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RESEARCH ARTICLE

Evaluating the impact of Respiratory Syncytial Virus immunisation strategies on antibiotic use and drug resistant bacterial infections in England [version 1; peer review: 2 approved with reservations]

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Abstract

Background: Vaccines against viruses have been proposed as a novel means to reduce antibiotic use, which would, in turn, decrease selection for antibiotic resistant bacteria. However, the impact of this intervention is poorly quantified, and likely depends on setting-specific epidemiology. Therefore, with increasing confidence in a new vaccine against respiratory syncytial virus (RSV), it is important to quantify the impact of these vaccines on antibiotic prescribing and any downstream reduction in drug resistant bacterial infections.
Methods: Here we integrate results from a dynamic transmission model of RSV and a statistical attribution framework to capture the impact of RSV vaccines on the reduction in antibiotic prescribing due to averted primary care visits in England.
Results: Under base case assumptions, we find that the most impactful RSV vaccine strategy targets children aged 5–14 years, resulting in an annual reduction of 10.9 (8.0–14.2) antibiotic courses per 10,000 person years across the entire population, equivalent to reducing annual all-cause primary care prescribing by 0.23%. Our results suggest that this reduction in antibiotic use would gain 130 disability-adjusted life years and avert £51,000 associated with drug resistant bacterial infections. Seasonally administering monoclonal antibodies (mAbs) to high-risk infants under 6 months is the most efficient strategy, reducing per person year antibiotic prescribing by 2.6 (1.9–3.3) antibiotic courses per 1,000 mAb courses.
Conclusions: Under optimistic conditions, the cost-effectiveness of RSV vaccine strategies in England would likely not be altered by integrating the benefits of preventing drug resistant infections in addition to RSV disease prevention.

Open Peer Review

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Any reports and responses or comments on the article can be found at the end of the article.

Keywords
Vaccination, Monoclonal antibodies, Antibiotic Resistance, Antibiotic use, Respiratory Syncytial Virus, Primary care prescribing, Respiratory disease

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Introduction

Vaccines against viral pathogens have been suggested as a novel means to reduce antibiotic resistance. By reducing the number of viral infections, fewer antibiotics would be used either inappropriately against viral disease as a precautionary measure for non-specific symptoms, or to treat bacterial co-infections[1,2]. Consequently, this reduction in antibiotic use would exert less selection for resistance on highly prevalent commensal bacteria that can lead to invasive disease.

Respiratory syncytial virus (RSV) is a major cause of acute lower respiratory tract infections in young children globally[3]. RSV can cause mild upper respiratory tract symptoms across all age groups and these infections can often result in primary care visits[4]. Data from high income countries suggest that antibiotic prescribing is common amongst primary care visits attributable to RSV infection, and consequently, reducing RSV infections may be beneficial to control antibiotic resistance across highly prevalent bacterial species[5,6]. Currently there are seven RSV vaccine formulations in Phase III clinical trials, including those targeting children, pregnant women, and the elderly. While information of the potential effect of RSV vaccines on antibiotic use is limited, secondary analysis from a recent trial suggests that a maternal vaccine could reduce all-cause antibiotic use by 20% and 10% in infants under 3 months in high- and low-income settings, respectively[7]. This effect was largely due to reducing lower respiratory tract infections in babies born to mothers in receipt of a vaccine.

In this study we evaluate the likely impact of the new generation of RSV vaccine strategies on antibiotic prescribing across all age groups in England and use these predictions to quantify the reduction in antibiotic resistance outcomes.

Methods

Literature review

We searched Pubmed using the terms: ("Respiratory Syncytial Virus, Human"[MeSH Terms] OR "Respiratory Syncytial Virus Infections"[MeSH Terms]) AND ("antibiotic" OR "antibiotics" OR "antimicrobial" OR "antimicrobials") up to 3 November 2021. We included all those studies that evaluated the impact of an RSV vaccine on antibiotic use, or that estimated antibiotic use in the community, outpatient or long-term care facility settings that was either i) coincident with respiratory infection symptoms with virologically confirmed RSV infection, or ii) attributed to RSV via statistical methods. We excluded all studies that reported antibiotic use only in hospitalised individuals or those attending emergency care, and excluded all review and commentary articles. We included patients of all ages and in any risk group.

Intervention programmes

We evaluated the impact of 12 potential RSV immunisation strategies on antibiotic prescribing rates in England. Specifically, we predicted the impact of a suite of vaccine strategies relying on vaccines that are currently under evaluation in clinical trials that can be administered via age groups or risk groups feasibly and affordably[8]. These strategies are: vaccination of infants at two months (seasonally - VAC INF S, or year round - VAC INF A); vaccination during the third trimester of pregnancy (seasonally - MAT S, or year-round - MAT A); seasonal vaccination of toddlers aged 2–4 years (VAC 2-4 S), primary school children aged 5–9 years (VAC 5-9 S) or primary and secondary school children aged 5–14 years (VAC 5-14 S); and, seasonal administration of long-acting monoclonal antibodies. These monoclonal antibody strategies are, in increasing order of number of doses given: very high risk infants under 8 months currently eligible for Palivizumab (MAB VHR S), high risk infants at birth as well as those currently eligible for Palivizumab (MAB HR S), high risk infants under 6 months as well as those currently eligible for Palivizumab (MAB HR S+), all infants at birth (MAB ALL S), or all infants under 6 months (MAB ALL S+).

We considered the efficacy against infection of long acting monoclonal antibodies and of maternal vaccination to be consistent with respective clinical trials, but that vaccine efficacy against infection in infants, toddlers and older children is consistent with natural infection, in the absence of clinical trial data[8] (Table 1). We assumed that vaccine uptake was consistent with other vaccine strategies delivered to the same age groups, and the monoclonal antibody uptake was the same as that for Palivizumab[8]. We assumed that all vaccine strategies were administered in addition to Palivizumab while all monoclonal antibody strategies replaced Palivizumab.

Antibiotic courses averted

We first calculated the age-specific reduction in the number of antibiotic courses per 1,000 person years due to each of these 12 vaccine strategies by multiplying the age-specific fraction of primary care visits averted with the age-specific number of primary care visits attributable to RSV that result in an antibiotic prescription.

i) Primary care visits averted: We calculated the average proportional reduction in primary care visits for 0–5 months, 6–23 months, 2–4 years, 5–17 years, 18+ years using a dynamic transmission model for RSV in England[8]. We calculated the average reduction across a 10-year time horizon after implementation of each immunisation strategy relative to the current status quo, Palivizumab administered seasonally to very high-risk infants[8]. For each intervention, we generated 1,000 estimates that captured uncertainty in the RSV incidence and the intervention impact via the joint posterior model parameter distribution using the efficacy and uptake parameter estimates (Table 1).

ii) RSV-attributable primary care antibiotic prescribing: In our base case analysis, we used estimates from a previous statistical attribution model that calculated the prescribing

Table 1. Intervention assumptions. Each intervention was compared to status quo Palivizumab administered seasonally to very high-risk infants[8].

