essential to assessing the true public health burden of influenza and that it is needed to help improve planning and evaluation of control measures. Finally, we identify the public health, surveillance, modelling, and biological challenges and propose avenues of research for the coming years.

Author summary

Influenza is responsible for major morbidity and mortality burdens worldwide. Mathematical models of influenza virus transmission have been critical to understanding the virus epidemiology and planning public health strategies for infection control. It is increasingly clear that microbes do not act in isolation but potentially interact within the host. Therefore, studying influenza alone may lead to misinterpretation of transmission or severity patterns. Here, we review the literature on bacteria and viruses that interact with influenza, proposed interaction mechanisms, and mathematical modelling studies that include interactions. We report evidence that, beyond the classic secondary bacterial infections, many pathogenic bacteria and viruses probably interact with influenza. Public health relevance of these pathogen interactions is detailed, showing how possible misreading or a narrow outlook could lead to mistaken public health decision-making. We describe the role of mechanistic transmission models in investigating this complex system and obtaining insight into interactions between influenza and other pathogens. Finally, we highlight the benefits and challenges in modelling and speculate on new opportunities made possible by taking a broader view, including basic science, clinically, and for public health.

Introduction

Influenza virus is a major contributor to the global disease burden, and exploration of its pathogenesis, epidemiology, and evolution has occupied generations of scientists. Its complex seasonality, antigenic drift of surface proteins, wide spectrum of severity, and capacity to cross species and cause epidemics or pandemics are all characteristics that make the virus so difficult to control [1].

The human respiratory tract is an important reservoir of bacteria, fungi, viruses, bacteriophages, archaea, and eukaryotes [2], harboring diverse communities of commensal, opportunistic, and pathogenic microorganisms. It has been suggested that some exist in nonneutral relationships [3], with competition for resources, synergism with the host immune system, or physiological modifications that alter the normal colonization or infection processes. The contribution of species-level interactions to the influenza burden is largely unknown.

In terms of public health, our current understanding of influenza transmission or severity may therefore be incomplete or misguided due to ignorance of the effect of interacting pathogens. On one hand, large-scale influenza vaccination programs may unexpectedly impact other infections due to an indirect rise or fall in the risk of contracting them [4]. For example, if influenza outcompetes another virus and holds it at bay, an influenza vaccination program could result in an upsurge in the competitor. On the other hand, the introduction of measures to control bacterial infections (e.g., pneumococcal vaccines) may decrease the risk of secondary bacterial pneumonia often associated with severe outcomes of influenza.

Seasonal influenza generates a large burden each year during the wintertime in temperate regions and with more complex seasonal patterns in tropical regions [5]. Influenza pandemics frequently occur outside of the usual season and generate an unpredictable and often large burden in morbidity, mortality, and cost [6,7]. This burden has historically been the result of secondary bacterial infections [8,9]. Lung specimens from 1918 to 1919 influenza fatalities were found to be, in more than 90% of cases, positive for at least one bacterium [10]. Bacteriologic and histopathologic results from published autopsy series also suggest that deaths from

the 1918 influenza pandemic mostly resulted from pneumonia with *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Streptococcus pyogenes*, multiple infections being common [10]. Deaths during the 1957 and 1968 pandemics were less closely related to bacterial pneumonia [10]. Because emergence and circulation of pandemic influenza take place out of season, and therefore in different climatic and ecological milieus than seasonal strains, pandemic strains may encounter different coinfecting pathogens. It is therefore critically important to pandemic preparedness to understand competitive and synergistic relationships with other species, both at the individual level from a clinical perspective or at a population level from an epidemiological perspective. It is vital to improve our understanding and control of transmission and the risk of developing disease on infection.

Mathematical modelling has been a key tool in infectious diseases for many years, allowing researchers to probe the complex intricacies of transmission and play forward the effects on an individual to see the impact on population-level infection dynamics [11]. Counterfactuals, or 'what if' scenarios, can easily be tested and compared, where vaccination rates, contact patterns, health behaviours, or any number of other factors are varied, to assess impact.

Models of influenza virus transmission have proved very useful in expanding knowledge of influenza biology, evolution, and epidemiology. For example, models of evolutionary change and immunity aim to predict the dominant strain of influenza in the coming season [12]. Spatially explicit models have convincingly linked commuting movements to the spread of influenza in the United States [13]. Models have also been crucial to public health, contributing to the optimization of control strategies, including the use of vaccines and antivirals [14–20]. As the modelling field has developed, there has been an effort to improve realism by incorporating heterogeneity in human contact patterns, age-related susceptibility, cross immunity after previous infections [19,21–24], and the potential effect of environmental variables on transmission [13,25]. Notably, the vast majority of modelling work has neglected the microbial environment: most mathematical and computational models of influenza are focused on single or sequential influenza infections and have broadly simplified pathogen ecology. For example, despite secondary bacterial infections being recognized as an important cause of mortality, models have not been exploited to estimate the indirect effect of seasonal influenza vaccination on the incidence of severe bacterial infections in the elderly. Furthermore, modelling used to plan vaccine interventions during the 2009 pandemic in the United Kingdom considered influenza transmission alone [26].

The authors of relatively recent literature reviews gathered biological and epidemiological evidence for interactions between influenza virus and respiratory bacteria or viruses [3,27,28] but did not consider mechanistic transmission models. Mathematical models make it possible to investigate mechanisms of interaction and visualize the pathological and epidemiological patterns that result from them. Comparison of model outputs to data enables estimation of both the probability of such interactions and the strength of the interaction. Estimation can be made across geographic regions (e.g., winter seasonal vs year-round transmission), for different virus subtypes (e.g., seasonal vs pandemic), and in different age groups (e.g., infants vs elderly). Computational and mathematical models to study influenza with other respiratory pathogens are currently underutilized.

In this article, we report evidence of interaction of influenza with other pathogens and systematically review modelling studies on influenza coinfection. Our aim is to build a case for a more expansive use of mathematical models including influenza with other pathogens. For this, we address how different interference mechanisms might lead to unexpected epidemiological patterns and misinterpretations, identify public health needs, identify modelling and biological challenges, and propose avenues of research for the future.

Mechanisms of interaction

Here, 'interaction' refers to any process by which infection caused by one pathogen affects the probability, timing, or natural history of infection by another. This process includes a wide range of mechanisms that can involve direct connections between the two pathogens, e.g., at the cellular level, or indirect interactions through an intermediate factor that influences the other. The indirect consequences of these interactions are described later. For influenza virus, interactions with bacterial or viral species can occur at several scales (Fig 1). Interacting pathogens may have two distinct profiles: natural human commensals—usually bacteria—which cause mainly asymptomatic carriage or mild symptoms often for long durations of weeks to months, or epidemic pathogens causing infection for shorter durations, from a few days to a few weeks. These two distinct epidemic profiles potentially involve different modes of interaction and lead to different levels of consequences. Here, we detail proven and potential interaction mechanisms (Fig 1).

