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Risk modelling the mortality impact of antimicrobial resistance in secondary pneumococcal pneumonia infections during the 2009 influenza pandemic

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ABSTRACT

Objectives: The aim of this study was to estimate the impact of antimicrobial resistance (AMR) in secondary pneumococcal pneumonia infections on global mortality during the 2009 influenza pandemic, to estimate future pandemic mortality risk and to inform pandemic preparedness.

Methods: Risk analysis modelling was conducted using a multivariate risk formula. Literature reviews were conducted to generate global central estimates for each of the parameters of the risk formula in relation to the 2009 influenza pandemic, secondary pneumococcal pneumonia, rates of AMR, and pneumococcal vaccine efficacy as a component of pandemic preparedness.

Results: Global *Streptococcus pneumoniae* AMR was estimated at 21.8% to 27.6%, and contributed to 1.8% to 2.3% of deaths during the 2009 influenza pandemic. When directly applied to mortality due to multidrug resistance, pneumococcal vaccination could potentially prevent 1277 to 3754 deaths and could have reduced mortality from multidrug-resistant *S. pneumoniae* to 1% to 1.2%.

Conclusions: AMR in secondary pneumococcal infections contributed towards a small percentage of the global mortality during the 2009 influenza pandemic. Increased *S. pneumoniae* AMR could result in a three- to four-fold rise in mortality due to secondary pneumococcal infections in future influenza pandemics. Pneumococcal vaccination has an important role in preventing pneumococcal co-infections and combating AMR in all populations, and should be considered a key component of influenza pandemic preparedness or early action plans.

Introduction

Antimicrobial resistance (AMR) is an important factor for consideration in pandemic preparedness. Any reduction in treatability poses a potential risk to national and international security and economic stability when applied to pandemic-related pathogens (McArthur and Tsang, 2017). Increasing AMR among pathogens responsible for the development of community-acquired pneumonia (CAP) (e.g., *Streptococcus pneumoniae* and *Haemophilus influenzae*) (Adam, 2002) is especially concerning given their propensity to cause bacterial infections secondary to viral influenza. AMR could contribute towards worsening morbidity and an increasing mortality burden when associated with future influenza pandemics (Reinert, 2009; MacIntyre and Bui, 2017).

The 2009 influenza pandemic caused by the influenza A H1N1pdm09 virus was responsible for approximately 18 500 laboratory-confirmed deaths globally, but the true mortality burden has been estimated to be 10- to 15-fold higher (Dawood et al., 2012; Simonsen et al., 2013). These global estimates do not surpass seasonal influenza mortality estimates of 250 000 to 500 000 deaths per year during severe H3N2 seasons (World Health Organization (WHO), 2016). However, the burden of H1N1pdm09 was atypical in that approximately two-thirds of all deaths occurred in the 18–64-year-old demographic, thereby contributing to greater overall consequences through years of life lost (Dawood et al., 2012; Simonsen et al., 2013). The mean age at death was 53 years during the 2009 pandemic, compared to >80 years during seasonal influenza (Bishop et al., 2009). Advances in intensive care and interventions such as extracorporeal membrane oxygenation (ECMO) have also contributed to survival compared to past influenza pandemics (de St Maurice et al., 2016).

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Secondary bacterial co-infections involving *S. pneumoniae* and other commonly identified pathogens (e.g., *H. influenzae* and *Staphylococcus aureus*) have played a substantial role in contributing to the morbidity and mortality of past influenza seasons and pandemics (Jia et al., 2017; Morens et al., 2008; Gupta et al., 2008; Cillóniz et al., 2012; MacIntyre et al., 2018). Approximately one in four seasonal and pandemic influenza-related deaths have been found to have secondary bacterial co-infections, with *S. pneumoniae* identified as one of the most prevalent pathogens (Gupta et al., 2008; Cillóniz et al., 2012; MacIntyre et al., 2018). Retrospective analysis of lung biopsies from autopsied cases during the 1918–1919 influenza pandemic also determined pneumococci to be present in 23.5% of samples (Morens et al., 2008). The risk of developing bacterial pneumonia and the risk of death from the pneumonia are both known to significantly increase in the setting of a preceding viral infection such as influenza (Rothberg and Haessler, 2010).