Intervention	Value (95% interquantile range of sampled distribution if used)	Notes
Monoclonal antibodies		
Delay between administration and protection (days)	None	9
Average period of protection (days)	275	9
Efficacy against symptomatic infection (%)	70.1 (52.3–81.0)	10
Uptake (%)	90%	Same as Palivizumab[8]
*Maternal vaccination**		
Average period of protection (days)	133.5 (119.6–146.1)	Same as estimated maternal immunity
Efficacy against symptomatic infection (%)	41.4 (4.1–64.2)	From Novavax Resvax trial**
Uptake (%)	60	Same as Tdap uptake in 3rd trimester[8]
Childhood / adolescent vaccination		
Delay between administration and protection (days)	11.4 (2.8–22.1)	Same as influenza antibody delay[11]
Average period of protection (days)	358.9 (350.7–364.7)	Assumed to be same as natural immunity[8]
Efficacy against any infection (%)	9-56%***	Assumed to be same as natural immunity[8]
Uptake (%)	90 (<1y) 45 (2-4y) 60 (5+y)	Assumed to be same as primary series (<1y) or LAIV (2+y)[8]

LAIV: live attenuated influenza vaccine

* Effect on infant; effect on mother assumed the same as childhood vaccination

**https://www.globenewswire.com/news-release/2019/02/28/1744163/14446/en/Novavax-Announces-Topline-Results-from-Phase-3-PrepareTM-Trial-of-ResVax-for-Prevention-of-RSV-Disease-in-Infants-via-Maternal-Immunization.html

***Mean efficacy shown for illustrative purposes. Vaccination provides temporary protection against any disease, before individual move into a reduced susceptibility state, consistent with natural exposure. The efficacy is not used explicitly in the model, but a range can be calculated as $1 - [s + (1-s)r_i]$ for i=1,2,3, where s is the probability of seroconversion after vaccination (s = 83.0% (75.0–88.0%)) and r_i is the risk of infection after i previous exposures relative to after i-1 previous exposures (r_1 = 0.89 (0.85–0.93), r_2 = 0.81 (0.74–0.85), r_3 = 0.33 (0.31–0.37)).

rates in primary care attributable to RSV in England and Wales (calculated as the number of antibiotic courses per 100,000 person years for the age groups 0–5mo. 6–23mo, 2–4y and 5–17y)[5]. For each of the five age groups, we assumed the point value and confidence intervals to be from a triangular distribution with a mode and 95% confidence intervals, respectively and generated 1,000 samples from these distributions (Table 2).

We performed sensitivity analyses on the RSV-attributable antibiotic prescribing. Specifically, we used an alternative study from Scotland that calculated both the total primary care prescriptions and the fraction of these prescriptions attributable to RSV for infants for 0–11mo and for 1–4yr[6] (Table 2). To calculate the proportion of RSV-attributable prescriptions for 5–17y we assumed that the ratio of prescribing for those aged 5–17y to those aged 2–4y was the same as the base case study. In the first sensitivity analysis we assumed that the antibiotic prescribing rate in those aged 18+y was the same as that for those aged 5–17y. In the second sensitivity analysis we assumed that there was no RSV-attributable antibiotic prescribing for those aged 18+ (Table 2). We calculated the results stratified by the same age groups as our base case

Table 2. RSV-attributable antibiotic prescribing assumptions.

	RSV-attributable antibiotic prescribing (courses per 100,000 person years, 95% Confidence Interval)				
	0–5mo	**6–23mo**	**2–4y**	**5–17y**	**18+y**
Base case*					
Analysis A	8328 (5547–10265)	11916 (8432–13684)	7495 (5084–9051)	1091 (686–1427)	1091 (686–1427)
Sensitivity analysis**					
Analysis B	2758 (2086–3428)	3350 (2821–3918)	3635 (2876–4425)	559 (306–912)	559 (306–912)
Analysis C	2758 (2086–3428)	3350 (2821–3918)	3635 (2876–4425)	559 (306–912)	0 (0–0)

* assumption 18+y the same as 5–17y

** underlying rates <1 year (2,770, 95% Confidence Interval: 2078, 3409);1–4 years (3,645 95% Confidence Interval: 2,891, 4,400); ratio of 5–17y to 2–4y same as base case values.

analysis, weighting by 2019 Scottish age group population sizes, and generated 1,000 simulations as per the base case analysis.

Impact of averted prescribing

We first converted the averted number of antibiotic courses to averted defined daily doses (DDD) (assumed to be seven per antibiotic course[12]). We then followed previously published methodology by using a statistical model to calculate the population impact of the averted DDD on resistant infections, and calculated the health gain from these averted resistant infections in terms of the averted deaths, and the disability-adjusted life years (DALYs) gained[13,14]. We then calculated the averted cost of these drug resistant infections (in 2020 GBP) by multiplying the number of averted drug resistant infections by the 2020 cost of a drug resistant infection. This cost was assumed to be $1415 in 2015 USD[15], deflated to 2014 prices, before converting to 2014 GBP using equivalent health purchasing power, then inflated to 2020 prices at a rate of 2.3% per year giving a price of £586.83 per drug resistant infection.

Analysis

We conducted our analysis using R and plotted our results using ggplot2.

Results

Our search found 285 articles, 57 of which were excluded after title and abstract screening. After full text review, 10 articles met our inclusion criteria (Table 3). Only one of these studies evaluated the impact of RSV infection on antibiotic use in a low-income setting[16], with the others conducted in the US and Europe. Studies covered a range of ages, with estimates from either children, all household members, or the elderly. Studies provided estimates of one or more of the following: the rate of RSV-associated antibiotic use in the population, the rate or proportion of antibiotic use per RSV episode, and the rate or proportion of RSV episodes per antibiotic course. Studies were either retrospective or prospective cohorts or statistical attributable models. Differences in study design and reporting prevent straightforward comparisons between the estimates. For our analysis, we used the two study estimates that are both in the UK, and because of their similar study design, study population and age-stratification, this led to more comparable estimates.

We first assessed the impact of RSV immunisation strategies on primary care visits. Our model found that only four intervention strategies were able to reduce primary care visits by more than 5% in non-targeted age groups through herd protection: seasonal administration of monoclonal antibodies to <6 months (MAB ALL S+), seasonal (VAC INF S) or year-round (VAC INF A) administration of infant vaccination, and seasonal administration of vaccine to 5–14y (VAC 5-14 S). Conversely, many strategies did not reduce GP visits by 5% within the target age group (Table 4).

There was a substantial difference in the annual number of antibiotic courses averted across both age group and intervention strategy. For infants <6 months, the largest number of courses averted were for mAb strategies administered to

Table 3. Literature review of respiratory syncytial virus (RSV)-associated antibiotic use in the community, outpatient visits, and long-term care facilities.

Study first author (year) (reference)	Country	Population	Study Type	Reported Outcome (95% Confidence Intervals where indicated)					
				Rate of RSV-associated abx use in population		Abx use per RSV episode		RSV episodes per abx course	
				No. abx courses in vc RSV cases / 1000 py	*No. primary care abx courses attributable to RSV / 1000py*	*No. abx courses / RSV-related primary care visit*	*% of vc RSV cases receiving abx courses*	*% of abx courses in study population with vc RSV*	*% of abx courses in background population attributable to RSV*
Ellis (2003)[17]	United States	Nursing home residents over 65y presenting with fever or respiratory symptoms	Retrospective cohort	Not high risk: 62.4 (43.4–81.3) High risk: 75.6 (58.7–92.5)				Not high risk: 3.3 High risk: 2.8	
Caram (2009)[18]	United States	LTCF for older adults presenting with RTI	Prospective cohort				29% (2/7)		
Turner (2012)[16]	Thailand (Maela)	Children birth to 2y in refugee population presenting with pneumonia	Prospective cohort	240 (220–260)					
Meijboom (2013)[19]	Netherlands	Over 60y	Statistical analysis			0.75*			
Taylor (2016)[5]	United Kingdom	Children with recorded primary care antibiotic prescription	Statistical analysis of EHR		<6mo: 83.28 (55.47–102.65) 6-23mo: 119.16 (84.32–136.84) 2-4y: 74.95 (50.84–90.51) 5-17y: 10.91 (6.86–14.27)				<6mo: 19.7 6-23mo: 14.6 2-4y: 13.6 5-17y: 4.2†
Heikkinen (2017)[20]	Finland	Healthy children prospective study attending outpatient clinic (0-13y)	Prospective cohort				All: 54 (162/298) <1y: 91 (10/11) 1y: 63 (30/48) 2y: 64 (58/90) 3-6y: 48 (59/124) 7-13y:20 (5/25)**		