Within-host interactions

At the cellular level, interactions involve both direct and indirect mechanisms. First, influenza genes or gene products can enhance or inhibit the replication of other viruses or potential infection by bacteria by direct interaction with pathogen proteins or nucleic acids [29]. Furthermore, indirect competition for host resources can occur, when pathogens compete for target cells, receptors, or cellular products required for replication. Influenza-infected cells may also release cell signalling molecules that could increase or decrease the probability of coinfection.

During infection, influenza virus impairs innate and adaptive host defences [30,31]. Mechanisms include altered neutrophil recruitment and function, leading to defective bacterial clearance, diminished production of alveolar macrophages [32], and inhibition of T cell–mediated
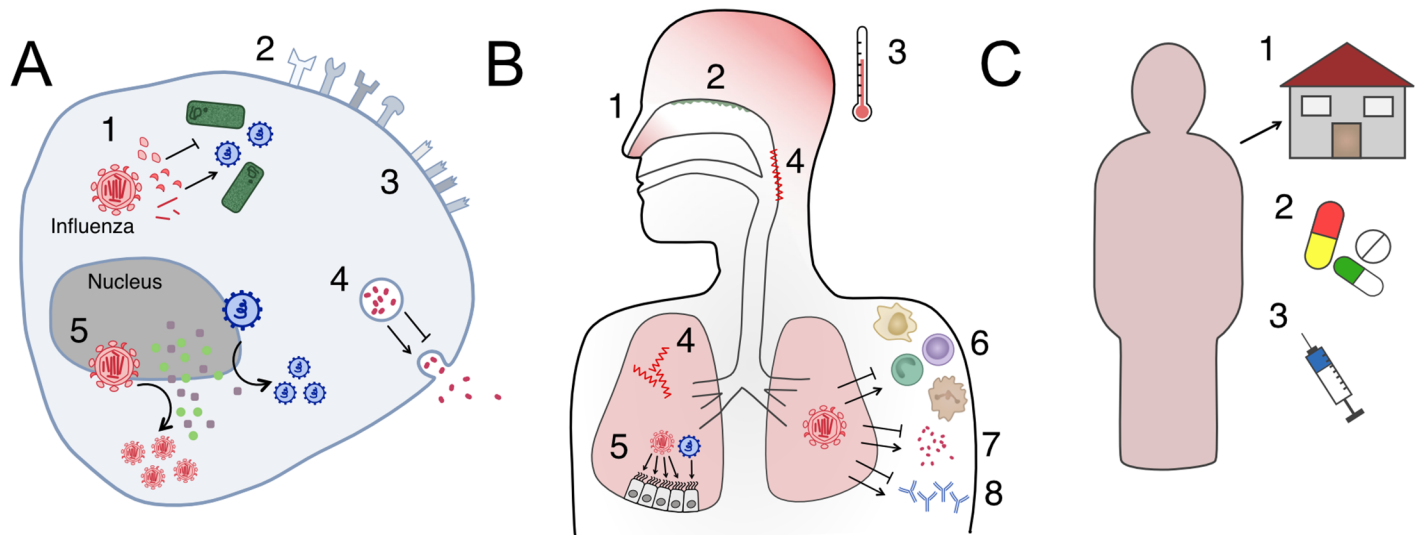
Fig 1. Influenza interactions with other pathogens occur within host or at the population level. Each interaction could either inhibit or enhance coinfection, depending on the combination of pathogens. (A) Cellular-level interactions: (1) direct interactions between viral products; (2) altered receptor presentation; (3) cell damage, e.g., its surface receptors; (4) modification of release of immune system mediators; (5) competition for host resources among influenza and other pathogens. (B) Host-level interactions: (1) change of transmissibility due to symptoms; (2) individual variation in commensal microbiota; (3) effect of symptomatic responses to infection; (4) tissue damage, e.g., in the nasopharynx or lung; (5) competition for host resources, e.g., target cells for infection; (6) immune cell–mediated interaction; (7) immune signalling–mediated interaction; (8) antibody-mediated interaction. (C) Population-level interaction: (1) behavioural responses to disease; (2) medication use; (3) vaccination behaviour. Bacterial interaction mechanisms include A1–5, B1–4 and 7, C1–3. Viral interaction mechanisms include A1–2 and 4–5, B1–3 and 4–8, C1–3.

immunity [31]. Infection with a second virus could be modulated similarly, e.g., by the production of cross-reactive antibodies or cell-mediated immunity that prevents or facilitates this infection. Physiological changes induced by the host response to infection have consequences on other pathogens. For instance, lung tissue damage [32] and the induction of type-1 interferon signalling were shown to promote bacterial colonization [31] and broadly inhibit viral replication [33]. Damage to lung cells caused by influenza infection, such as influenza neuraminidase stripping sialic acids from the cell surface, amplifies bacterial adherence and invasion [27] and could potentially change the likelihood of infection by another virus. Symptomatic responses to infection, like fever, have also been shown to act as 'danger signals' for bacteria, e.g., meningococci, which react by enhancing bacterial defences against human immune cells [34]. In contrast, fever may diminish viral replication rate, thereby lowering the probability of coinfection. From the other side, the 'influenza preinfection' respiratory flora of individuals may also partially account for the variability of severity and outcome [28]. For example, *Staphylococcus aureus* colonization was shown to trigger viral load rebounds and reduce influenza virus clearance in animal studies [35–37].

Population-level interactions

Human behavioural responses to influenza infection can also indirectly impact transmission of bacteria or other viruses. For example, people with severe influenza symptoms are likely to stay home, modifying their contact patterns and making acquisition of second infections unlikely [38,39]. On the other hand, individuals with milder symptoms may maintain their regular activities, which could increase bacterial transmission to other individuals (as observed for tuberculosis [40]) or increase the chance of acquiring a second infection. Person-to-person variation in care seeking and medication use, such as antivirals, antibiotics, antipyretics, or vaccine(s) uptake, also influences the risk of coinfection. For example, use of the pneumococcal conjugate vaccine has decreased carriage of the pneumococcal vaccine strains in some contexts [41,42], and vaccination against *H. influenzae* type b has decreased carriage of the bacteria [43,44]. These vaccination campaigns may therefore decrease the chance of observing influenza–bacteria coinfections.

Evidence of interaction

Several literature reviews have described evidence of interactions between influenza and other respiratory bacterial or viral pathogens [3,27]. In this section, we briefly summarize the viral and bacterial species with evidence for interaction with influenza in recent laboratory and epidemiological studies (details on the search strategies are provided in S1 Appendix, section A).