S. pneumoniae, with over 90 serotypes of varying pathogenicity and resistance prevalence, has the ability to cause significant morbidity and mortality in the young (<5 years), old (>65 years), and vulnerable populations (Hackel et al., 2013; Song et al., 2012; Moberley et al., 2013; Falkenhorst et al., 2017; World Health Organization (WHO), 2014). Worldwide, pneumococci remain the causative pathogen in roughly one-quarter to one-third of all adult CAP cases; however estimates differ due to regional epidemiology (Gupta et al., 2008; Said et al., 2013). Adults most commonly present with pneumococcal pneumonia. However those with pneumonia and bacteraemia, or invasive pneumococcal disease (IPD), experience the most severe form of pneumococcal infection, which is associated with greater than 20% mortality (Moberley et al., 2013; Falkenhorst et al., 2017; Said et al., 2013; Tin Tin Htar et al., 2017; Harboe et al., 2009; Simonsen et al., 2011).

Multiple large-scale studies and systematic reviews have examined country-specific and regional AMR trends of *S. pneumoniae* in the past two decades, but few have used the data to develop global estimates. Variability between countries and regions ranges from the extremes of 0% to over 95%, adding to complications in calculating true global resistance incidence (World Health Organization (WHO), 2014; Felmingham et al., 2005; Van Bambeke et al., 2007). Pneumococci serotype distribution, as well as region-specific resistance patterns, relate to local epidemiology and factors such as vaccine availability, immunization programme dynamics, antibiotic use patterns, and the spread of particular clones (Hackel et al., 2013; Liñares et al., 2010).

Globally the highest proportions of penicillin- and macrolide (specifically erythromycin)-resistant isolates have been observed in *S. pneumoniae* serotypes 6A, 6B, 9V, 14, 15A, 19A, 19F, and 23F (Hackel et al., 2013; Liñares et al., 2010; Lynch and Zhanel, 2009). Penicillin non-susceptibility amongst *S. pneumoniae* strains has also been shown to influence macrolide and other antibiotic susceptibilities, leading to the development of co-resistance (Webber et al., 2017). Co-resistance was found to be significantly more likely in the serotypes with the highest proportions of individual drug resistance (Hackel et al., 2013). These trends were evidenced by high rates of region-specific co-resistance for penicillin (and other beta-lactams) and macrolide resistance in Africa (64% for both drug classes) and North America (38.5% and 23.5%, respectively) (Tomic and Dowzicky, 2014).

In light of growing AMR concerns, vaccination is an important available preventive strategy for pneumococcal disease. Two types of approved pneumococcal vaccine are currently used globally, which include the multivalent conjugate vaccines (PCV7, PCV10, PCV13) and the 23-valent polysaccharide vaccine (PPV23). Approximately one-quarter of IPD cases in older adults and an estimated 10% of CAP cases are caused by PCV13 serotypes (Webber et al., 2017; Tomczyk et al., 2014; Bonten et al., 2015). Serotypes unique to the PPV23 vaccine were found to cause a further 38% of IPD in older adults over age 65 years (Pilishvili and Bennett, 2015).

Introduction of the PCV7 vaccine into childhood vaccination programmes around the turn of the 21st century was associated with a decline in penicillin and erythromycin non-susceptible pneumococci in some countries, due to a decline in vaccine-type (VT) IPD and the nasopharyngeal colonization of resistant *S. pneumoniae* isolates in children (Simonsen et al., 2011; Sings, 2017; Kyaw et al., 2006). Both vaccines have had indirect 'herd' benefits for all adult age groups by decreasing the burden of pneumococcal disease caused by VT strains in addition to reducing overall *S. pneumoniae* resistance as a consequence of decreasing resistant VT strain prevalence (Simonsen et al., 2011; Tomczyk et al., 2014; Kyaw et al., 2006).