Study first author (year) (reference)	Country	Population	Study Type	Reported Outcome (95% Confidence Intervals where indicated)					
				Rate of RSV-associated abx use in population		Abx use per RSV episode		RSV episodes per abx course	
				No. abx courses in vc RSV cases / 1000 py	*No. primary care abx courses attributable to RSV / 1000py*	*No. abx courses / RSV-related primary care visit*	*% of vc RSV cases receiving abx courses*	*% of abx courses in study population with vc RSV*	*% of abx courses in background population attributable to RSV*
Smithgall (2020)[21]	United States	Household study all ages presenting with ARI symptoms	Prospective household				24 (16/66)		
Toivonen (2020)[22]	Finland	Healthy children 0-2y presenting with ARI	Prospective birth cohort				35 (102/289)**		
Korsten (2021)[23]	Belgium/ United Kingdom/ Netherlands	Healthy community people 60+ y presenting with ARI	Prospective cohort				2/36 (6%)		
Fitzpatrick (2021)[6]	United Kingdom	Children under 5y with recorded community antibiotic prescribing	Statistical analysis of EHR						All: 6.92 (5.59– 8.25) <1y: 5.16 (3.91– 6.41) 1-4y: 5.80 (4.55– 7.04)

abx: antibiotic; py: person years; vc: virologically confirmed; EHR: electronic health records; ARI: acute respiratory infection

* calculated using excess antibiotic prescriptions and GP visits from the RSV season in the Netherlands[24]

**very low rate of hospitalizations so assumption that all antibiotics are community-prescribed

† from antibiotic prescriptions limited to those used against respiratory disease: broad spectrum penicillins, macrolides, tetracyclines

all infants, and for any of the infant or maternal vaccine strategies. Similarly, those aged 6–23 months benefitted from mAb or infant vaccine strategies. For older children, only vaccines that targeted their age group led to substantial benefits in annual averted antibiotic courses (Figure 1).

The strategies that performed best at reducing antibiotic prescribing across the whole population were, in decreasing order: 5–14y vaccination (a reduction of 10.9, 95% Credible Interval (CI): 8.0–14.2 antibiotic courses per 10,000 person years; VAC 5-14 S), 2–4y vaccination (6.6, 95% CI: 5.0–8.3; VAC 2-4 S), seasonal monoclonal antibody administration to all infants under 6 months (6.0, 95% CI:4.4–7.5; MAB ALL S+), then 5–9y vaccination (5.0, 95% CI: 3.6–6.7; VAC 5-9 S), then year-round infant vaccination (4.6, 95% CI: 3.8–5.5; VAC INF A). The remaining strategies averted on average fewer than three antibiotic courses per 10,000 person years across all simulations (Figure 1). The best performing strategy of seasonal child and adolescent vaccination (VAC 5-14 S) averted 0.23% (95% CI: 0.16–0.29%) of the total antibiotic prescriptions (for any indication or aetiology) recorded in 2018. Monoclonal antibody administration to high risk

Table 4. Predicted reduction in respiratory syncytial virus (RSV)-attributable primary care visits in England.

Intervention (Programme code)*	Annual number of vaccine or mAb courses given	Percentage of RSV-attributable primary care visits averted for each vaccine or mAb intervention strategy** (95% credible interval)				
		0–5mo	6–23mo	2–4y	5–17y	18+y
Monoclonal antibodies						
MAB VHR S Seasonal mAb Very high risk <8mo	2,218	0.064 (0.0094 – 0.12)	0.037 (-0.0033 – 0.076)	0.013 (-0.0031 – 0.029)	0.00011 (-4.6e-05 – 0.00041)	0.00023 (7.2e-05 – 4e-04)
MAB HR S Seasonal mAb Very high risk <8mo High risk at birth	11,679	1.4 (1 – 1.6)	0.73 (0.55 – 0.87)	0.28 (0.2 – 0.33)	0.0016 (0.00038 – 0.0028)	0.00096 (7.6e-05 – 0.002)
MAB HR S+ Seasonal mAb Very high risk <8mo High risk <6 mo	22,907	1.9 (1.5 – 2.3)	1.8 (1.4 – 2.1)	0.72 (0.55 – 0.84)	0.0088 (0.0043 – 0.013)	-0.004 (-0.0068 – 0.0016)
MAB ALL S Seasonal mAb All infants at birth	252,581	27 (21 – 32)	4.4 (3.4 – 5.1)	1.6 (1.2 – 1.8)	0.037 (0.024 – 0.053)	0.17 (0.13 – 0.22)
MAB ALL S+ Seasonal mAb All infants <6 mo	547,818	38 (30 – 44)	16 (12 – 19)	3.9 (3 – 4.5)	0.11 (0.077 – 0.15)	0.35 (0.24 – 0.44)
Maternal vaccination						
MAT S Seasonal maternal vaccine 28–32wga pregnancy	165,257	7.7 (3.6 – 12)	-0.47 (-0.83 – -0.12)	-0.15 (-0.24 – -0.055)	0.055 (0.037 – 0.075)	0.28 (0.23 – 0.32)
MAT A Year round maternal vaccine 28–32wga pregnancy	406,442	12 (6.1 – 17)	-0.11 (-0.42 – 0.14)	-0.26 (-0.42 – -0.11)	0.16 (0.12 – 0.21)	0.59 (0.51 – 0.68)
Childhood vaccination						
VAC INF S Seasonal vaccine Infants 2 months	251,162	24 (21 – 25)	5.5 (4.9 – 6.1)	0.6 (0.51 – 0.69)	-0.0034 (-0.017–0.0079)	0.27 (0.2 – 0.34)
VAC INF A Year round vaccine Infants 2 months	617,724	34 (30 – 36)	13 (11 – 14)	1.3 (1.1 – 1.5)	0.006 (-0.026 –0.028)	0.48 (0.35 – 0.63)
VAC 2-4 S Seasonal vaccine Toddlers 2–4 years	917,008	0.91 (0.74 – 1.1)	0.55 (0.44 – 0.71)	21 (19 – 22)	0.6 (0.43 – 0.79)	1.2 (1 – 1.5)

Intervention (Programme code)*	Annual number of vaccine or mAb courses given	Percentage of RSV-attributable primary care visits averted for each vaccine or mAb intervention strategy** (95% credible interval)				
		0–5mo	6–23mo	2–4y	5–17y	18+y
VAC 5-9 S Seasonal vaccine Children 5–9 years	2,046,820	-0.32 (-0.43 – -0.14)	0.19 (0.11 – 0.34)	1.3 (1 – 1.6)	13 (8.2 – 16)	3.1 (2.6 – 3.7)
VAC 5-14 S Seasonal vaccine Children 5–14 years	4,093,640	-0.96 (-1.2 – -0.6)	-0.017 (-0.18 – 0.25)	2 (1.5 – 2.5)	26 (23 – 28)	7.5 (6.1 – 8.9)

* Monoclonal antibody programmes replace current Palivizumab programme, all other programmes are in addition.

