

Effect of Pediatric Influenza Vaccination on Antibiotic Resistance, England and Wales

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Vaccines against viral infections have been proposed to reduce prescribing of antibiotics and thereby help control resistant bacterial infections. However, by combining published data sources, we predict that pediatric live attenuated influenza vaccination in England and Wales will not substantially reduce antibiotic consumption or adverse health outcomes associated with antibiotic resistance.

Antibiotic use drives the spread of antibiotic resistance. A considerable proportion of antibiotic prescriptions are prescribed unnecessarily for conditions that are either self-limiting or nonbacterial in etiology (1). Because influenza is often treated inappropriately with antibiotics, expanding access to influenza vaccines has been proposed as a means of reducing unnecessary prescribing and preventing resistant infections (2).

In 2013, England and Wales began rolling out the live attenuated influenza vaccine (LAIV) for 2–16-year-old children (3). Here, we estimate the potential effect on antibiotic prescribing and antibiotic resistance.

The Study

We assumed that some influenza cases lead to general practitioner (GP) consultations and some GP consultations lead to antibiotic prescriptions. Our age-stratified analysis focused on community antibiotic use as the driver of resistance, because hospitalizations for influenza are rare relative to GP consultations (4).

To estimate the influenza-attributable consultation rate, we used a previous time-series statistical attribution covering the 1995–2009 influenza

seasons in the United Kingdom (5), yielding a population-wide average of 14.7 influenza-attributable GP consultations per 1,000 person-years (Table 1). For our uncertainty analysis (Appendix Table, <https://wwwnc.cdc.gov/EID/article/25/12/19-1110-App1.pdf>), we used a lower estimate of 11.8 per 1,000, from a longitudinal study of the 2006–2011 influenza seasons in England (6), and a higher estimate of 21.4 per 1,000, from a time-series statistical analysis of the 2000–2008 influenza seasons in England and Wales (4).

We estimated that 726 antibiotic prescriptions are written for every 1,000 influenza-attributable GP consultations (5). For our uncertainty analysis, we used a lower estimate of 313 per 1,000, derived from electronic health records of prescriptions within 30 days of a consultation for influenza-like illness (ILI) or acute cough in England during 2013–2015 (7).

We assumed that LAIV prevents 49% of symptomatic influenza cases on average, using a previously published mathematical model of pediatric LAIV in England and Wales, which assumes 50% uptake and either 70% (matched-year) or 42% (unmatched-year) efficacy among 2–16-year-olds (3). This reduction is consistent with a pilot study comparing consultation rates in treatment with control areas before and after LAIV rollout (8). For our uncertainty analysis, we used lower and higher estimates of 32% and 63% fewer influenza cases from the same model, assuming an uptake of 30% and 70%, respectively.

To predict the healthcare benefits of reducing unnecessary prescribing, we used linear regression with a country's rate of primary-care antibiotic use as the predictor variable and previously published 2015 estimates of adverse health outcomes associated with 16 resistant bacterial strains across European countries (9) as the response variables. We adopted a

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Table 1. Projected effect of pediatric LAIV on antibiotic prescription rates, England and Wales*

Age group	Influenza-attributed consultation rate†	Prescriptions per consultation	Direct prescribing rate reduction, unmatched‡	Direct prescribing rate reduction, matched‡	Overall LAIV effectiveness§	Overall prescribing rate reduction¶
0–6 mo	29.7 (23.7–35.9)	0.597 (0.474–0.719)	–	–	0.574 (0.501–0.651)	10.2 (7.03–13.5)
6 m–4 y	29.7 (23.7–35.9)	0.597 (0.474–0.719)	7.46 (5.31–9.64)	12.4 (8.85–16.1)	0.663 (0.618–0.714)	11.8 (8.31–15.4)
5–14 y	22.1 (17.6–26.7)	0.588 (0.466–0.708)	5.46 (3.89–7.06)	9.11 (6.48–11.8)	0.754 (0.709–0.794)	9.81 (6.97–12.8)
15–44 y	12.8 (10.2–15.4)	0.676 (0.536–0.814)	3.64 (2.59–4.70)	6.06 (4.31–7.83)	0.446 (0.394–0.502)	3.86 (2.66–5.09)
45–64 y	12.4 (9.84–14.9)	0.805 (0.639–0.970)	–	–	0.423 (0.374–0.484)	4.22 (2.90–5.58)
≥65 y	12.2 (9.67–14.7)	0.857 (0.680–1.03)	–	–	0.477 (0.397–0.561)	4.97 (3.34–6.68)
Overall	14.7 (11.7–17.7)	0.726 (0.576–0.875)	5.80 (4.13–7.49)	9.86 (7.01–12.9)	0.494 (0.446–0.549)	5.32 (3.74–7.00)

*All estimates reported as mean (95% highest density interval). LAIV, live attenuated influenza vaccine; –, age group not subject to pediatric LAIV.

†Per 1,000 person-years in England and Wales.

‡Reduction in antibiotic prescriptions among vaccinees per 1,000 vaccine recipients, not accounting for herd immunity, presented separately for unmatched and matched seasons.

§Reduction in influenza cases assuming a 50% uptake among children 2–16 years of age, accounting for herd immunity.

¶Per 1,000 person-years in England and Wales, accounting for herd immunity.

published cost estimate of \$1,415 per resistant infection (2016 USD) (10), adjusted for inflation and health-care purchasing power parity to £520 (2015 GBP).