Serotype 'replacement' has led to some non-vaccine type (NVT) serotypes developing resistance characteristics and predominating, although the selection pressure of vaccines varies by strain and is only one of several factors in the development of *S. pneumoniae* resistance (Reinert, 2009; Song et al., 2012; Liñares et al., 2010). This phenomenon has been observed particularly with serotype 19A (Kyaw et al., 2006; Blasi et al., 2012). Introduction of the PCV13 vaccine in the USA in 2010 resulted in a decline in the prevalence of the highly resistant strain 19A (22% of all strains in 2008–09 decreasing to 10% in 2012–13), but subsequently resulted in other strains becoming more frequent (35B, 15B, 23B), and contributed to the emergence of multidrug resistant (MDR) strains (35B, 15B, 23A) (Richter et al., 2014). Of these emerging resistant strains, only 15B is covered by the PPV23 vaccine. The rising prevalence of NVT serotypes may rescind some of the previous gains in herd immunity of the lower valency vaccines (Blasi et al., 2012). Undoubtedly pneumococcal vaccine dynamics play an important role in the assessment of *S. pneumoniae* AMR and its effects on pneumococcal disease incidence and outcomes.

The effects of AMR on the treatability of bacterial–viral co-pathogenesis, as well as the role of pneumococcal vaccination, must be a consideration in pandemic influenza preparedness (Morens et al., 2008; Morens and Fauci, 2007; Grundmann et al., 2011). The aim of this study was to estimate the magnitude and influence of AMR in influenza-associated *S. pneumoniae* bacterial co-infections during the 2009 influenza pandemic.

Methods

A previously developed risk analysis formula was used (MacIntyre and Bui, 2017), where the mortality impact of AMR in a pandemic (I) is estimated by considering four key factors: the availability of a drug to treat the infection (A), the degree of AMR of the pathogen (D), the proportion of deaths preventable by the treating drug (P), and total mortality (M). These determinants are expressed using the following equation: $I = A \times D \times P \times M$.

Availability of the treatment drug

This analysis primarily focused on beta-lactams (i.e., penicillin) and macrolides (i.e., erythromycin) as the most frequently prescribed and reported resistant drugs in the treatment of *S. pneumoniae* infections worldwide. The representation of the availability of penicillin or erythromycin is binary with 'yes' coded as '1' for the quantitative analysis. If there were no available drugs to treat *S. pneumoniae* infections, with 'no' represented by '0', then the impact of AMR would have been zero, as treatability remains unchanged despite any documented AMR (MacIntyre and Bui, 2017). While drug availability or access may vary widely by region and economic status, in employing global estimates for this analysis the assumption is that the aforementioned drugs are readily available.

Degree of Streptococcus pneumoniae *resistance*

The prevalence of *S. pneumoniae* resistance was determined by conducting a literature review of published peer-reviewed studies using PubMed, Cochrane Library, and university library databases that reported global resistance estimates from the past two decades (1997 onwards). Historical data for *S. pneumoniae* resistance were considered in this analysis as they contributed to the assumptions and estimates for resistance in the time period surrounding the 2009 influenza pandemic. Studies reporting single country or localized region estimates were excluded to attempt to rationalize the effect of single-country bias, noting the lack of estimates from low-income countries and sporadic nature of studies across the time frame. A meta-analysis reviewing single-country estimates of *S. pneumoniae* resistance and 2009 influenza pandemic mortality was outside the scope of this risk calculation, but the review of the literature indicated a high level of variation in individual countries.

Data were sourced from estimates arising from three major global longitudinal studies, The Alexander Project (Adam, 2002; Felmingham and Gruneberg, 2000; Schito et al., 2000), Tigecycline Evaluation Surveillance Trial (TEST) (Hackel et al., 2013; Tomic and Dowzicky, 2014), and Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin (PROTEKT) (Reinert, 2009; Schito and Felmingham, 2005). Median values for individual drug resistance and MDR were used in the risk calculations given the limited number and range of available global estimates. The majority of the available literature focused on penicillin and/or macrolide resistance. Documented co-resistance amongst penicillin and erythromycin was categorized in some studies as MDR, while other studies classified MDR by inclusion of three or more drugs. For the purposes of this analysis, MDR estimates included any documented *S. pneumoniae* resistance to two or more agents.