Influenza–bacteria interactions

Experimental results suggest that most of the pathogenic and commensal bacteria in the nasopharynx may directly or indirectly interfere with influenza infection during host colonization or infection (Table 1). The best-studied influenza–bacteria interaction is with *Streptococcus pneumoniae* [3]. Influenza is thought to increase bacterial adherence and facilitate the progression from carriage to severe disease [28,45], although evidence from population studies is not so clear-cut [46–49]. Influenza was also shown to impair methicillin-resistant *Staphylococcus aureus* (MRSA) clearance in coinfected mice, thereby increasing their susceptibility to MRSA infection [50]. Similarly, in mice, increased severity of *H. influenzae* induced by influenza was suggested, based on experiments of sequential infection with sublethal influenza then *H. influenzae* doses [51]. Notably, ecological studies revealed a positive association between influenza and *Neisseria meningitidis* incidence [52] and in vitro studies suggested that direct interaction

Table 1. Bacteria whose colonization or infection course may be affected by interaction with influenza.

Bacterial species	Study system	Effect	Illustrative publications
S. pneumoniae	Animal	Synergistic/ Facilitating	Smith 2013 [97]; Wolf 2014 [137]; Siegel 2014 [138]; McCullers 2010 [139]; Ghoneim 2013 [32]; Peltola 2006 [140]; Walters 2016 [141]; Nakamura 2011 [142];
	Human	Synergistic/ Facilitating	Walter 2010 [143]; Nelson 2012 [144]; Opatowski 2013 [102]; Shrestha 2013 [107]; Weinberger 2013 [89]; Jansen 2008 [145]; Kuster 2011 [146]; Nicoli 2013 [88]; Ampofo 2008 [147]; Grabowska 2006 [148]; Murdoch 2008 [149]; Edwards 2011 [150]; Weinberger 2014 [151]; Grijalva 2014 [152];
		Neutral/Unclear	Kim et al. 1996 [47]; Watson 2006 [48]; Toschke 2008 [49]; Zhou 2012 [153]; Damasio 2015 [154]; Hendricks 2017 [91]
S. aureus	In vitro and Animal	Synergistic/ Facilitating	Niemann 2012 [155]; Davison 1982 [156]; Tashiro 1987 [37]; Zhang 1996 [157]; Chertow 2016 [158]; Sun 2014 [50]; Braun 2007 [35]; Iverson 2011 [159]; Robinson 2013 [160]
	Human	Synergistic/ Facilitating	Sherertz 1996 [161]; Hageman 2006 [162]; Finelli 2008 [163]; Reed 2009 [164]
		Neutral	Kobayashi 2013 [165]
H. influenzae	Animal	Synergistic/ Facilitating	Lee 2010 [51]; Michaels 1977 [166]; Bakaletz 1988 [167]; Francis 1945 [168]
	Human	Synergistic/ Facilitating	Morens 2008 [10]
N. meningitidis	In vitro and Animal	Synergistic/ Facilitating	Rameix-Welti 2009 [53]; Loh 2013 [34]
		Neutral	Read 1999 [169]
	Human	Synergistic/ Facilitating	Cartwright 1991 [170]; Hubert 1992 [52]; Jacobs 2014 [171]; Brundage 2006 [172]; Jansen 2008 [145]; Jacobs 2014 [171]; Makras 2001 [173]
M. tuberculosis	Animal	Synergistic/ Facilitating	Florido 2015 [174]; Florido 2013[55]; Volkert 1947 [175]; Redford 2014 [176]
	Human	Synergistic/ Facilitating	Walaza 2015 [177]; Oei 2012[178]; Noymer 2011 [179]; Noymer 2009 [180]; Zurcher 2016 [181]
		Neutral	Roth 2013[182]
S. pyogenes	Animal	Synergistic/ Facilitating	Klonoski 2014 [183]; Okamoto 2003 [184]; Okamoto 2004 [185]; Hafez 2010 [186]
	Human	Synergistic/ Facilitating	Scaber 2011 [187]; Zakikhany 2011 [111]; Tasher 2011 [188]
		Neutral	Tamayo 2016 [189]

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between influenza A neuraminidase and the *N. meningitidis* capsule enhanced bacterial adhesion to cultured epithelial cells [53]. Lastly, in patients with pulmonary tuberculosis, there is evidence of increased risk of severe outcomes on influenza infection [54]. This finding was supported by experiments in mice [55] that demonstrated that *Mycobacterium tuberculosis* and influenza coinfected mice mounted weaker immune responses specific to *M. bovis* Bacillus Calmette–Guerin (BCG) in the lungs compared with mice infected with BCG alone.

Virus–virus interactions

Within its family, influenza interacts between types (A and B), subtypes (e.g., H3N2, H1N1), and strains. Competitive exclusion due to homologous immunity is widely accepted [56,57] and has been applied extensively in models of influenza strain coexistence [58,59]. Antigenic change (measured through antigenic distance) occurs constantly in influenza, strongly indicating that the virus escapes from immunity resulting from prior infection by genetic change [60]. Interestingly, there is mounting evidence that the first influenza infection is important and may affect severity of future infections [61–63]. Some evidence also supports the finding that influenza can interact with other influenza viruses and noninfluenza respiratory viruses via nonspecific immunity following infection [64,65].

Table 2. Viruses that may be affected by interaction with influenza.

Virus	Study system	Effect	Illustrative publications
RSV	Population incidence	Competitive	Anestad 2007 [190]; Anestad 2009 [191]; Casalegno 2010 [77];, Anestad 1987 [192]; Yang 2012 [79]; Nishimura 2005 [193]; Glezen 1980 [76]; Pascalis 2012 [83]; Yang 2015 [67]; van Asten 2016 [194]; Meningher 2014 [195]; Velasco-Hernandez 2015 [117]
		Neutral	Navarro-Mari 2012 [68]
	Coinfection detection	Competitive	Greer 2009 [84]; Martin 2013 [196]
	Laboratory investigation	Competitive	Shinjoh 2000 [197]
Rhinovirus	Population incidence	Competitive	Casalegno 2010 [66]; Casalegno 2010 [77]; Pascalis 2012 [83]; Linde 2009 [198]; Anestad and Nordbo [199]; Cowling 2012 [65]; Yang 2015 [67]
		Neutral	Yang 2012 [79]; Navarro-Mari 2012 [68]; van Asten 2016 [194]
	Coinfection detection	Competitive	Tanner 2012 [200]; Mackay 2013 [201]; Nisi 2010 [86]; Greer 2009 [84]; Martin 2013 [196]
	Laboratory investigation	Competitive	Pinky and Dobrovolny 2016 [112]
Influenza	Population incidence	Competitive	van Asten 2016 [194]
	Coinfection detection	Competitive	Nisii 2010 [86]; Sonoguchi 1985 [56]
	Laboratory studies	Competitive	Easton 2011 [202]; Laurie 2015 [57]
HPIV	Population incidence	Competitive	Yang 2012 [67]; Anestad 1987 [192]; Yang 2015 [67]
		Neutral	Mak 2012 [78]
	Coinfection detection	Competitive	Pascalis 2012 [83]
		Neutral	Murphy 1975 [85]; Nisii 2010 [86]; Greer 2009 [84]; Martin 2013 [196]
	Laboratory investigation	Synergistic/ Facilitating	Goto 2016 [203]

Abbreviations: HPIV, human parainfluenza virus; RSV, respiratory syncytial virus.

