Use of mathematical modelling to assess the impact of vaccines on antibiotic resistance

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Antibiotic resistance is a major global threat to the provision of safe and effective health care. To control antibiotic resistance, vaccines have been proposed as an essential intervention, complementing improvements in diagnostic testing, antibiotic stewardship, and drug pipelines. The decision to introduce or amend vaccination programmes is routinely based on mathematical modelling. However, few mathematical models address the impact of vaccination on antibiotic resistance. We reviewed the literature using PubMed to identify all studies that used an original mathematical model to quantify the impact of a vaccine on antibiotic resistance transmission within a human population. We reviewed the models from the resulting studies in the context of a new framework to elucidate the pathways through which vaccination might impact antibiotic resistance. We identified eight mathematical modelling studies; the state of the literature highlighted important gaps in our understanding. Notably, studies are limited in the range of pathways represented, their geographical scope, and the vaccine–pathogen combinations assessed. Furthermore, to translate model predictions into public health decision making, more work is needed to understand how model structure and parameterisation affects model predictions and how to embed these predictions within economic frameworks.

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Introduction

The United Nations General Assembly named antimicrobial resistance as one of the greatest global health challenges faced nowadays, with the largest burden arising from bacterial resistance to antibiotics.[1] In Europe alone, 25 000 people die every year from hospital-acquired drug-resistant bacterial infections[2] and on a global scale, existing trends in antibiotic resistance predict an additional 10 million deaths yearly and an economic loss of up to US$10 trillion by 2050.[3,4]

Resistance to new drugs can emerge in as little as a decade[5] and few new antibiotics are in the pipeline.[6] Vaccines have been proposed as an innovative tool for reducing infection and carriage of antibiotic-resistant pathogens.[7] However, several potentially interacting mechanisms have been proposed for how vaccines might reduce antibiotic resistance,[7–9] highlighting the complexity of predicting the benefits of vaccination to control antibiotic-resistant pathogens.

One well established method for understanding the complex interactions between pathogens, hosts, and their environment is mathematical modelling. Mathematical models of infectious disease dynamics have been used to understand and predict the impact of vaccination and antibiotic resistance.[10,11] These models can quantify the factors governing the acquisition and transmission of antibiotic resistance, and predict the protective effect of vaccines on their recipients and the population. Furthermore, such models can be readily integrated within economic frameworks to project the economic costs and benefits attributable to antibiotic resistance and vaccination. Establishment of the cost-effectiveness of interventions can aid policy decision making about funding for control of antibiotic resistance and vaccination programmes.

In this Review, we assess how models can be and have been used to quantify the impact of vaccines on antimicrobial resistance. We outline the mechanisms that might affect the emergence and spread of antibiotic-resistant colonisation and infection and we identify how mathematical models can accurately capture these mechanisms to quantify the pathways through which vaccines impact antibiotic resistance. We then use this framework to structure a literature review assessing the extent to which existing mathematical models have captured these causal pathways. Finally, we identify key areas for further modelling research and discuss how mathematical modelling can inform public health decision making on the use of vaccines to control antibiotic resistance.

Modelling of the causal pathways in the antibiotic resistance–vaccine system

Vaccination can reduce the acquisition of antibiotic resistance in a population through diverse and interacting causal pathways. To ensure consistency and

Key messages

- Direct and indirect pathways exist through which vaccination affects both the number of cases of resistant disease and the amount of antibiotic use
- Because of the multiple pathways through which vaccination acts, the impact of vaccination on transmission and emergence of antibiotic resistance is likely to be non-linear
- Although mathematical models are suitable to capture these non-linear effects of vaccines on antibiotic resistance dynamics, existing models do not capture characteristics that might be important to inform public health strategies
- For mathematical models to inform public health decision making, they will need to incorporate pathogen-specific and country-specific disease transmission as well as an economic evaluation to translate the model predictions into cost-effectiveness analysis

precision of language, we made three key distinctions in terminology.

First, we identified five levels at which vaccines might act: (1) at the direct level, by providing immunological protection against carriage and infection; (2) at the population level, by reducing the transmission of pathogens between individuals; (3) at the pathogen level, by altering mutation rates and selection pressures that affect the emergence and spread of resistance in bacteria; (4) at the health level, by modulating the extent to which bacterial carriage progresses to symptomatic disease; and (5) at the care level, by changing health-care seeking and prescribing behaviour within the health-care system (figure 1). In the mathematical modelling of vaccination and antibiotic resistance section, we discuss the mechanisms that operate at these levels, their onward and often dynamic impact on other levels (figure 2), and how these mechanisms can be parameterised in dynamic models.