Proportion of deaths preventable by drug

A systematic review conducted for a separate study was employed to determine the proportion of global H1N1pdm09 influenza deaths complicated by co-/secondary bacterial infections and the proportion of those infections specifically attributable to *S. pneumoniae* (MacIntyre et al., 2018). The product of these two proportions established the overall proportion of deaths preventable by drug treatment (assuming full susceptibility), or essentially the mortality burden of *S. pneumoniae* co-infections in the 2009 influenza pandemic. Median values for both subset proportions were again used as the central measure for the risk analysis in an effort to best represent the range of limited data points and diminish the impact of outlier estimates.

Mortality

Projected global mortality ranges from the 2009 influenza pandemic were sourced primarily from two retrospective studies by Simonsen et al. (2013) and Dawood et al. (2012). The mean of the estimated mortality ranges were calculated from the upper and lower bound confidence intervals for each study. The risk analysis was performed using each mean incidence for penicillin-resistant, erythromycin-resistant, and MDR infections separately in order to provide the best- and worst-case scenario of AMR impact depending on the proposed mortality ranges.

Vaccine efficacy

Vaccine efficacy (VE) for the PCV13 and PPV23 pneumococcal vaccines was obtained by examining large-scale reviews and meta-analyses in the Cochrane Library and PubMed databases. These included the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) results for PCV13 (Webber et al., 2017; Bonten et al., 2015) and three meta-analyses for PPV23 (Moberley et al., 2013; Falkenhorst et al., 2017; Kraicer-Melamed et al., 2016). Individual VE was taken as a mean of pooled percentage estimates for the prevention of all pneumococcal disease outcomes and applied to mortality estimates in an effort to rationalize the discrepancies in discerning the burden of IPD versus non-bacteraemic pneumococcal pneumonia during the 2009 influenza pandemic. Efficacies for all-cause CAP were excluded given their non-specificity for pneumococcal outcomes.

For the purposes of this risk analysis, VE was applicable to the prevention of *S. pneumoniae* infection affecting the subset proportion of co-/secondary bacterial infections attributable to *S. pneumoniae*. Vaccine uptake of 100% was assumed, as the study aimed to estimate the hypothetical maximal impact of prevention by vaccination. PCV13 and PPV23 were assessed separately to reflect differences in their reported efficacies, noting that these estimates also include vaccine failures.

Results

Degree of Streptococcus pneumoniae *resistance*

The median estimate for global *S. pneumoniae* MDR was 27.6%, the highest of all the median resistance estimates. Global estimates of penicillin and erythromycin resistance of *S. pneumoniae* isolates were represented by median values of 21.8% and 27%, respectively.

Lynch and Zhanel (Lynch and Zhanel (2009)) reported worldwide *S. pneumoniae* MDR to range from 15% to 30% using three or more antibiotic classes as a criterion for inclusion, thereby likely underestimating proportions by ignoring resistance to two agents. Global data from the PROTEKT study estimated all degrees (from two-drug up to seven-drug) of MDR strains of *S. pneumoniae* at a combined 41.8%, but the estimate incorporated vast country-specific ranges from as low as 3.8% (UK) up to 97.3% (China) (Reinert, 2009). When also considering earlier data from PROTEKT, estimates for MDR were 38.6% for the decade (Schito and Felmingham, 2005). The exclusion of the earlier data in this study produced higher estimates and may be indicative of rising MDR in *S. pneumoniae* isolates.

Proportion of deaths preventable by drug

The incidence of any co-/secondary bacterial infection specific to the 2009 influenza pandemic has been reported in various studies, ranging from 23% to 34% (Cillóniz et al., 2012; MacIntyre et al., 2018; Koon et al., 2010; Centers for Disease Control and Prevention (CDC), 2009; Chertow and Memoli, 2013). Of these estimates, the proportion attributable to *S. pneumoniae* was subject to significant variation from 2% to 62%, likely related to differences in regional epidemiology, testing methods, and study populations (Cillóniz et al., 2012; MacIntyre et al., 2018; Koon et al., 2010; Centers for Disease Control and Prevention (CDC), 2009; Safaeyan et al., 2015). Median values for the proportion of H1N1pmd09 influenza cases with bacterial co-infections and the proportion of bacterial co-infections attributable to *S. pneumoniae* were 29% and 28.5%, respectively. This translates to a range of 9451 to 24 737 deaths due to *S. pneumoniae* co-infection in the 2009 pandemic before considering any drug-specific resistance.