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Many noninfluenza viruses are also suspected of interfering with influenza virus acquisition, based on different types of studies (Table 2). During the 2009 influenza pandemic, Casalegno et al. reported that in France, the second pandemic wave was delayed due to the September rhinovirus epidemic [66], although this shift was not observed in other countries [67,68] and may have been affected by variable reporting rates. Coinfection by the two viruses might also enhance disease severity for individuals [69–71], although evidence is discordant [72–74]. Similarly, competitive interaction with respiratory syncytial virus (RSV) has been posited for many years [75,76], and some evidence was found for delayed RSV epidemics due to the second wave of the 2009 pandemic in France [77] and tropical regions [78,79]. There is discrepancy in the findings of interaction between influenza and RSV; while most studies found increased severity [74,80,81], others found no effect [69] and some found less severity [82]. Competitive interaction with parainfluenza viruses was also inferred, based on less frequent coinfection pairs than expected [83], but that observation is not consistent across studies [84–86]. In terms of severity, parainfluenza and influenza coinfection is usually more severe than influenza alone [69,71,87] but not always [72,73].

The general pattern is that bacteria tend to synergize with influenza, often boosting transmission of either pathogen or increasing invasion of the bacteria following influenza infection. It is not always clear whether this is a true synergy—in which both pathogens benefit—or rather that influenza facilitates bacterial invasion. In contrast, viral pathogens tend to form

competitive interactions with influenza, although whether these are direct, specific interactions with particular other viruses or the result of an 'early advantage' to the first infector remains unclear. This pattern may occur because of the differing natural histories of bacteria and viruses; while the former tends to infect hosts for long time periods, the latter has shorter infections more similar to the natural history of influenza itself. This is a complex system in which each host–pathogen or pathogen–pathogen interaction phenomenon may impact the others. Surprisingly, however, such interactions remain poorly studied and, in particular, very few modelling studies have addressed these questions.

Impact of interactions at the population level

Although coinfections occur at the host level, their consequences are far-reaching (Fig 2). Coinfection may alter the natural history, severity, or timing of illness in an individual and thereby modify the morbidity, healthcare-seeking behaviour, and treatment of that individual. Heterogeneity in these can affect the probability of, and timing of, reporting disease, thereby transferring the effect from individual hosts to the population level.

Development and implementation of public health policies rely on analyses of population surveillance data on influenza epidemics and burden. Policies then generate changes in medical interventions at the population level, e.g., change in vaccination targets, or at the individual level, e.g., recommendations for antibiotics or antivirals in certain groups. These public health interventions then have their own impacts on the dynamics of pathogens and coinfections. Therefore, because coinfections may alter surveillance data, and policies based on evidence from surveillance data may alter coinfection or interference risk, there is a complex cycle of dependence, which highlights the difficulty—as well as the potential importance—of assessing the impact of coinfections (Fig 2).

To date, most of the published quantitative analyses of interactions rely on statistical association between incident cases of influenza-like illness (ILI) and other infections based on
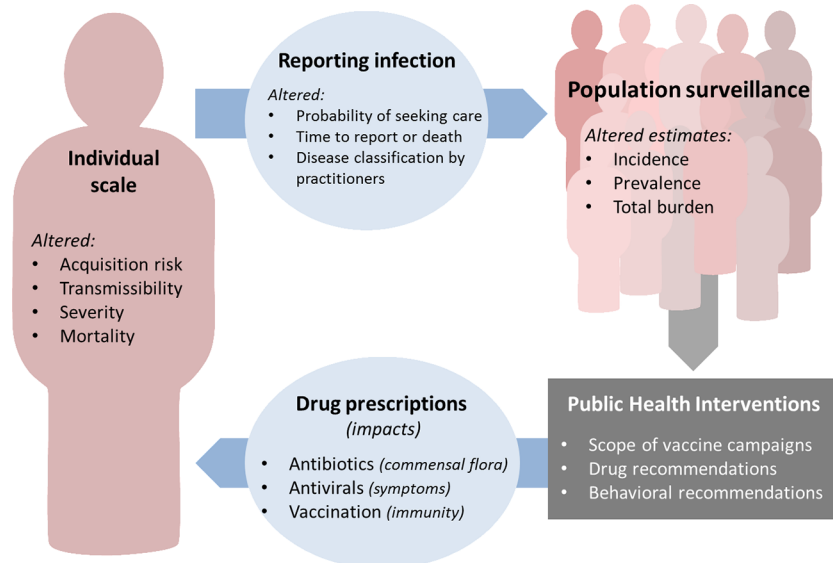
Fig 2. Cycle of factors affected by nonneutral interactions at the individual level and their impact on influenza surveillance, treatment, prevention, and control. Factors that affect coinfection on an individual scale can feed forward to an effect on population surveillance through their effects on the reporting of infection. Decisions on public health interventions are made in response to population-level data. These interventions then take effect at the individual level, to give a feedback loop both generated and impacted by effects of coinfection.

regression and correlation analyses [88,89]. A major methodological challenge of detecting interactions is that significant correlation between epidemics of two pathogens in surveillance data may result from either a true biological direct or indirect interaction or may be confounding as a result of the two pathogens sharing common ecological conditions (e.g., cold weather). Regression models describe simple functional links between, for example, the incidence time series, onset or peak time, or epidemic magnitude or severity. Despite their apparently simple formulation, they rely on strong statistical assumptions on the shape of the data and the association [90]. Regression models are also used to calculate correlations between reported time series at different time lags. When properly controlled for confounding variables, they have proved very useful tools to detect signals of associations. Other methods have been proposed through the deployment of seasonal autoregressive integrated moving average (SARIMA) models to analyse time series [91], Granger causality [92,93], or seasonality patterns [94]. However, these models do not formalize the transmission process or biological mechanism of interaction, so the interaction mechanism cannot be determined nor the strength of interaction quantified. Furthermore, this lack of mechanistic formulation prevents easily interpretable predictions that are required to support public health decision-making.