Second, we distinguished between vaccines given against the focal pathogen or pathogen strains (ie, the bacterial pathogen being considered in terms of antibiotic resistance) and those used against non-focal pathogens (ie, viruses or bacteria that can indirectly affect antibiotic resistance in the focal pathogen). This terminology allows the phenomenon of pathogen resistance to be distinguished from vaccination and (different) pathogen (strains).

Third, we identified the target outcome and proxy outcome. The goal of any antibiotic resistance control programme is to reduce the number of infections caused by bacteria that are either fully or partly resistant to one or more antibiotics. We refer to this goal as the target outcome. A proxy outcome, which is often used to measure the effectiveness of an antibiotic resistance control programme, is a reduction in the propensity to seek health care, including the number of people taking antibiotics. We captured these outcomes in our framework (figure 2).

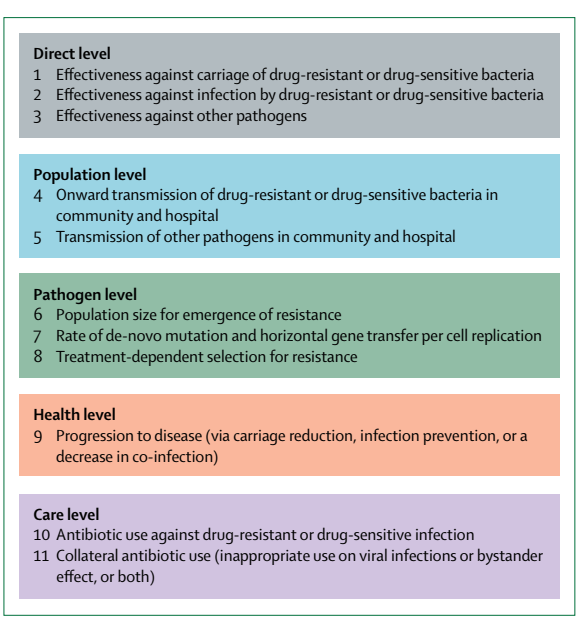

Figure 1: **Mechanisms of vaccines that can impact antibiotic resistance at five levels**

We distinguished bacterial carriage (or colonisation) from bacterial disease, with only the latter presenting symptomatically. Depending on the pathogen, accurate modelling of bacterial transmission might require differentiation between these two states. For example, although *Mycobacterium tuberculosis* relies on symptomatic active infection to transmit between people, other bacteria such as *Escherichia coli*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* are a common and largely harmless part of a person's microbiome. Bacteria belonging to this latter group can colonise individuals and transmit to others without progressing to symptomatic infection. This variation in the outcome of colonisation presents challenges not only to the design and implementation of vaccination programmes, but also to the understanding of basic epidemiology of antibiotic resistance. These challenges include estimation of the true prevalence of resistance and rate of transmission, and quantification of the impact of vaccination on the carriage population and subsequent disease cases.

Personal protection for vaccines at the direct level

Vaccines against bacterial carriage can protect recipients from colonisation by drug-sensitive and drug-resistant strains of the focal pathogen. If fewer people are colonised with resistant strains, fewer progressions to drug-resistant infections (target outcome) in the vaccinated population will occur. Additionally, fewer disease cases overall for sensitive and resistant strains will reduce antibiotic use (proxy outcome) in the vaccinated population.

As seen in the pneumococcal conjugate vaccination (PCV) against *S pneumoniae*, vaccination against bacterial carriage can result in complex dynamics of strain replacement if the vaccine targets only a subset of serotypes.[12] Therefore, modelling the impact of vaccination against carriage requires modelling the potential effect of strain replacement and competition between strains at a population level. Accurate quantification of such effects requires an estimate of the existing prevalence of strain carriage in the vaccinated population, the effectiveness of the vaccine against the colonisation of drug-sensitive and drug-resistant strains, and ideally the prevalence of dual strain carriage.

Although we have focused on vaccines against colonisation by the focal pathogen, vaccines that only reduce symptomatic bacterial infection and vaccines against non-focal pathogens can also play a part in the control of antibiotic resistance.