Mortality

Global mortality for the 2009 influenza pandemic was projected at between 123 000 and 203 000 (Simonsen et al., 2013) and between 105 700 and 395 600 (Dawood et al., 2012) in two retrospective modelling studies. Therefore, the mean range of predicted mortality was 114 350 to 299 300 deaths for the lower and upper bound estimates.

Vaccine efficacy and reduction of pandemic mortality

CAPiTA recently established the VE of PCV13 in a large-scale randomized controlled trial (RCT), and the vaccine was found to be most effective in the prevention of IPD (75%) (Webber et al., 2017; Bonten et al., 2015). The highest VE for PPV23 was also demonstrated for IPD in RCTs included in two systematic reviews, at 73% (Falkenhorst et al., 2017) and 74% (Moberley et al., 2013), respectively. Estimates of mean VE for all pneumococcal outcomes were 49% for PCV13, with a range of 29% to 75% (Tin Tin Htar et al., 2017; Webber et al., 2017; Bonten et al., 2015; Sings, 2017), and 55% for PPV23, with a range of 27% to 74% (Moberley et al., 2013; Falkenhorst et al., 2017; Kraicer-Melamed et al., 2016; Suzuki et al., 2017).

Applying the mean estimates for PCV13 and PPV23 to the estimated impact of laboratory-confirmed penicillin- and erythromycin-resistant *S. pneumoniae* in the 2009 influenza pandemic, PCV13 may have prevented 1007 to 2615 deaths and 1237 to 3239 deaths, respectively, while PPV23 may have prevented 1137 to 2976 deaths and 1408 to 3686 deaths, respectively. Looking at the mortality due to laboratory confirmed MDR, PCV13 could have potentially prevented 1277 to 3345 deaths (1.1%) and PPV23 may have prevented 1434 to 3754 deaths (1.3%) independently.

Impact

The estimated sole impact of penicillin-resistant *S. pneumoniae* in the 2009 influenza pandemic was approximately 2060 to 5392 deaths (1.8%), while erythromycin resistance in isolation would have contributed to approximately 2551 to 6679 deaths (2.2%). MDR estimates were slightly higher at 2608 to 6827 deaths (2.3%). The parameters of each variable used in the formula are summarized in Table 1.

Vaccination could have reduced the mortality due to laboratory-confirmed MDR *S. pneumoniae* during the H1N1pdm09 by as much as half (i.e., overall MDR mortality 1% to 1.2%). If the highest estimates (e.g., 90%) of regional *S. pneumoniae* AMR estimates were applied to the global H1N1pdm09 mortality, the impact would result in an attributable mortality up to three- to four-times greater (7.4%) than current global estimates, or 8505 to 22 263 deaths (Figure 1).

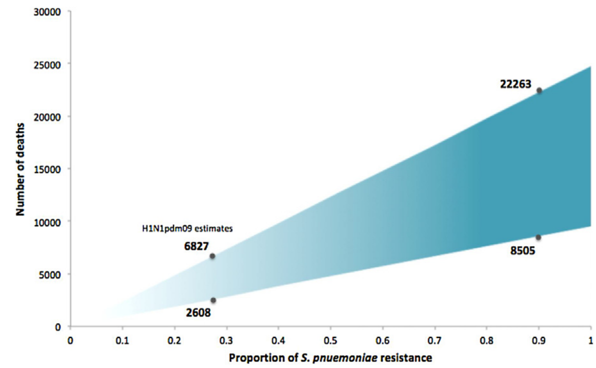

Figure 1. Projected mortality range due to increasing *Streptococcus pneumoniae* resistance using H1N1pdm09 mortality estimates.