Due to the complex phenomena and many feedback loops, mechanistic models are needed to dissect the cause and effect of the different components (Box 1) [95]. The role of modelling

Box 1. Mathematical modelling definitions

Mathematical versus **statistical models**: A **mathematical model** (or **transmission** or **mechanistic model**) is a mechanistic description by mathematical equations of how the number of infected entities changes over time. For example, a mathematical model of transmission between people might explicitly track the number of infected people and describe how many contacts they make, how often these contacts lead to transmission, and how this is affected by temperature. Depending on the scale of the model, entities can be cells, individuals, or groups of individuals (e.g., a household, a city). **Statistical models** do not include a mechanistic link between quantities but only rely on an observed association, often in the form of a probability distribution. So, in the case of the statistical model, you might say that you see more cases when the temperature is low, without explicitly explaining why.

Individual-based model versus **compartmental models**: **Individual-based models** (or **agent-based models**) include a description of the properties (e.g., age, immune status, risk factors) of each of the individuals in the studied population. In contrast, **compartmental models** group individuals with similar characteristics together into compartments and look at relationships between these compartments. The most famous compartmental in epidemiology is the SIR model, based on three compartments, Susceptible-Infectious-Recovered, which is the basis of most of the existing models of pathogen transmission. Compartmental models are easier to fit to data (see next section) and interpret. Individual-based models are more flexible when it is important to integrate a wide range of characteristics of the population but are comparatively slow to implement and run, more difficult to interpret, and require good data on each characteristic that is modelled.

Model fitting: Models are built around a structure (the mechanisms), which is modulated by parameters governing the rates of change between compartments, disease states, behaviours, etc. Historically, parameters have been estimated using results from studies

published in the literature. In recent years, with the increased availability of epidemiological data, modelers try whenever possible to fit the model to data (also called **parameter inference** or **calibration**). For this, they use algorithms that explore 'parameter space', which is the set of all possible values for parameters, and retain sets of parameters that explain the observed data best. Fitting can be computationally intensive if the model includes many parameters. More efficient fitting algorithms allow fitting of more complex models and thus the study of potentially more interaction mechanisms.

is two-fold: first, mathematical modelling provides a common language to integrate heterogeneous mechanisms and test competitive hypotheses. By doing so, models contribute to building basic knowledge about infection processes. Second, modelling enables assessment of potential intervention scenarios by predicting their impact.

For these reasons, public health interventions based on modelling of infectious diseases have become informative and effective. For example, in the UK, a transmission model fitted to a vast range of ILI and influenza surveillance data demonstrated that vaccinating children against influenza will have the same protective effect on people over 65 years old as vaccinating those individuals [96]. This outcome is a consequence of the diminished community transmission that results from reducing infections in children. Such an impact would be impossible to identify without mechanistic models. Box 2 summarises the potential benefits of coinfection transmission models.

Box 2. Benefits of coinfection transmission models

- Allow causal relationships to be drawn from the data by testing hypotheses regarding interaction mechanisms

  - For example, using models to analyse the cellular dynamics observed in vivo in mouse coinfection experiments, it is possible to design models of hypothesised immunological pathways and determine which most closely fits observed patterns [97].

- Evaluate contributions to influenza burden with more precision

  - For example, year-to-year influenza epidemics have a different estimated reporting fraction. A model could be used to determine whether coinfection or concurrent epidemics of other viruses are the reason for an increased (or decreased) probability of reporting infection.

- Predict or project incidence of coinfections, including during pandemics

  - For example, fitting multipathogen models to respiratory virus surveillance data would allow quantitative assessment of the hypothesis that during the 2009 pandemic, influenza affected the timing of rhinovirus, RSV, and influenza by competition [66,77].

- Optimize prevention and control of influenza infections and their complications

- For example, a model of influenza and pneumococcal pneumonia could determine optimal target groups for pneumococcal vaccination, based on both the bacterial carriage rates in each age group and the expected influenza vaccination rates in those age groups.

- Estimate the costs and benefits of intervention strategies

  - For example, a model-based analysis of in vitro experimental data could allow assessment of the impact of early antiviral or antibiotic treatment on probability of pneumococcal invasion [98,100]. Combined with population, it would be possible to assess the impact on secondary bacterial infections.

Models of influenza interactions

Despite mounting evidence of influenza–bacteria interactions and the concurrent increasing use of dynamic modelling to study infectious diseases in recent decades, influenza interactions have rarely been modelled. Interestingly, previous literature reviews describing evidence of interactions between influenza virus and other respiratory bacterial or viral pathogens neglected mathematical models that, despite their limited number, provide insight into mechanisms of interaction and their consequences [3,27]. We have systematically reviewed the literature for models incorporating influenza with bacteria or noninfluenza viruses (details on the search strategies are provided in S1 Appendix, section A).

Influenza–bacteria interaction

The only influenza–bacterium interaction that has been integrated into mathematical modelling studies is the influenza–pneumococcus system, both within host and at the population level.

Several dynamic models of coinfection at the cellular level were proposed relatively recently [97–101]. In a study combining modelling and empirical data from mice coinfected with two different influenza viruses and two pneumococcus strains, Smith et al. assessed the likelihood of different immunological interaction mechanisms [97]. They found a role of macrophage dysfunction leading to an increase of bacterial titres and increased virus release during coinfections [97], although their results suggest that coinfection-induced increase of bacterial adherence and of infected cell death were not very likely. Shrestha et al. used an immune-mediated model of the virus–bacterium interaction in the lungs to specifically quantify interaction timing and intensity [98]. They assumed that the efficiency of alveolar macrophages, which are a critical component of host immunity against bacterial infections, was reduced by viral infection and tested the impact of inoculum size, time of bacterial invasion after influenza infection, and the potential impact of antiviral administration. The model predicted that enhanced susceptibility to invasion would be observed four to six days after influenza infection, suggesting that early antiviral administration after influenza infection (<4 days) could prevent invasive pneumococcal disease. Smith and Smith modelled a nonlinear initial dose threshold, below which bacteria (pneumococcus) declined and above which bacteria increased. Using data from mice experiments, they showed that this threshold was dependent on the degree of virus-induced depletion of alveolar macrophages. Because macrophage depletion varies through the course of influenza infection, this important finding may explain why risk of bacterial invasion also changes over the course of infection, with particularly low dose requirement in the first few days of infection [99]. In a follow-up study, the same authors analysed published data

from influenza–pneumococcus coinfected mice treated with antiviral, antibiotic, or immune modulatory agents. They found that antivirals are more efficient at preventing secondary infection when used in the first two days of influenza infection and also found an important benefit of immunotherapy, especially for low bacterial loads [100]. Lastly, in a within-host model, Boianelli and colleagues investigated the efficacy of different oseltamivir treatment regimens in influenza–pneumococcus coinfected individuals using parameters drawn from human and mouse studies. They found that increasing the dose of oseltamivir, but not duration of treatment, might increase both its antiviral and antibacterial efficacy [101].