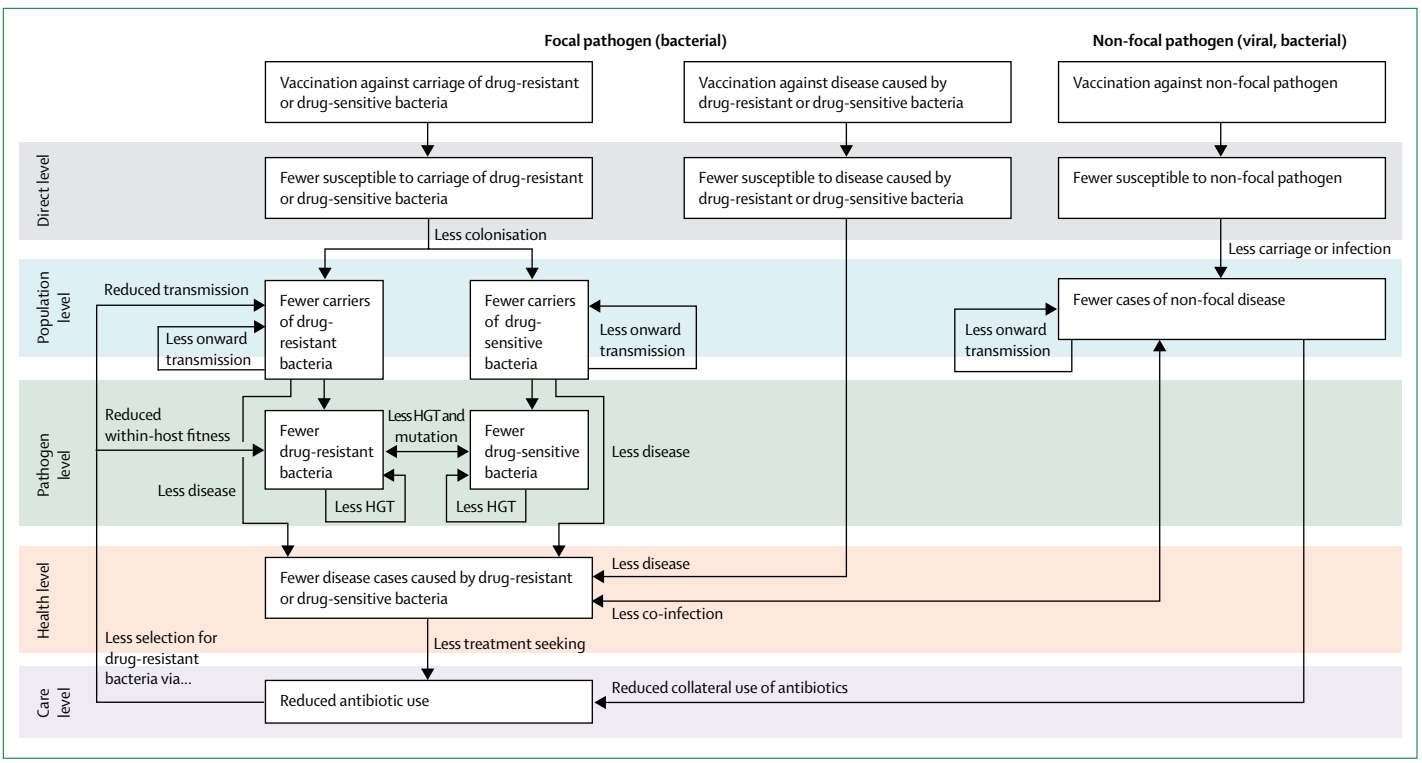

Figure 2: **Pathways through which vaccination against focal bacteria and non-focal bacteria and viruses can control antibiotic resistance.**
HGT=horizontal gene transfer.

Prevention of carriage and transmission at the population level

By protecting recipients from bacterial colonisation or disease, vaccines also indirectly protect non-recipients from onward transmission. For instance, post-introduction studies of *Haemophilus influenzae*[13,14] and PCV[15,16] found reduced disease prevalence in vaccinated children and unvaccinated individuals of the same and other age cohorts. A major strength of mathematical modelling is its ability to predict such herd effects of vaccination by modelling infectious contact between individuals, potentially stratified by age, geographical location, or other demographic factors. When only personal protection against bacterial colonisation is accounted for, the total reductions in antibiotic-resistant cases and antibiotic use in the total population are underestimated. To accurately capture this indirect effect, a mathematical model should include a transmission component—ie, the model should be dynamic in which the force of infection depends on the number (or relative frequency) of infectious individuals. Model structure and transmission parameters will vary with the setting that is most relevant to the acquisition of the resistant bacteria. For bacterial strains that are mostly transmitted in the community, quantification of the rate of daily contacts between individuals will be essential, whereas for resistant bacteria associated with nosocomial infections, a model will also need to capture hospital exposure. The transmission pathways identified within the mechanistic framework apply to community and nosocomial transmission.

Evolution of resistance at the pathogen level

The spread of resistance in bacterial populations is a dynamic process. A major challenge in the development of vaccination policy for controlling antibiotic resistance is the prediction of how bacterial strains targeted by a vaccine might evolve in response to the vaccination programme. Mathematical modelling helps to predict the impact of a vaccination programme—ie, not only the rate at which new resistant strains might emerge in the short term but also the long-term dynamics of replacement or the coexistence of sensitive and resistant bacterial strains in the population.