**Proportion averted relative to the status quo strategy of Palivizumab seasonally administered to very high risk infants <1mo

mAb: monoclonal antibodies; wga: weeks gestational age; MAB VHR S: very high risk infants under 8 months currently eligible for Palivizumab; MAB HR S: high risk infants at birth as well as those currently eligible for Palivizumab; MAB HR S+: high risk infants under 6 months as well as those currently eligible for Palivizumab; MAB ALL S: all infants at birth; MAB ALL S+: all infants under 6 months; MAT S: seasonal vaccination during the third trimester of pregnancy; MAT A: year round vaccination during the third trimester of pregnancy; VAC INF S: seasonal vaccination of infants at two months; VAC INF A: year round vaccination of infants at two months; VAC 2-4 S: seasonal vaccination of toddlers aged 2–4 years; VAC 5-9 S: seasonal vaccination of primary school children aged 5–9 years; VAC 5-14 S: seasonal vaccination of primary and secondary school children aged 5–14 years.

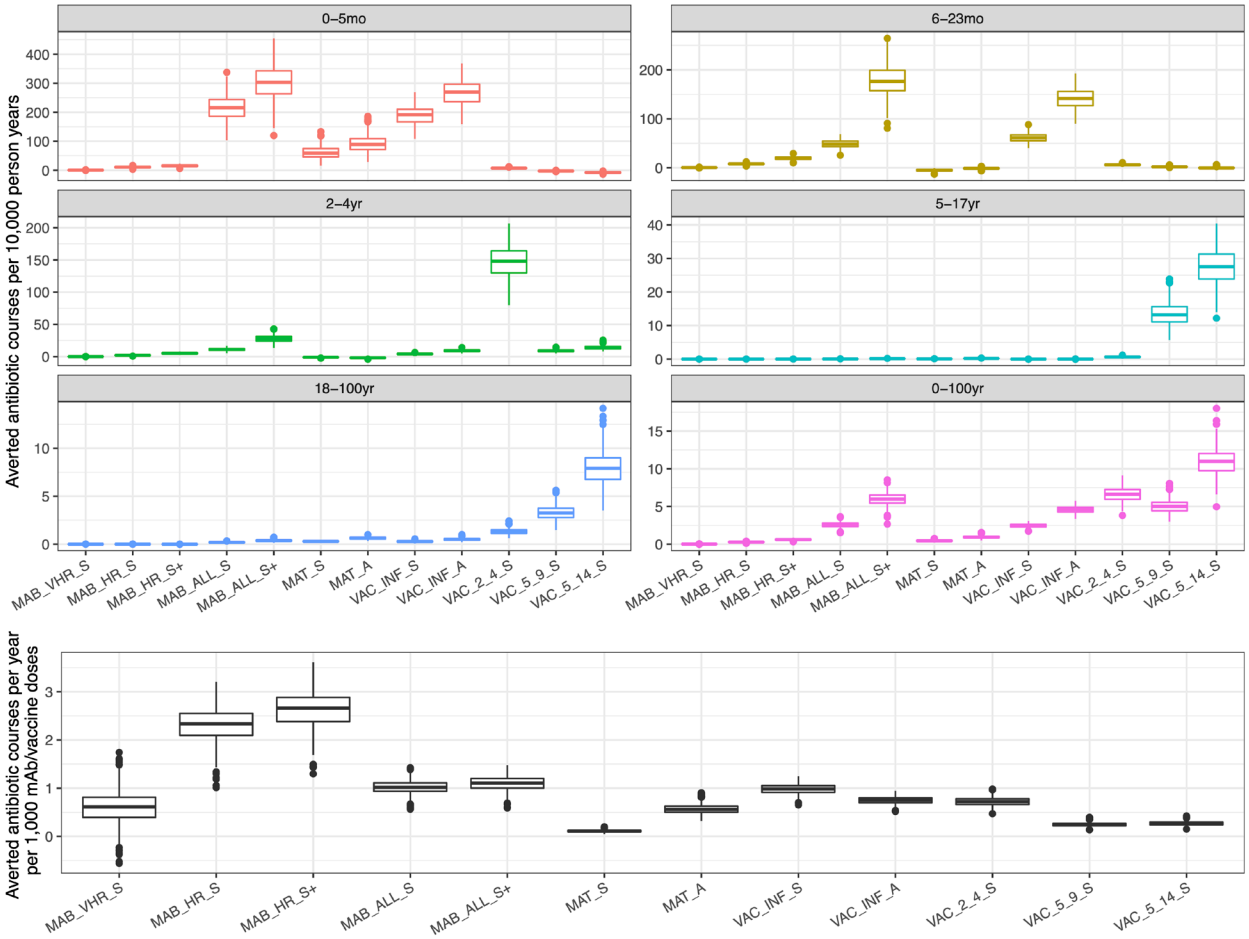

Figure 1. Averted antibiotic courses for each of the monoclonal antibodies (MAB), maternal vaccination (MAT) and age-targeted vaccination (VAC) interventions under base case assumptions (upper panel). Efficiency of each of the strategies at averting antibiotic courses (lower panel) under base case assumptions. Note the different y-axis scales.