Discussion

Preventable bacterial co-infection and AMR played a role during the 2009 influenza pandemic in contributing to the global mortality. At a minimum, 1.8% to 2.3% of global deaths were attributable to *S. pneumoniae* resistance, with potentially at least half preventable through pneumococcal vaccination. Mortality due to MDR (2.3%) was likely most indicative of the true minimum impact given the frequent crossover of drug resistance, as evidenced by documented beta-lactam and macrolide co-resistance (Tomic and Dowzicky, 2014; Schito and Felmingham, 2005). These estimates of minimum impact are due to the limitations in relying upon laboratory confirmation for counted cases, noting the majority of global influenza cases are never laboratory-confirmed. Therefore the true impact of preventing secondary pneumococcal infections would also be greater.

Application of the formula for areas with higher region-specific *S. pneumoniae* MDR (e.g., Asia) would translate to a much greater mortality from influenza-related secondary pneumococcal infection (Reinert, 2009; Kim et al., 2012). This may partially explain why approximately 51% of all H1N1pdm09 deaths were localized to Southeast Asia and Africa (Dawood et al., 2012). Given the typically limited availability of diagnostics and surveillance in these regions, influenza mortality figures and incidence of secondary bacterial infections due to pneumococci are expected to be disproportionately higher. Mortality figures can also be underestimated in countries with adequate surveillance as a consequence of a propensity to diagnose pneumococcal disease more readily only when presenting as invasive disease (i.e., confirmative sterile blood culture rather than non-sterile specimen sputum) and erroneously attributing deaths to an exacerbation of a chronic condition rather than relating to influenza (Dawood et al., 2012; Simonsen et al., 2013; MacIntyre et al., 2018).

A continued rise in penicillin non-susceptible pneumococci isolates in combination with 1918 pandemic level infectivity could see increasing mortality due to *S. pneumoniae* co-infections irrespective of advances in supportive measures such as critical care and ECMO, which was used extensively during the 2009 pandemic (MacIntyre et al., 2018). Increases in global

Table 1
Risk analysis parameters for the impact of *Streptococcus pneumoniae* antimicrobial resistance on H1N1pdm09 mortality.

H1N1pdm09 mortality estimates	Lower bound estimate: 114350	Upper bound estimate: 299300	
Availability of drug		1 – yes	
	Low	Median	High
Degree of global *S. pneumoniae* resistance			
Penicillin	14.1%	21.8%	33.3%
Erythromycin	21.9%	27%	36.3%
MDR	15.3%	27.6%	59.3%
Proportion of preventable deaths			
Proportion with secondary bacterial infection	25%	29%	34%
Proportion of secondary bacterial infections with *S. pneumoniae*	2%	28.5%	62%

MDR, multidrug-resistant.

S. pneumoniae AMR prevalence could translate to a three- to four-fold rise in future influenza pandemic mortality due to secondary pneumococcal infections (Figure 1). In light of an increased potential for treatment (i.e., antibiotic therapy) failures, mitigating the impact of pneumococcal disease during pandemic influenza must instead focus on preventative measures such as vaccination (McGarry et al., 2013).

Overall pneumococcal mortality (i.e., the case fatality ratio) in the vaccine era has been reported from 5% to 27% (Bruce et al., 2008; Klemets et al., 2008), of which drug-sensitive, drug-resistant, and MDR infections are subset proportions. Considering the estimates of *S. pneumoniae* resistance for penicillin, erythromycin, and MDR (Table 1), approximately three-quarters of all pneumococcal deaths are actually due to drug-sensitive isolates. Therefore at current estimates, 1.4% to 5.9% of total pneumococcal mortality, in the absence of pandemic circumstances or a co-infection, is associated with AMR. While these estimates and the 1.8% to 2.3% of the estimated total 2009 pandemic mortality due to *S. pneumoniae* AMR may not represent a large proportion, they are potentially vaccine-preventable. Pneumococcal vaccination is often overlooked in pandemic preparedness and management (Itzwerth et al., 2018), representing a missed opportunity to reduce pandemic disease burden.