The initial emergence of antibiotic resistance in a sensitive strain within a human population occurs either through de-novo mutation or horizontal gene transfer from resistant strains.[17] Therefore, the total rate at which resistant genes appear depends on the total number of sensitive bacteria, and for horizontal gene transfer, their frequency of co-colonisation with resistant strains, regardless of whether they are the same species or not. Moreover, the mutation rate might vary with the level of antibiotic use because of stress-induced mutagenesis.[18] To accurately parameterise the rate at which resistance mutations are gained or lost, a model might need to

quantify the rate at which bacteria acquire new mutations affecting resistance (or partial resistance if biologically plausible) and genes affecting resistance are horizontally transferred between strains co-colonising a host. Because of their low frequency and stochastic nature, events of de-novo emergence might be quantified best in a stochastic mathematical framework.[19,20] In addition to horizontal gene transfer between strains colonising the same human host, spillover events of antibiotic resistance from animal reservoirs might occur, although the importance of horizontal gene transfer from this source is unclear.[21,22]

The persistence and spread of a resistant strain probably depends on whether the fitness benefit of resistance outweighs any fitness cost associated with the resistance mechanism. The magnitude of the fitness benefit depends on the scale of antibiotic use in the population. For example, previously undetected resistant bacteria might proliferate in an individual after antibiotic use.[23] Because vaccination can reduce the prevalence of antibiotic treatment, it can decrease selection for antibiotic resistance in all bacterial strains carried by the host, including co-colonising and commensal bacterial strains exposed to antibiotics during treatment. In mathematical models, the fitness asymmetry between sensitive and resistant strains is not consistently parameterised.

To capture strain dynamics for which onward transmission depends on transient within-person pathogen interactions, it is possible to embed a within-host model of infection inside a population transmission model. Each strain's replication rate is dependent on the antibiotic status of the person and the frequency of other co-colonising strains. However, such a hierarchical model is both computationally intensive, and, more importantly, difficult to calibrate with experimentally validated parameters. For these reasons, mathematical models usually omit within-host dynamics and only capture transmission between colonised and susceptible individuals.[24] The validity of this omission depends on whether these within-host processes are important for resistance to persist within the population. Once resistance has emerged and transmission drives its ongoing persistence, tracking of de-novo mutation and horizontal gene transfer might not be necessary.

Although antibiotic treatment selects for antibiotic resistance, reductions in antibiotic use might not select for reversion to antibiotic sensitivity if the resistance gene does not impose a fitness cost to the bacterium. Populations of streptomycin-resistant *E coli* can develop secondary mutations that compensate for the fitness cost of an initial resistance mutation.[25] This observation suggests that removal of the selection pressure caused by streptomycin use might not select for reversion to sensitivity. In such a case, a reduction in antibiotic use would have minimal effect on the transmission of existing resistant strains. Conversely, a vaccine targeting serotypes that have a high frequency of resistance could confer a fitness advantage to serotypes that have a low frequency of resistance, and thus potentially decrease resistance in the short term. However, in the long term, non-vaccine serotypes could increase in frequency to fill the ecological niche and might be more frequently exposed to antibiotics, thus acquiring increased resistance through horizontal gene transfer or selection for de-novo mutations. Although pneumococcal serotypes not in heptavalent PCV (PCV7) are more likely to be penicillin-sensitive than serotypes in PCV7, studies[26,27] have found that penicillin resistance in non-PCV7 serotypes increases after the introduction of PCV7 vaccination. Whether a rebound occurs in the long term after the introduction of vaccination depends on whether population transmission is interrupted by vaccination and the vaccine-targeted antigen is mechanistically associated with resistance.[28] Mathematical modelling can help to predict the outcome of these complex scenarios.

Progression to disease at the health level

Some vaccines might provide protection against symptomatic infection without fully preventing carriage.[29] Similar to a vaccine preventing carriage, a vaccine reducing the risk of disease progression will reduce resistant infections (target outcome), antibiotic use (proxy outcome), and co-infections that require antibiotic treatment. However, unlike a vaccine that blocks carriage, vaccines that only prevent disease might maintain carriage levels in the population without affecting cascade pathways (ie, population and pathogen; figure 2). Capturing this effect requires estimation of the differential effect of a vaccine's protection against disease versus carriage.

Reductions in infections by non-focal pathogens (eg, viruses or bacteria) can also reduce secondary bacterial co-infections. For example, influenza infection significantly increases an individual's susceptibility to invasive pneumococcal disease[30] and triggers the pathways identified for vaccination against bacterial carriage and disease. To parameterise this effect of vaccines against non-focal pathogens, mathematical models should include an estimate for the vaccine's effectiveness against the non-focal pathogen and requires a dynamic transmission component to capture the effect of herd protection. Increased disease risk of the focal bacteria caused by the non-focal pathogen could be estimated from either retrospective or prospective cohort studies. Although the clearance rate of sensitive strains in the presence of treatment is amenable to measurement, the risks of co-colonisation with sensitive and resistant strains, relative transmission, and acquisition are substantially more difficult to estimate, although they are important for the parameterisation of resistant strain dynamics.[31]