At the population level, there have been several models to assess influenza interactions with bacteria and test hypotheses regarding the main mechanisms [102–106]. The comparison of pneumococcal transmission models to analyse time series of pneumococcal meningitis and viral respiratory infections in France highlighted two important processes in colonized individuals: (1) a virus-related increase in pneumococcal pathogenicity and (2) an enhanced between-individual transmissibility of bacteria [102]. Models of transmission of bacterial pneumonia fitted to US data also highlighted significant interactions, mainly due to influenza-associated increase of individual risk of pneumonia [103,107]. Recently, in a simulation study, Arduin et al. used a flexible individual-based model of influenza–bacteria interaction to assess the population consequences and associated burden of a range of pneumococcus–influenza interaction mechanisms [108]. Population dynamic models have also been used to test the public health impact of control measures [104–106]. Different strategies of antibiotic use (as treatment or prophylaxis) and of vaccination were assessed by modelling the dual transmission of pneumococcus and influenza [104]. For a 1918-like pandemic, this model suggested that widespread antibiotic treatment of individuals with pneumonia would significantly lower mortality, whereas antibiotics in prophylaxis would effectively prevent pneumonia cases. A different model evaluated the benefit of vaccinating the UK population against pneumococcus in the context of pandemic influenza using different scenarios: 1918-like, 1957/1968-like, or 2009-like virus [105]. This indicated that pneumococcal vaccination would have a major impact only for a pandemic with high case fatality and secondary pneumococcal infection rates (e.g., the 1918-like), with less influence in other scenarios.

Viral interaction

Influenza–influenza interactions predominate in models of two viruses, with limited investigation of influenza–RSV interactions and no models of other viruses.

Within host, several models of multistrain influenza infections were proposed [109–111], especially examining the interval before the secondary infection. One model of RSV–influenza interaction at the cellular level explored the hypothesis of the viruses interacting through competition for resources within the cell [112]. This indirect competition was sufficient to explain the observed rate of virus replication. The model also explored how the speed of virus replication confers an advantage to the first infecting pathogen and determined the 'head start' on infection that the slower-replicating virus would require to maintain dominance.

Population models have been used extensively to examine the dynamics of influenza and multistrain influenza systems (for a review see [113]) although many fewer studies examined multispecies systems. Because the influenza virus comprises two types, multiple subtypes, and potentially numerous strains of each, many viruses may be circulating at any given time, providing varying degrees of cross-protection after recovery and sometimes with complex dynamics of within-species strain replacement due to genetic drift or reassortment. There is evidence of competition between strains, with some models requiring short periods of heterologous immunity after infection to create the ladder-like phylodynamic structure of influenza viruses [114], although recent

studies could capture this feature without this mechanism [58]. One comprehensive early model tested four mechanisms of interaction between influenza types using data from Tecumseh, Michigan, but the data were insufficient to distinguish the mechanisms [115]. Influenza–influenza models must also account for the complex immune history of hosts, related to which there is mounting evidence that the timing of an individual's influenza encounters, and especially the first infection, shapes their future response [61–63]. The methods for modelling influenza–influenza interactions should be extended into interactions with other viruses.

One model for pandemic influenza, in which coinfection with other respiratory pathogens leads to enhanced influenza transmission, was proposed to explain the multiple waves of the 1918 influenza pandemic in the UK [116]. A recent example of influenza and RSV cross-species analysis in a climatically driven model provided some evidence that RSV dominates influenza, but the model was not explicitly fitted to data [117].

Illustration from a simple model

To demonstrate how both synergistic and competitive interactions can be modelled, we used a simple transmission model and simulated the effect of interactions (Box 3, Figs 3 and 4 and S1

Box 3. A simple model of interaction

The simple model in Fig 3 tests two interaction mechanisms: increased (or decreased) infectiousness on coinfection and decreased (or increased) probability of coinfection occurring. These are the two most commonly suggested mechanisms, the first of the 'bacterial type' and the second of the 'viral type' (Fig 4).

In Fig 3, all individuals start in the Susceptible (S) class and move to the Infectious classes when they are infected by either pathogen 1 (I_1) or 2 (I_2).

Infected (and infectious) compartments are shown in colour, where red is infectious with pathogen 1, blue marks infectious with pathogen 2, and infected and infectious with both pathogens in purple. Infection rates are given by the four forces of infection ($\lambda_1, \lambda_2, \lambda_{12}, \lambda_{21}$). After being infected by one pathogen, individuals can either be coinfected by the other pathogen and move to the coinfection compartments in purple (I_{12} or I_{21}), or they can recover at rates γ and move to the Recovered compartments (R_1 and R_2). Coinfected individuals (I_{12} and I_{21}) recover and remain in the doubly recovered compartments, R_{12} and R_{21}. Individuals in R_1 or R_2 are subject to force of infection λ_2 or λ_1, respectively, i.e., of the pathogen they have not yet had. On infection with the other pathogen, they move to the consecutive infection compartment (C_{12} or C_{21}). After recovery, those individuals move to the doubly recovered compartments (R_{12} and R_{21}).

Parameters β_1 and β_2 are the baseline transmissibility of pathogen 1 and 2, respectively. There are four interaction parameters modulating the pathogen's transmissibility: σ_1 and σ_2 are the change in infectiousness of coinfected classes, where a value less than 1 makes the coinfected class less infectious, and a value greater than 1 means coinfected individuals are more infectious. Parameters δ_1 and δ_2 alter the probability of acquisition of a second infection following a first infection, where a value less than 1 makes coinfection less likely, and a value above 1 makes it more likely.

Details on the model equations and computer code generating the trajectories are given in S1 Appendix, section B and S1 Code.

Appendix, section B). We show how these interactions occurring at the individual level can impact the epidemics at the population level. The 'bacterial type' interaction firstly shows an increase in bacterial prevalence when influenza infection increases bacterial transmission, in a facilitative interaction. In a synergistic interaction, where coinfection increases transmission of both influenza and bacteria, prevalence of bacteria increases, and the epidemic of influenza has a quicker and higher peak. In the 'viral type' competitive interaction, progressively decreasing the probability that a second pathogen can infect an already infected host causes the epidemic peaks to separate in time. It also decreases the peak size of the outcompeted pathogen without altering the number of people infected in total (Fig 4).