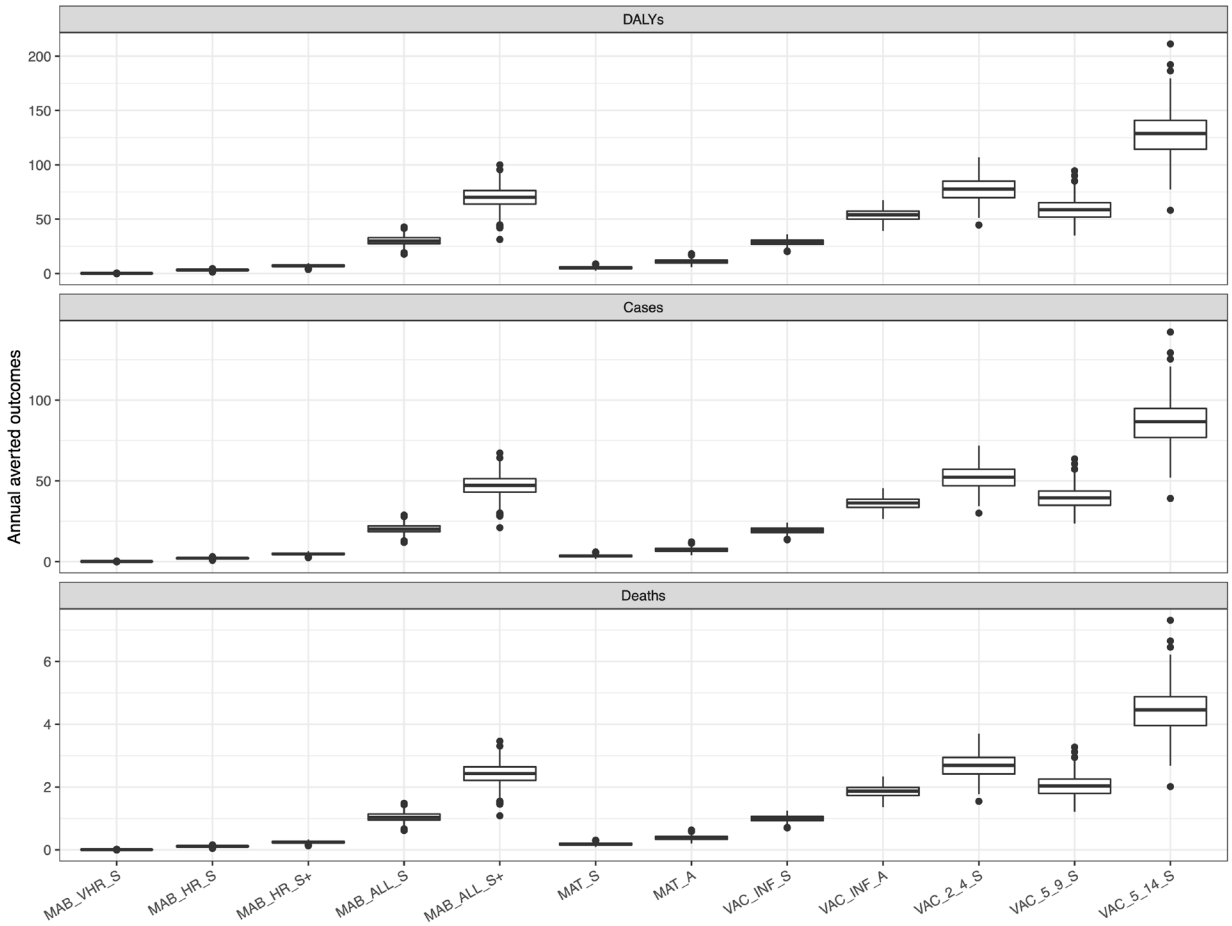

Figure 2. Population impact of the reduction in antibiotic prescribing for each of the monoclonal antibodies (MAB), maternal vaccination (MAT) and age-targeted vaccination (VAC) interventions under base case assumptions.

infants most efficiently reduced antibiotic use per intervention course, reducing the number of antibiotic courses per person year by 2.6 (95% CI: 1.9–3.3) per 1,000 mAb doses (Figure 1).

We calculated that seasonally vaccinating those aged 5–14 years (VAC 5-14 S) would lead to an annual gain of 128 (95% CI: 91–165) DALYs due to averting drug-resistant bacterial infections. This annual gain in DALYs is attributable to 86 (95% CI: 61–111) infections and 4 (95% CI: 3–6) deaths caused by drug-resistant bacteria (Figure 2). The annual averted cost of these drug resistant cases, which would be in addition to averted costs due to RSV disease, is £51,000 (95% CI: 36,000–65,000) in 2020.

The sensitivity analyses projected less impact of RSV vaccines on antibiotic use. Under the first sensitivity analysis, the 5–14y vaccine strategy (VAC 5-14 S) averts 5.8 (95% CI: 3.1–9.5) antibiotic courses per 10,000 person years, equivalent to around 0.1% (95% CI: 0.06–0.2%) of all prescriptions in 2018 (Figure 3, Figure 4). Under the alternative assumptions in the presence of no RSV-attributable prescribing over the age of 17 years, we found that toddler vaccination and child/adolescent vaccination were equally impactful in averting antibiotic courses. For comparison, under these most conservative assumptions, the child and adolescent strategy averts 2.5 (95% CI: 1.4–4.0) antibiotic courses per 10,000 person years, leading to a total annual gain of 29 DALYs (95% CI: 17–46) (Figure 5, Figure 6).

Discussion

Our study found that under the highest estimated RSV-attributable prescribing rates, the most impactful child and adolescent vaccination strategy was able to avert a quarter of a percent of the annual antibiotic prescriptions in England. This effect is limited due to a combination of factors: first,

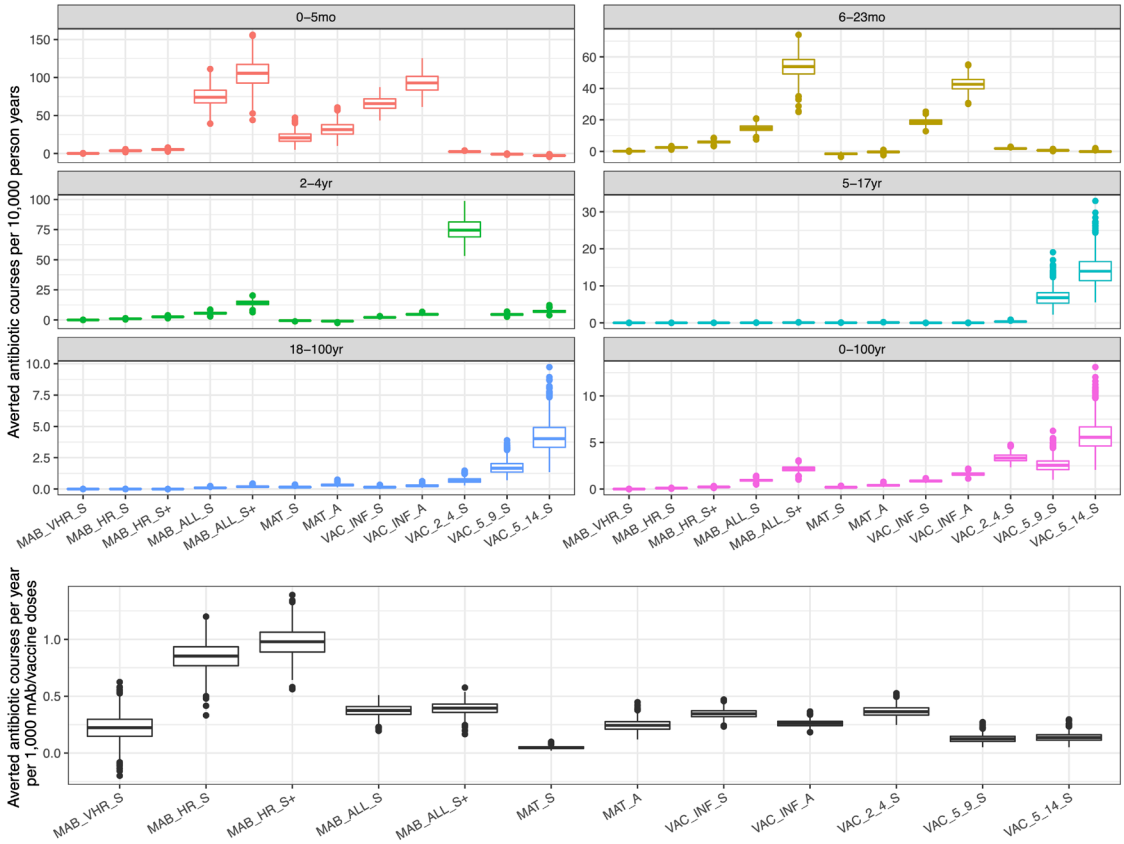

Figure 3. Sensitivity analysis (analysis B) of averted antibiotic courses for each of the monoclonal antibodies (MAB), maternal vaccination (MAT) and age-targeted vaccination (VAC) interventions (upper panel), and efficiency of each of the strategies at averting antibiotic courses (lower panel). Note the different y-axis scales.

vaccination targeting the young will not substantially decrease the number of primary care visits across older age groups, so the average impact across the entire population is small. Second, antibiotic use attributable to RSV decreases with age, dropping from 20% for those under 6 months to 4% for ages 5–17 years. Finally, the assumed efficacy and uptake of the vaccine limits the total reduction in primary care visits.