Health-care seeking and antibiotic use at the care level

By reducing the frequency of bacterial or viral disease, vaccination can reduce the number of patients who are ill and seeking antibiotic treatment.[7] For example, in a

case-control study[32] in California, a PCV7-vaccinated cohort had 6% fewer antibiotic prescriptions and 8% fewer visits to primary care than the unvaccinated cohort. After the introduction of the ten-valent *S pneumoniae* vaccine in the Netherlands in 2011, prescription of antibiotics for respiratory infection in children aged 2–7 years reduced by up to 24%.[33] Moreover, vaccination can also reduce the chance of resistance emerging by reducing the number of people colonised with sensitive bacterial strains if they use antibiotics to treat diseases caused by other pathogens.

Vaccination of individuals against viral infections can also reduce antibiotic use. Antibiotics are often used for viral infections because of the difficulty in the identification of the bacterial cause in patients with symptoms of acute infection.[34] Compared with other provinces in Canada that only vaccinated susceptible populations against seasonal influenza, Ontario began a universal influenza immunisation programme in 2000. This programme significantly reduced the number of patients admitted to hospital and visiting general practitioners for pneumonia and influenza compared with other provinces, and also reduced antibiotic prescriptions by 144 000 across the province.[35] Many cases might exist where inappropriate prescribing occurs, especially in settings where antibiotics are available as an over-the-counter self-prescribed treatment. For example, over-the-counter antibiotics are often used for diarrhoeal and respiratory disease in some low-income and middle-income countries.[36,37] Thus, the introduction or expansion of many vaccine programmes, such as those against influenza and rotavirus, might alleviate antibiotic use. Any antibiotic used against a non-focal pathogen might select for resistance emergence in a focal, co-colonising commensal or asymptomatic bacteria, which is termed the bystander effect. In our framework, we combined antibiotic use leading to the bystander effect with inappropriate antibiotic use and denoted this as collateral antibiotic use. To parameterise health-care-seeking behaviour, mathematical models need to include the rate of antibiotic use for the bacteria (and virus) of interest as well as use of background antibiotics.

Mathematical modelling of vaccination and antibiotic resistance

We reviewed the literature to identify all mathematical models that have investigated the dynamics of antibiotic resistance in the context of vaccination. Using the framework described (figure 1; figure 2), we stratified the eight models identified (table 1) according to which vaccination, transmission, pathogen, health, and care mechanisms they incorporate. We excluded two studies: Temime and colleagues,[45] who assessed only capsular switching in *S pneumoniae* and not treatment resistance, and Kunkel and colleagues,[46] who assessed resistance emergence to preventive therapy (with specific examples of malaria, HIV, and tuberculosis), rather than preventive therapy to reduce drug resistance.

	Model	Bacterial pathogen(s) and disease outcome	Resistance to drug class or type	Vaccine
Temime et al (2004)[38]	1	*Streptococcus pneumoniae*	Penicillin (penicillin G)	PCV7
Temime et al (2005)[39]	2	*S pneumoniae*-related meningitis	Penicillin (unspecified)	PCV7
Opatowski et al (2008)[40]	3	*S pneumoniae*	β-lactams, macrolides, and ketolides	PCV7
Van Effelterre et al (2010)[41]	4	*S pneumoniae*	β-lactams and macrolides	PCV7
Tekle et al (2012)[42]	5	Hospital-acquired *Staphylococcus aureus*	Meticillin	Hypothetical vaccine targeting resistant genotype
Joice and Lipsitch (2013)[28]	6	Community-acquired MRSA, *S pneumoniae**	Meticillin	Hypothetical vaccines targeting resistant determinants
De Cèlles et al (2015)[43]	7	*S pneumoniae*-related meningitis	β-lactams (penicillins and cephalosporins) and macrolides	PCV7
Mitchell et al (2015)[44]	8	*S pneumoniae*	Penicillin	PCV-type

PCV7=seven valent pneumococcal conjugate vaccine. MRSA=meticillin-resistant *Staphylococcus aureus*.
*Also analysed influenza virus.

Table 1: **Mathematical modelling studies that have assessed the impact of vaccination on bacterial drug resistance**

Model summaries

Of the eight studies, six assessed only *S pneumoniae*,[38–41,43,44] one assessed only *S aureus*,[42] and one assessed *S pneumoniae* and *S aureus*.[28] The studies[38–41,43,44] that assessed only *S pneumoniae* did so in the context of the pneumococcal conjugate vaccine, PCV7. The other two studies[28,42] investigated a hypothetical vaccine. Most models use continuous population, deterministic ordinary differential equations to quantify the time evolution of transmission dynamics, which are either numerically[38–42] or analytically solved.[28] Two models are stochastic and use a discrete population, continuous time stochastic master equation formulation[43,44] that provides multiple solutions for each model run to better capture the dynamics of small populations. We used the framework previously developed to identify the mechanisms captured by these eight models (table 2).