Limits of the current view

Historically, scientific and medical studies have tended to focus on host–pathogen interactions in an independent manner by studying each pathogen alone. We highlighted here, as others [3,27, 28], that many respiratory viruses and bacteria have been linked to influenza epidemiology, based on in vivo evidence and from individual and epidemiological studies. These nonneutral interactions, mostly facilitative for bacteria and competitive for viruses, probably have individual- and population-level effects on influenza pathogenicity, burden, and potentially its epidemic profile.

Mathematical models are crucial to guide public health decision makers, who, for ethical or cost reasons, cannot conduct large-scale trials. Two examples of interventions based on modelling results and mobilizing important public resources are pandemic preparedness (stockpiling of antivirals, use of vaccine doses) [118] and national immunization programs [20]. Neglecting the cocirculating pathogens—i.e., adopting influenza tunnel vision—and the indirect impact of coinfections may potentially affect the estimation of the risk associated with influenza infection and, consequently, the accuracy of model predictions. Interaction strength may also change from year to year and depend on the circulating influenza strains. For evaluation of interventions, this neglect can lead to overestimation of the impact—if burden was measured without considering the changing landscape of coinfection in the population—or underestimation—if the effect of an intervention does not account for the potentially decreased burden of an interacting pathogen as a result of diminished influenza transmission. For all these reasons, we think that adopting a more holistic approach to modelling of respiratory pathogens will improve their surveillance and the strategy to control them.

Opportunities

Considering influenza virus in its ecological context and its interactions as a cause of the associated morbidity and mortality should offer opportunities for prevention and treatment. In
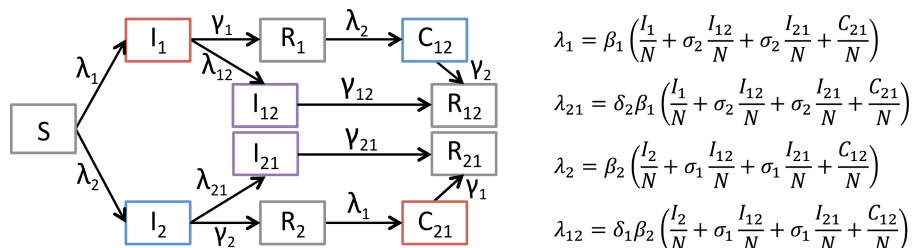
Fig 3. Illustration of a simple model of two circulating pathogens in interactions. Schematic of the compartments and rates of transition between compartments, with equations of the forces of infection by pathogen 1 (λ_1), pathogen 2 (λ_2) for susceptible hosts, and pathogen 1 (λ_{21}) and pathogen 2 (λ_{12}) for hosts already infected by the other pathogen. The full system of ordinary differential equations describing the changes of the compartment's populations over time is described in S1 Appendix, section B. Details of the model and parameters are provided in Box 3.

https://doi.org/10.1371/journal.ppat.1006770.g003
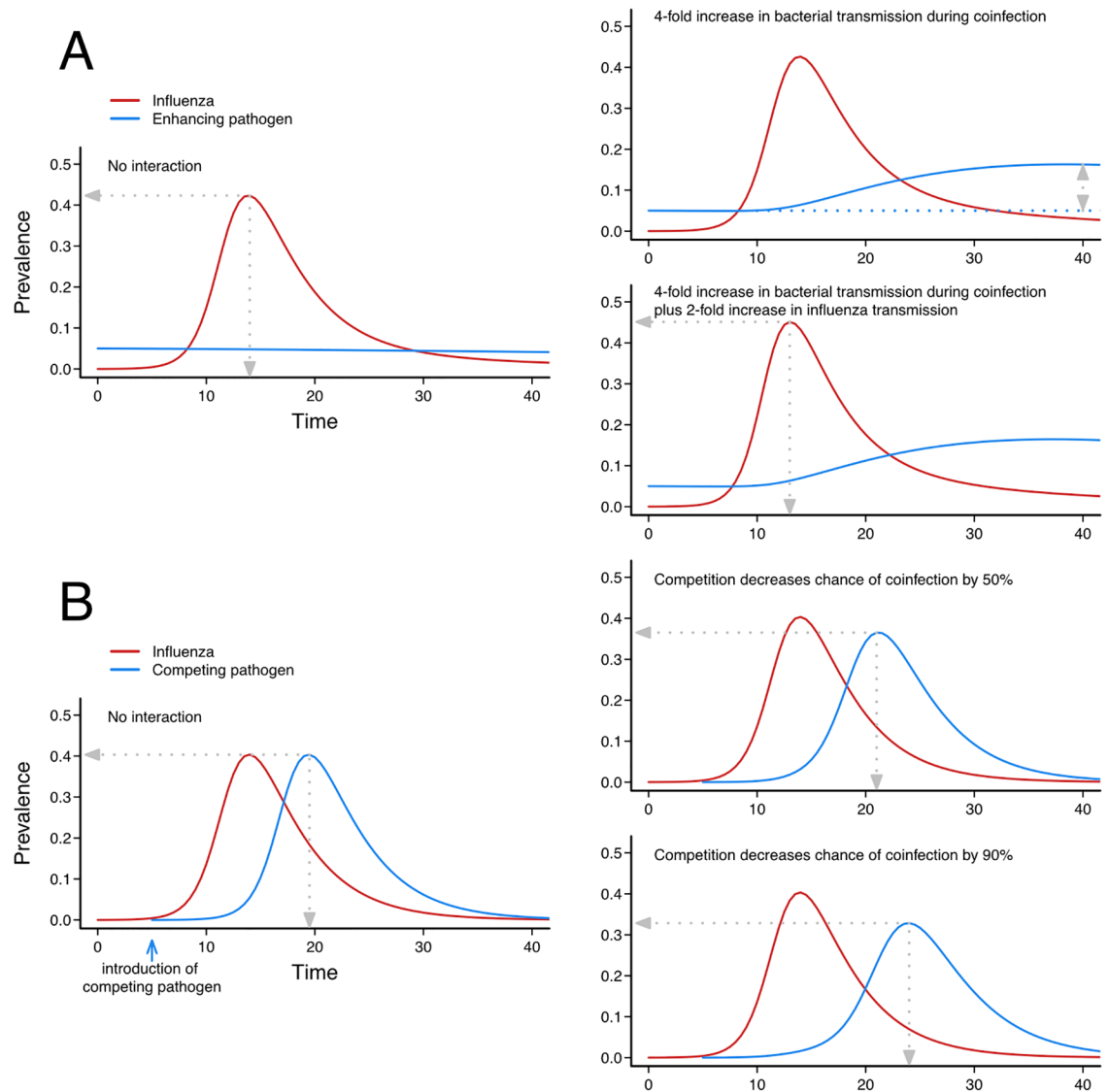
Fig 4. Example model outputs showing effect of synergistic and competitive interaction. Box 3 gives details on the model that produces these epidemic trajectories. (A) In the baseline enhancing scenario, an endemic bacterial pathogen (blue) occurs at 5% prevalence. An influenza epidemic occurs with no interaction, and the bacterial prevalence does not change. If the presence of influenza coinfection increases bacterial transmissibility by 4-fold ($\sigma_1 = 4$), then there is a transient rise in bacterial prevalence. If there is also an increase in influenza transmissibility during coinfection ($\sigma_1 = 4$ and $\sigma_2 = 2$), then there is also a higher and earlier influenza peak as a result of coinfection. (B) In the baseline competition scenario, the second epidemic pathogen is introduced later than influenza. The two pathogens have the same transmission characteristics (same γ, same β). If there is only a 50% chance of infection with pathogen 2 when individuals are infected with pathogen 1 ($\delta_1 = 0.5$), then the epidemic trajectory of pathogen 2 is lower and later. If competition is even stronger ($\delta_1 = 0.1$) so there is a 90% reduction in chance of coinfection, the profile of pathogen 2 is even further separated from pathogen 1. Computer code generating these trajectories is given in S1 Code.