Our analysis found that the combination of age-targeted RSV vaccination and age-specific variability in the RSV-associated antibiotic prescribing rates led to substantial differences in the potential reduction in antibiotic prescribing across age groups. For example, the most impactful strategy for the youngest age group, administering monoclonal antibodies to those under 6 months, would avert antibiotic prescriptions at a rate 30 times higher than is estimated in the entire population. Further, the size of the immunisation strategy largely predicts the total impact of averting antibiotic use, with the notable exception of vaccinating toddlers aged 2–4 years and monoclonal antibody administration of monoclonal antibodies to those aged less than 6 months. The impact of these two strategies across the entire population was relatively impactful due to both high coverage and efficiency.

Our analysis finds comparable estimates to the only empirical study where antibiotic use in infants born to maternally RSV-vaccinated mothers in high income countries was reduced by 3.6 (-1.8 – 7.6) courses per 100 births during the first 3 months of life[7]. By comparison, our base case analysis suggests that there would be 1.13 (0.49 – 1.95) averted courses per 100 births over the first 3 months of life for the babies born to vaccinated mothers. Our estimate assumes that i) 92% of RSV-associated GP visits in the 0–5mo group are attributable to 0–2mo olds (consistent with our calibrated mathematical model), and ii) antibiotic administration is equally likely within the 0–5mo age group as within the 0–2mo age group. Direct comparisons between this trial and our modelling estimates for the seasonal maternal vaccine strategy are difficult for four reasons. First, as prescribing protocol is generally more conservative for very young infants, our birth cohort

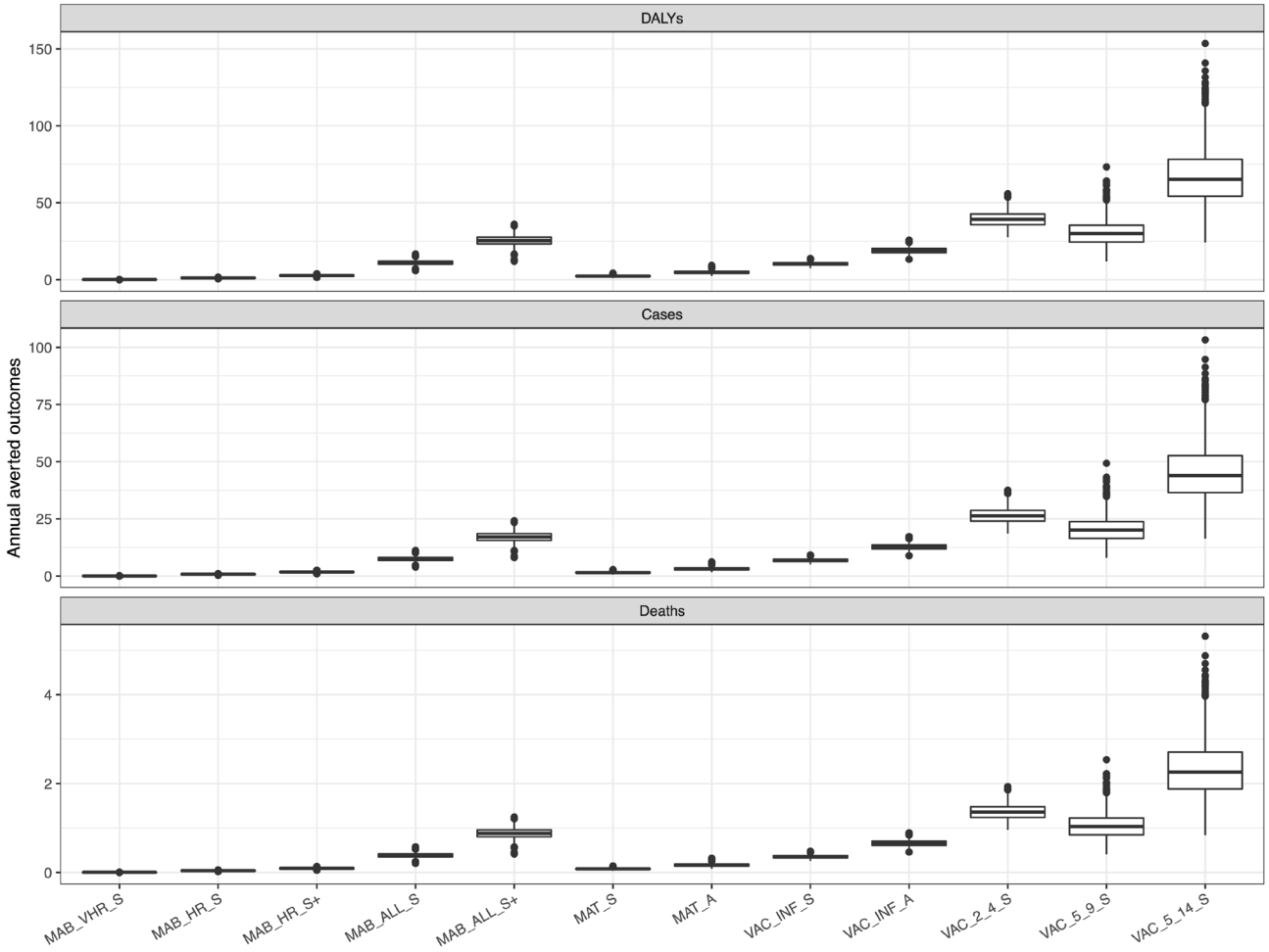

Figure 4. Sensitivity analysis (analysis B) for the population impact of the reduction in antibiotic prescribing for each of the monoclonal antibodies (MAB), maternal vaccination (MAT) and age-targeted vaccination (VAC) interventions.

estimate is likely to be an underestimate. Second, the empirical estimates use data collected across multiple countries, with antibiotic prescribing by local primary care providers in addition to trial clinicians. Prescribing protocols likely differ between countries, and indeed the vast majority of participant years in the high-income setting analysis were in the United States rather than the UK. Third, the trial was underpowered to detect changes in antibiotic use, and the relatively large confidence intervals – that overlap a null effect – are difficult to interpret with certainty. Fourth, the ecological study design on which our estimates are based rely on attributing antibiotic prescribing to RSV retrospectively; this statistical attribution method may underestimate or overestimate the antibiotic use as a result of RSV. Conversely, the empirical results allow direct estimates of antibiotic use reduction without confirmed RSV infection, thus bypassing the need to directly attribute antibiotic use to RSV. Indeed, the high efficacy against all-cause hospitalisations for respiratory disease in both the maternal vaccine trial and a recent monoclonal antibody trial suggest RSV is responsible – either directly or indirectly – for more severe lower respiratory infections than is currently thought[25].