Mechanism of vaccine at the direct level

All six models[38–41,43,44] that assessed the impact of PCV on resistance dynamics assumed that vaccine effectiveness is unrelated to the resistance determinants (and therefore vaccine effectiveness depends only on serotype), whereas the other two studies[28,42] that investigated a hypothetical vaccine assumed that its target is linked to resistance determinants. This difference in assumption leads to a different prediction regarding the impact of vaccination on resistance prevalence: unlike models with the link between vaccination and resistance, models without the link predict that vaccination will not significantly reduce resistance in the long term because resistance re-emerges in non-vaccine serotypes.

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
Vaccine effectiveness distinguishes between drug-sensitive and drug-resistant bacteria	N	N	N	N	Y	Y	N	Y
Vaccine effectiveness against non-focal viral infections	N	N	N	N	N	N	N	N
Difference between transmission rates of drug-sensitive and drug-resistant bacteria	N	N	N	Y	Y	Y	Y	Y
De-novo acquisition of resistance	Y*	Y*	Y*	N	N	N	N	N
Treatment alters pathogen fitness via:								
Increased decolonisation rate of drug-sensitive strains	Y	Y	Y	Y	Y	Y	Y	Y
Increased risk of de-novo resistance emergence	Y	Y	Y	N	N	N	N	N
Reduced acquisition rate of drug-sensitive strains	N	Y	N	Y	N	N	Y	N
Health-care seeking tracked as a function of resistance incidence:								
Treatment rate	N†	Y‡	N†	N†	N§	N§	N†	N
Clinical outcome	N¶	N	N¶	Y	Y‖	N¶	Y	N¶

*Resistance acquisition or accumulation (loss) in treated (untreated) individuals only. †Fixed antibiotic rate independent of carrier status. ‡Treatment rate is either reduced for vaccinated children or for all children. This rate is fixed and is not a dynamic rate that relates directly to incidence. §No treatment stratification; only individuals who are infected are treated at a constant rate. ¶If vaccine protection is not associated with probability or severity of disease, total reductions in infection outcome can be deduced (but disease and disease severity are not explicitly tracked). If vaccine protection is not associated with probability or severity of disease, total reductions in infection outcome cannot be deduced. ||Only patients admitted to hospital are considered.

Table 2: **Resistance mechanisms accounted for in the mathematical models that capture the dynamics of vaccines and antimicrobial resistance**

Transmission and strain dynamics at the population level

Because all models capture transmission, they account for the direct and indirect reductions in bacterial carriage and infection of the target serotypes by vaccination. However, the sizes of these indirect effects vary because of the model structures and parameterisations (eg, cross-protection mechanisms and relative rates of social mixing).

Models create asymmetry between sensitive and resistant strains by use of one or more of the following mechanisms: reduced transmission rate of resistant strains (a fitness cost of resistance), reduced acquisition rate of sensitive strains for individuals during or immediately after antibiotic use, increased decolonisation rate of sensitive strains during antibiotic use, or a possible emergence of resistance within colonised people who are using antibiotics (a within-person mechanism). The eight models use either two or three of these mechanisms. All models assume a faster clearance rate with treatment than without treatment for sensitive strains. Only models that track the status of antibiotic treatment include a reduced acquisition rate in the presence of antibiotic use for sensitive strains. These combinations of imparting of a treatment-dependent fitness to resistant and sensitive strains lead to multiple pathways promoting persistence of resistant genotypes. These pathways act in the absence of vaccination to set the prevalence of prevaccination resistance in the population and thus are likely to modify the effect of vaccination on resistance dynamics.

There is no model agreement on whether self-protection or cross protection of serotypes (in the case of *S pneumoniae*) or strains (sensitive or resistant) exist. Likewise, mechanisms for co-colonisation and dual strain transmission differ between models. However, the underlying dynamics of resistant strains depend strongly on these assumptions.[31]

Emergence of resistance at the pathogen level

Although all models account for potential persistence of resistance via transmission mechanisms, only models 1–3 capture the emergence of de-novo resistance (table 2). Inclusion of the de-novo emergence of strains depends on whether emergence is an important driver of resistance dynamics over the time, geographical, and population scale modelled. The models that account for de-novo acquisition of resistance allow preferential emergence in people treated with antibiotics (models 1–3). When the emergence of resistance within a person is not captured, only transmission between people rather than de-novo mutation or horizontal gene transfer during co-colonisation is assumed to drive the persistence of drug resistance. Two studies[40,41] characterise two drug classes (model 4) and three drug classes (model 3) with independent accumulation of resistance to account for multidrug resistance. All other studies[28,38,39,42–44] assess resistance to a single drug or drug class.