The indirect effects of PCV13 in preventing IPD and non-invasive pneumococcal disease are known to surpass those of PCV7. When modelled in comparison to an influenza pandemic with similar impact to the H1N1pdm09 virus, childhood vaccination with PCV13 was estimated to prevent 120 500 more pneumococcal cases (combined IPD and hospitalized pneumonia) and 3700 more deaths than PCV7 across all age groups (McGarry et al., 2013). The emergence of NVT MDR strains (e.g., 35B, 23A) may pose continued difficulties for the prevention and treatment of *S. pneumoniae* secondary bacterial infections in influenza pandemics. However, resistant and susceptible VT strains included in PCV13 and PPV23 are still likely to prevent a clinically significant proportion of pneumococcal disease and subsequent deaths in healthy adults who are at the greatest risk of increased morbidity and mortality from secondary bacterial co-infection during an influenza pandemic (Pilishvili and Bennett, 2015; Richter et al., 2014).

Studies report a demonstrated VE of PPV23 against both IPD and non-invasive pneumococcal disease in healthy adults despite lower immunogenicity and efficacy in immunocompromised populations, adults with chronic disease, and older adults (Moberley et al., 2013). The superior VE in younger adults has important implications for pandemic preparedness given the burden of the 2009 influenza pandemic was predominantly in 18–50-year-olds. Routine PPV23 vaccination of all low-risk adults against pneumococcal disease during seasonal or non-pandemic influenza periods is not likely to be cost-effective. However the administration of the PPV23 vaccine is prospectively an essential component to early pandemic action plans and a potential predictor of pandemic impact.

This model examined the impact of *S. pneumoniae* AMR on H1N1pdm09 mortality and explored the potential influence of pneumococcal vaccination in preventing resistant co-infections during future influenza pandemics. With an overall pneumococcal mortality ranging between 5% and 27% (Bruce et al., 2008; Klemets et al., 2008) regardless of any documented resistance, vaccination could also be integral to the prevention of drug-sensitive pneumococcal co-infections during influenza pandemics.

While *S. pneumoniae* was not the sole cause of secondary bacterial pneumonia in the 2009 influenza pandemic, it remains the leading bacterial cause of influenza-related co-infections (Lynch and Zhanel, 2009; Chien et al., 2012). Future studies incorporating other pathogens commonly responsible for secondary bacterial infections (e.g., *H. influenzae*, *S. aureus*) would be useful in gaining a holistic view of the impact of AMR on pandemic as well as seasonal influenza. Active surveillance of these opportunistic pathogens could identify any unintended risks of widespread *S. pneumoniae* vaccine initiatives such as the predominance of *S. aureus*, which also colonizes the nasopharynx in up to 30% of the population (Morris et al., 2017). Importantly, necrotizing pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA) acquired in the community carries a 30% mortality and is known to have a high association to prior or concurrent influenza infection (Murray et al., 2010).

The quantification and consideration of specific antiviral resistance (e.g., neuroaminidase inhibitors) in seasonal and pandemic influenza would further inform treatability and mortality estimates. Currently circulating H3N2 and H1N1pdm09 viruses are already known to be resistant to adamantanes, and oseltamivir-resistant H1N1pdm09 infections have also been reported periodically, although infrequently, with 1.8% of tested isolates from the 2013–2014 season found to be resistant (Baz et al., 2009; Centers for Disease Control and Prevention (CDC), 2011). Surveillance of AMR in both *S. pneumoniae* and influenza should continue to be an important component of pandemic preparedness, especially amid the demonstrated lethal synergism of the two pathogens.

Antimicrobial resistance in secondary pneumococcal infections contributed towards a small, but clinically significant, proportion of the global mortality of the 2009 influenza pandemic. Pneumococcal disease is preventable by vaccination, but pandemic plans often fail to mention it as a component of preparedness (Itzwerth et al., 2018). Pneumococcal vaccination has an important role in preventing secondary pneumococcal infections, both sensitive and resistant, and should be a key component of influenza pandemic preparedness and early action plans.

Author contributions

CEB: led the study, conducted data collection, analysis and manuscript writing. CRM: conceived the study, contributed estimates of pneumococcal pneumonia during the 2009 pandemic from a separate study, developed the risk formula, supervised analysis, and contributed to manuscript writing.

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Ethical approval

Not required.

Conflict of interest

None.

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