Our study has limitations, most notably, to predict the reduction in prescribing and infections to drug resistant bacteria due to RSV pharmaceuticals, we use a combination of previously published model estimates. First, a dynamic model is used to evaluate the age-specific reduction in primary care visits resulting from a range of RSV immunisation strategies; second, we used results from a statistical attribution model to calculate the age-specific primary care antibiotic prescribing due to RSV in the UK; finally, we used a second statistical model that uses regression coefficients to evaluate the epidemiological and economic effects of antibiotic prescribing at a national level. There will be uncertainty and assumptions across these three models that will give rise to uncertainty in our results. Indeed, we have propagated all uncertainty captured in the

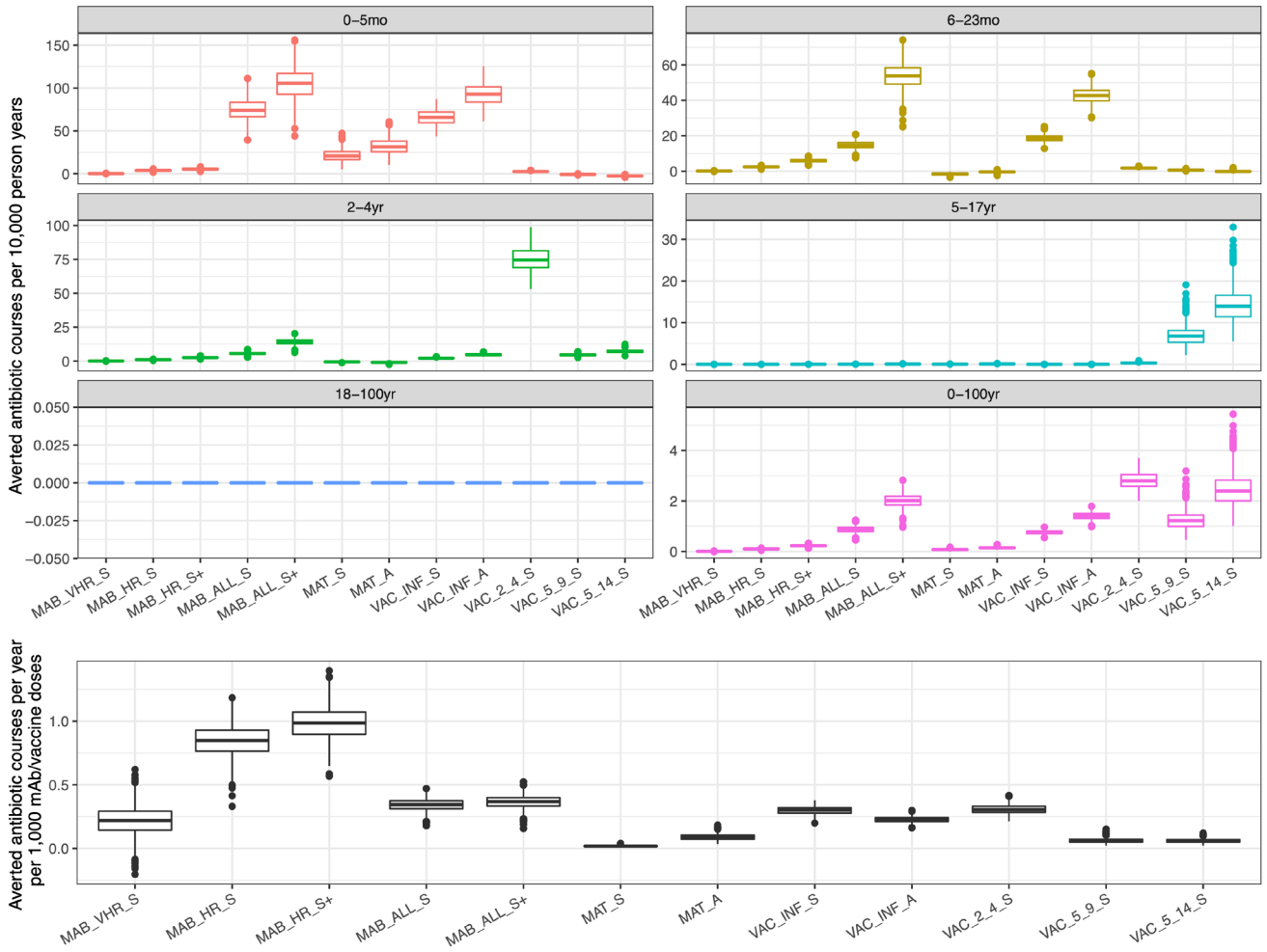

Figure 5. Sensitivity analysis (analysis C) of averted antibiotic courses for each of the monoclonal antibodies (MAB), maternal vaccination (MAT) and age-targeted vaccination (VAC) interventions (upper panel), and efficiency of each of the strategies at averting antibiotic courses (lower panel). Note the different y-axis scales.

models through our analysis. An important further limitation of our analysis is that details on RSV immunisation programmes are not currently known, therefore predicting the impact of a programme remains challenging. Instead, our work seeks to provide a qualitative assessment of the range of impact and relative success that these programmes can hope to achieve.

Given increasing interest in the use of vaccines, including viral vaccines, to control antibiotic resistance, it is advisable to consider averted resistance outcomes in the economic evaluation of vaccines. However, for RSV, our analysis suggests there would be a modest gain in DALYs attributable to averted drug resistant infections. Specifically, even the most impactful programme under the most optimistic scenario, a seasonal childhood vaccination for 5–14 year olds, would save £51,000 and 128 DALYs in drug resistant outcomes. Conversely, if this programme were to be administered at £20 per vaccine course, it would cost over £81 million and need to gain 4,100 quality-adjusted life years (QALYs) to be cost-effective in England (assuming a willingness-to-pay of £20,000/QALY). Therefore, the main benefit of RSV vaccination is likely to be in averting RSV itself, rather than averting antibiotic resistance due to by-stander selection. As noted previously[13], the analysis calculating antibiotic resistant outcomes assumes a counterfactual of no infection. Any deviation from this assumption would further reduce the impact of RSV vaccination on resistant outcomes[26].

Our results suggest that with a fixed uptake and efficacy of a vaccine, the impact of an RSV immunisation strategy on antibiotic prescribing is largely driven by the rate of antibiotic use attributable to RSV. For countries where antibiotic use due to RSV is high, the benefits of an RSV vaccine programme could be much larger and conceivably alter the cost-effectiveness of vaccination strategies. Indeed, a study in Maela, on the