Capturing of the use of antibiotics at the health and care level

The eight models can be stratified by those that explicitly capture general antibiotic use in the population (models 1–4, and 7) and those that assume instantaneous treatment for populations colonised by sensitive strains (models 5, 6, and 8). Inclusion of general antibiotic use in the population by tracking treated people captures three additional mechanisms: a reduced colonisation rate of sensitive strains in people treated with background antibiotics, an increased decolonisation rate of sensitive strains in asymptomatically colonised treated people (in

addition to that for symptomatic infection captured in all models), and an increased risk of de-novo acquisition of resistance for treated individuals. For the second class of models, antibiotic use occurs only in the infected class and acts to increase the clearance rate of only sensitive strains.

Regardless of the representation of treatment rate used, all models are affected by shortcomings because they do not capture an intrinsic and dynamic relationship between the number of symptomatic individuals and the rate of antibiotic use. Except for model 3, all models assume constant antibiotic use across the population. This assumption is invalid if mass vaccination reduces the rate at which people use antibiotics. Model 3 accounts for this phenomenon by reducing the extrinsic treatment rate for either vaccinated people (direct effect) or all individuals (direct and indirect effect) regardless of the status of symptomatic infection. An assumption of constant treatment rate might be appropriate when antibiotics are used to treat symptoms caused by pathogens that are not targeted by the vaccine—ie, when antibiotic resistance is promoted primarily by bystander selection,[47] which is likely to occur for bacteria such as *S pneumoniae* that are usually carried asymptomatically. However, when antibiotics are used to treat symptoms caused by the vaccine-targeted pathogen, models assuming a constant treatment rate might underestimate the impact of vaccination on reducing cases of antibiotic resistance.

Research gaps and future steps

Our review of the literature shows that modelling of vaccination and antibiotic resistance is scarce and limited to important but specific circumstances. Therefore, numerous opportunities exist to improve understanding of the use of vaccination to combat antibiotic resistance.

Pathways represented

We have shown that existing models do not consider all the pathways through which vaccination can impact antibiotic resistance. For instance, widely administered viral vaccines, such as those against seasonal influenza, might have a synergistic effect on antibiotic resistance with bacterial vaccines by reducing co-infection and inappropriate use of antibiotics for viral infections; however, no models exist that consider this pathway. The allowance of a treatment rate that is dependent on the incidence of symptomatic disease tracked would account for the dynamic pathways that are not captured in the models. The mechanism through which use of antibiotics affects the frequency of antibiotic resistance is difficult to parameterise within mathematical models. More work is needed to elucidate this mechanism if predictive models will be used for public health decision making.

Geographical scope

To provide accurate predictions for decision making, models of vaccination impact on antibiotic resistance need to capture local conditions of vaccine uptake, infection prevalence, health-care-seeking behaviour, and antibiotic use; therefore, country-specific models will be required. However, all models developed so far have used data from the USA[28,39,41,42,44] or France,[38–40,43] thus no models exist for the effects of vaccination on antibiotic resistance in low-income or middle-income countries. This factor represents a major lacuna in the understanding of antibiotic resistance dynamics. For example, Brazil, Russia, India, China, and South Africa together account for 75% of the increase in global antibiotic use from 2000 to 2010 (with many antibiotics accessed over-the-counter without prescription).[48] Furthermore, countries such as India and China are key developers for new vaccines and markets for mass vaccination campaigns.

Vaccine–pathogen combinations

The literature on vaccine impact on antibiotic resistance is restricted to two vaccine-targeted pathogens: *S pneumoniae* and *S aureus*. One notable omission is multi-drug-resistant tuberculosis, which is a growing threat that calls for attention from researchers in the field of mathematical modelling.[49] Many other resistant pathogens are problematic and might be targets for vaccine development in the future, including *Klebsiella pneumoniae* and *Neisseria gonorrhoea*. Increasing the number of pathogens targeted by models of vaccination and antibiotic resistance is a crucial next step. Because of the co-infection epidemiology of particular pathogens, the interaction effect of multiple vaccination programmes on antibiotic resistance can be assessed through the combination of multiple pathogens in one disease modelling framework.

Model structure and mechanism for vaccine effectiveness

Previous analyses show that the structure of antibiotic resistance models has a substantial impact on their predictions.[50] However, even if a model's structure avoids predicting a stable equilibrium frequency of resistant strains in the absence of any selection for or against them (ie, the model is structurally neutral),[50] many choices for model structure and parameterisation exist. How these choices affect the underlying assumptions about resistance dynamics and therefore the predictions on the effect of vaccination is unclear. To achieve robust decision making, formal quantification of any uncertainty in model predictions due to model structure and parameterisation will be essential.