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addition to influenza vaccines that (partially) protect against infection, antibacterial vaccines are also critical. For example, pneumococcal vaccines have been shown to have good efficacy against influenza-associated nonbacteremic pneumonias [119,120]. The 23-valent pneumococcal polysaccharide vaccine significantly lowered the risk of invasive pneumococcal disease and attributed mortality in the elderly [121]. Better understanding of possible influenza–pneumococcus interactions and integrating those into transmission models could potentially enable us to identify synergies between vaccination programs and optimize the use of both vaccines.

In addition, there may be opportunities for optimization of antibiotic and antiviral pre-
scriptions. First, antibiotics have historically been used to prevent secondary infections
[122,123]. Increasing rates of antibiotic resistance worldwide led to policies to decrease anti-
biotic consumption, focusing particular attention on reducing prescriptions for viral infec-
tions. Second, neuraminidase inhibitors were found to prevent some secondary bacterial
pneumonias in animal experiments, human epidemiological studies, and mathematical
modelling studies, beyond the window in which they directly impact the influenza viral load
[98,124,125]. Although antivirals may only modestly attenuate influenza symptoms, a body of
evidence suggests they could avoid severe and economically important outcomes of influenza
infection [125–128].

Lastly, accurate burden quantification is crucial to designing and implementing public
health interventions against influenza. Focusing efforts to better understand these interactions
is therefore critical, especially in the context of pandemic influenza but also to plan for seasonal
epidemics, by forecasting the onset and peak times and estimating the expected burden. To
improve our knowledge, models can be used to analyse available surveillance and experimental
data, generate hypotheses regarding interaction mechanisms at play in transmission or infec-
tion, and test their likelihoods. Competing assumptions on the biological interaction processes
can be assessed, and the strength of interactions can also be estimated. From a public health
viewpoint, such models would help better estimate the burden of influenza virus interactions
in terms of morbidity and mortality, the cost-effectiveness of interventions, and, critically,
more accurately predict the real impact of control measures.

Challenges

Integrating transmission and infection by multiple pathogens into mathematical models poses
several challenges. From a methodological perspective, modelling several pathogens with inter-
related natural histories makes classical compartmental approaches more difficult. Individual-
based frameworks (Box 1) are better adapted for this task. For example, this approach could be
used to investigate the effect of the interval between influenza infection and bacterial acquisi-
tion, which reportedly affects the risk of bacterial invasion [31,129]. Individual-based models
are often more computationally intensive and can introduce new difficulties in terms of
parameter estimation, requiring the design of new methods. Recent developments in statistical
inference methods, like particle Markov chain Monte Carlo (pMCMC) or maximum likeli-
hood estimation via iterated filtering (MIF) [130,131], now enable modelers to jointly fit com-
plex population-based models to multiple types of data, thereby allowing more data and more
diverse types of data to inform the model parameters.

Epidemiological data represent the second major challenge. To date, modelling studies
have been limited by the poor knowledge of respiratory viruses and bacteria circulating in the
community, especially because little is known about prevalence, incidence, at-risk populations,
and even epidemic profiles in different populations. Deeper understanding of the ecology of
the vast number of microorganisms that can contribute is needed. On an individual level, new
studies are required to assess the effect of coinfections rather than ecological associations from
incidence data. Important features include (i) coinfection-induced alteration of diseases' natu-
ral histories, e.g., increased acquisition and severity risk, changes of infection durations and
generation times; (ii) specific at-risk periods for secondary infection or invasion of the coin-
fecting pathogen, or at-risk periods for severe outcomes; and (iii) at-risk populations, as char-
acterized by individuals' age, comorbidities, or behavioural risk factors.

For population-level data, in most countries, surveillance of influenza acquisition is based
on networks of general practitioners who notify patients consulting for clinical symptoms of

ILI [132]. Surveillance data streams based on syndromic surveillance [133], inpatient data [134], and pathogen testing [135,136] should be combined, and linked at the patient level, to better identify noninfluenza infections or anomalous epidemics that could signal interaction. Improvement of data quality in patient records and detection of the biases inherent in different types of surveillance data are critical to achieve this goal. The latter could be reached by developing new microbiological tools, including new sampling kits able to rapidly detect multiple pathogens for use during medical consultations.

Public health decision-making for interacting pathogens is a difficult but important challenge. When multiple competing treatment options are available, a coherent framework is needed to determine the best strategy. While the question goes beyond influenza to interactions and coinfections for respiratory viruses in general (e.g., RSV), influenza is one of the most studied viral infections and is therefore the ideal first candidate to develop a more holistic mathematical modelling approach.

Conclusion

In this study, we examined the epidemiological and biological evidence supporting influenza virus interference and interaction with other pathogens. We highlighted opportunities to improve knowledge and control of the virus, if we can move forward from the tunnel vision of single-pathogen models. It is time to develop a more holistic approach to pathogen dynamics in mathematical modelling, with novel methodological innovations, and further efforts in data collection and surveillance. The motivation to do so lies in the real opportunity to improve public health practices and create better, more cost-effective interventions against influenza.

Supporting information

S1 Fig. PRISMA diagram for search for influenza–bacteria interactions.
(TIF)

S2 Fig. PRISMA diagram for search for influenza–other virus interactions.
(TIF)

S1 Appendix. Microsoft Word document providing details on the search strategy and the mathematical model.
(DOCX)

S1 Code. Computer code of the coinfection model.
(R)

Acknowledgments

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