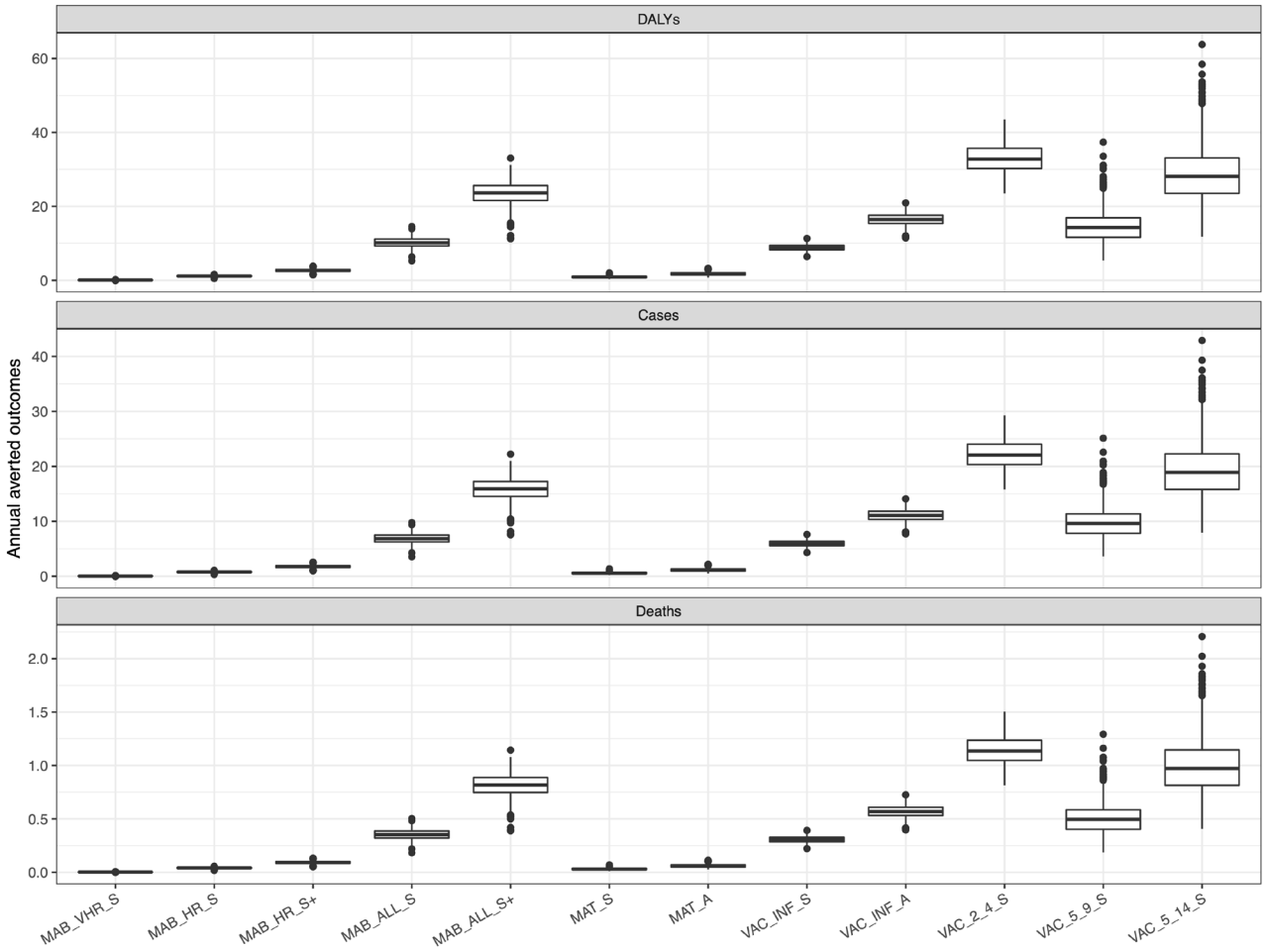

Figure 6. Sensitivity analysis (analysis C) for the population impact of the reduction in antibiotic prescribing for each of the monoclonal antibodies (MAB), maternal vaccination (MAT) and age-targeted vaccination (VAC) interventions.

Thailand-Myanmar border, found that young children who presented with antibiotic-indicated pneumonia who were later confirmed as RSV-infected did so at over twice the rate (240 courses given per 1000 children)[16] as children of the same age prescribed antibiotics in primary care attributable to RSV in the UK (110 courses given per 1000 children)[5]. As the clinical presentation and antibiotic prescribing were not comparable between the two studies, it is likely that a vaccine targeted at children in Maela would have more than double the impact on reducing antibiotic use compared with children in the UK. Moreover, it is not only the rate of RSV-associated symptoms that determines the effect of an RSV vaccine on antibiotics, but the magnitude of total antibiotic use. For settings where over-the-counter, unregulated antibiotic use comprise the majority of drug consumption – and where, as a consequence, multidrug resistance will be higher – the benefits of RSV vaccines on controlling drug resistance will likely be substantially larger.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Software availability

Source code available from: https://github.com/katiito/rsvvaccines_amr/tree/v1.0

Archived source code at time of publication: https://doi.org/10.5281/zenodo.7185502[27]

License: GNU GPL v3

Acknowledgements

An earlier version of this article can be found on medRxiv (https://doi.org/10.1101/2021.11.08.21266072)

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http://www.doi.org/10.5281/zenodo.7185502

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Aleksandra Kovacevic
Epidemiology and Modelling of Antibiotic Evasion, Institut Pasteur, Paris, France

This work provides valuable assessment of potential impact of an RSV vaccine on reduction in RSV-attributed antibiotic use and number of drug resistant infections in England by exploring different pediatric and maternal RSV immunization strategies. While the effect of the most effective immunization strategies on antibiotic use is very small at the population level, certain immunization strategies seem to be more effective than others in reducing percentage of RSV-attributable primary care visits across several age groups. More generally, results suggest that the impact of an RSV immunization strategy on antibiotic prescribing is driven by the rate of antibiotic use attributable to RSV, and therefore may be quite different in other countries. Authors find that integrating the benefits of preventing drug resistant infections in addition to RSV prevention in England, would likely not alter the cost-effectiveness of RSV vaccine strategies.

Major comments:

- Authors provide reference to prior work the model was based on. Is this new model exactly the same, and fitted the same way as the one cited? If not, what are the differences and why? Explaining this and giving a bit more information on the modeling process and utilizing the prior model is necessary for the study to be reproducible and at least some schematic should be provided in the supplement.
-
- There is no in-text information or detail on drug resistant infections used in the analyses. Which drug resistant infections/bacterial pathogens were considered and why? Was data skewed towards a particular age group and could that potentially affect the results?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
No

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: mathematical modeling, epidemiology, infectious disease modeling, antibiotic resistance, pathogen interactions, virus-bacteria interactions

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 14 December 2022

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Tiffany Fitzpatrick
Public Health Ontario, Toronto, ON, Canada

Atkins *et al.* have provided a valuable economic analysis of the potential impact of 12 next generation RSV prophylaxis and vaccination strategies on antibiotic use and drug resistant bacterial infections in England. This work provides urgently needed evidence to inform practice and policy given the widely anticipated approval of at least one of these new RSV prevention products in the next 12-18 months. Importantly, the authors' analysis provides detailed insights into the trade-offs between efficiency and impact across multiple pediatric and adult age groups, thereby providing crucial information for decision-making. Under optimistic conditions, the study findings suggest the cost-effectiveness of emerging RSV vaccination and prophylactic strategies in England would be minimally impacted by considering the prevention of drug resistant bacterial infections and averted antibiotic use in primary care.

Specific comments:

Methods:

While the modelling assumptions, parameterization of the compartmental model, and statistical analysis approach seem reasonable, insufficient information has been provided with the draft manuscript to fully assess their appropriateness. While some of this detail has been provided in the authors' prior work (i.e., details of the compartmental model), many other important details have not been provided. Providing these details in-text or as a supplement would allow the reader to assess the appropriateness of the analytical methods, as well as support reproducibility.

For example, the following items are not clear from the current manuscript or prior publications:

1. Methods pertaining to the statistical attribution model are lacking.

2. It would be helpful to provide details regarding any differences between the current compartmental model and the previously published model, e.g. 18-64 and 65+ have been collapsed in the current approach. Given the impact RSV has in older populations, differentiating between younger and older adults would be of interest.

3. How was the SEIR model fitted? Was it the same approach as previously used?

4. How were the age-specific number of primary care visits attributable to RSV that resulted in an antibiotic prescription determined?

Discussion section:

1. The current analysis only considers primary care visits, however, the cost effectiveness of these approaches might differ if inpatient outcomes are considered, particularly for drug resistant infections. It would be helpful, if this were mentioned in the discussion.

2. There is also an RSV vaccine for older adults that will also likely soon come to market. This will likely have substantial impact on the pediatric strategies; however, these strategies have not been included in the current analysis, which focuses on strategies within pediatric populations.

Minor comments:

1. For Figure 2, is this for outcomes over the 10 year study period? If so, it would be helpful if the title reflected this.

2. Was the upper age limit of the population assumed to be 100 years?

3. How was the proportion of bacterial infections that were drug resistant determined?

4. The fact that ggplot was used to create figures is of less relevance than how the modelling was performed; e.g. which ODE solver was used.

5. Was discounting used and, if so, at what rate?

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?
No

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology, mathematical modeling, statistical modeling, economic modeling, RSV, vaccination evaluation

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.