Modelling for economic decision making

In many countries, health economic evaluations of vaccine strategies inform vaccine decision making.[51] Hence if antibiotic resistance control is integrated into vaccine decision making, then the costs and health outcomes associated with antibiotic resistance should also be translated into economic evaluations. None of the

Search strategy and selection criteria

We searched PubMed for articles in English using terms ("mathematical" OR "dynamic" OR "transmission") AND ("model" OR "modelling" OR "modelling" OR "tool") AND ("AMR" OR "antimicrobial resistance" OR "antibiotic resistance" OR "microbial resistance") AND ("vaccine" OR "vaccinat*" OR "prophyl*") on May 22, 2017, which yielded 155 publications between January, 1977, and April, 2017. We manually screened out all studies that exclusively investigated non-bacteria (ie, viruses, macroparasites, and fungi), which left 45 articles. Last, we removed all articles that did not explicitly include a dynamic transmission model to assess the impact of a vaccine on antimicrobial resistance (defined as a model that included an explicit mechanism for transmission of pathogens from infected hosts to susceptible individuals).

modelling studies that explore vaccination impact on antibiotic resistance have incorporated economic outcomes.

By accounting for the pathways through which vaccination can impact antibiotic resistance, we have identified two important outcomes routinely used in epidemiological studies as study endpoints. First, the target outcome (ie, the number of resistant bacterial strain cases) and second, the proxy outcome (ie, the number of antibiotic doses taken). The number of resistant cases will be stratified by the antibiotic (sub) class and pathogen (or serotype), and the level of resistance of each case will be quantified by the concentration of antibiotic needed to inhibit the pathogen's growth (minimum inhibitory concentration). For countries where antibiotics are prescription only, the number and details of every prescription are routinely monitored. The target and proxy outcomes should be systematically quantified in any economic evaluation. For instance, by tracking of the number of resistant infections averted through vaccine implementation, the averted health-care costs that are associated with complications arising from caring of patients infected with resistant bacterial strains can be estimated.[52] The proxy outcome is perhaps more difficult to translate into an economic evaluation framework. However, this outcome is coupled with the target outcome via connected pathways; thus, we suggest that accounting for the proxy outcome in addition to the target outcome is unnecessary. In other words, by explicitly capturing the effect of a vaccine on antibiotic use, and the ensuing effect on the emergence and transmission of resistant strains, mathematical models can quantify the direct and community health-care benefits of reduced use of antibiotics.[52]

Several economists have suggested that the economic value of vaccines is underestimated since their potential effects on antibiotic resistance have been largely ignored in evaluations.[52] If economic assessments of vaccination programmes incorporated the potential effects on antibiotic resistance, vaccines that are not cost-effective or only cost-effective if given to a subset of the population might exceed the required cost-effectiveness threshold. Economic projections can provide the impetus for vaccine developers to invest in vaccine pipelines that can reduce antibiotic resistance and vaccine purchasers to favour such vaccines when allocating funds from vaccine budgets. The shortage of financial incentives has been blamed for the slow pace of vaccine development against pathogens whose resistance remains a substantial burden.[7] Through incorporation of the non-linear effect of vaccines on antibiotic resistance control, mathematical models can be readily integrated into economic models, helping to incentivise development and aid decision making for administration. Control of antibiotic resistance will probably involve a combination of strategies, including vaccination, improvements in diagnostic testing, promotion of antibiotic stewardship, and development (and eventual obsolescence) of new antibiotics, which require assessment of the relative costs and benefits. New technologies might affect the value of vaccines against organisms that can develop resistance. Therefore, economic evaluations of the added value of vaccines reducing antibiotic resistance will need to consider potential technological developments.

Conclusions

Vaccination has the potential to be a key tool in the reduction of antibiotic resistance, alongside new antibiotics, rapid diagnostics, improved antibiotic stewardship, and infection prevention and control practices. However, as we have shown, the mechanisms through which vaccination might impact bacterial resistance and prescription of antibiotics are complex and non-linear. Mathematical modelling provides a means to quantify these mechanisms and predict potential consequences of vaccination on antibiotic resistance. We have discussed how existing models capture these mechanisms and identify potential areas for model development. The models provide a strong foundation on which to develop new studies that predict the impact of novel vaccination strategies to target antibiotic resistance and incorporate clinical and economic benefits of reduced antibiotic resistance into economic evaluations of vaccination programmes. Although we have highlighted the important gaps in understanding, we anticipate that the role of mathematical models, when combined with economic evaluations, will be a growing force in shaping decision making in vaccination programmes and antibiotic resistance control.

Contributors

KEA, EIL, SRD, NGD, JVR, and MJ devised and designed the Review. KEA and NGD designed the figures. KEA reviewed the literature and wrote the manuscript. EIL, SRD, NGD, JVR, and MJ revised the manuscript. All authors read and approved the final manuscript.

Declaration of interests
We declare no competing interests.

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