We used Monte Carlo sampling to explore uncertainty across estimates for consultation rate, prescribing rate, and LAIV effectiveness, weighting age

groups by using 2015 demographic data for England and Wales. (Analysis code and data at http://github.com/nicholasdavies/laiv_amr_ew; additional details in the Appendix.)

We found that pediatric LAIV has the potential to reduce antibiotic consumption by 5.3 (95% highest

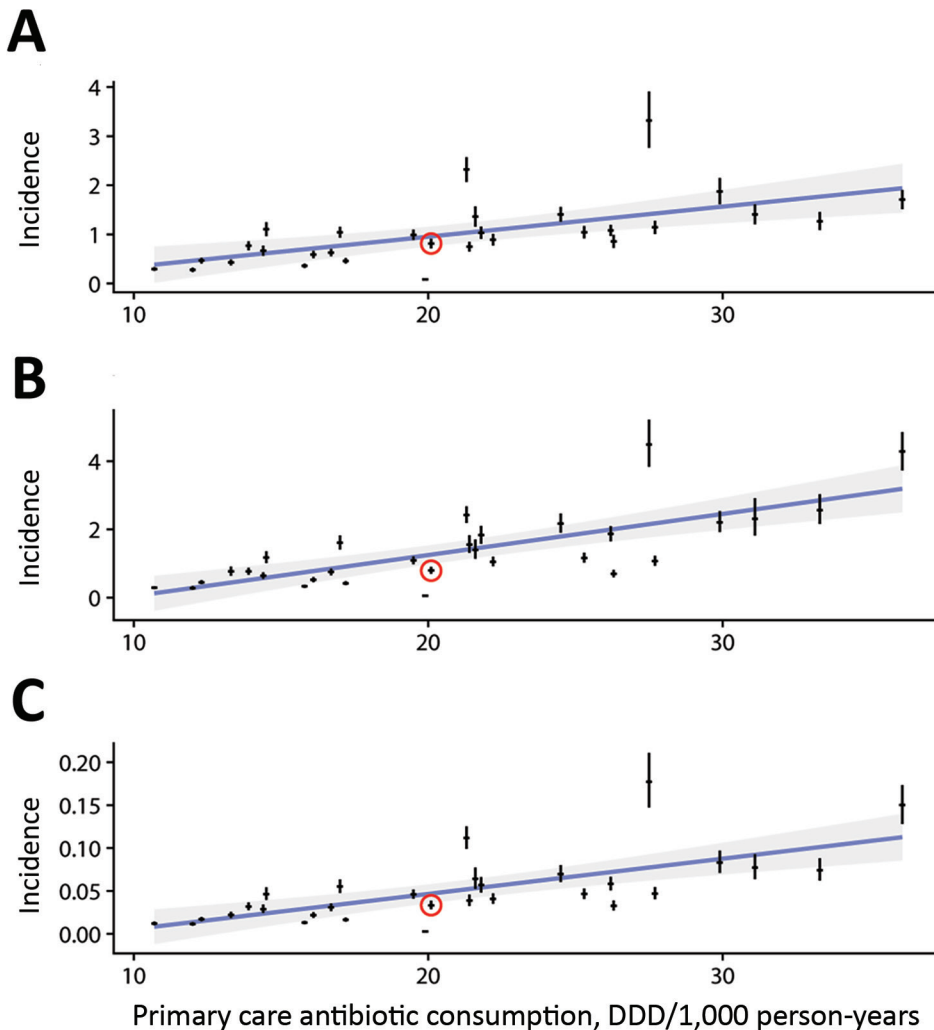


Figure 1. Estimated incidence of adverse health outcomes resulting from antibiotic-resistant infections, plotted against the overall antibiotic consumption in primary care settings in 30 countries in Europe, 2015. A) Antibiotic-resistant cases/1,000-person-years; B) attributable DALYs/1,000 person-years; C) attributable deaths/1,000 person-years. Red circles indicate datapoints for the United Kingdom; error bars indicate 95% CIs. Blue lines indicate linear regressions; gray shading indicates 95% confidence regions for linear regressions. DALYs, disability-adjusted life years; DDD, defined daily dose.

Table 2. Projected effect of pediatric LAIV on adverse health outcomes associated with antibiotic resistance, England and Wales*

Outcome	Estimate for 2015, England and Wales	Projected reduction in outcome resulting from LAIV, mean (95% HDI)
DALYs	46,039	642 (450–842)
Cases	47,080	432 (303–566)
Deaths	1,930	22 (16–29)

*DALYs, disability-adjusted life years; HDI, highest density interval; LAIV, live attenuated influenza vaccine.

density interval [HDI] 3.7–7.0) prescriptions per 1,000 person-years (Table 1) across the population of England and Wales, or 0.8% of the antibiotic dispensation rate for primary care in England and Wales in 2015. For comparison with secular trends, this rate has fallen by 2.5% each year during 2012–2018 in England (Appendix Figure). Focusing on vaccine recipients only, we estimated that the direct effectiveness of LAIV on antibiotic consumption is 5.8 (95% HDI 4.1–7.5) fewer prescriptions per 1,000 person-years in unmatched years and 9.9 (95% HDI 7.0–13) in matched years.

Although 0.8% is a small decrease in antibiotic use, it might appreciably improve the cost-effectiveness of pediatric LAIV if the healthcare costs of resistance are substantial enough (Figure 1). We estimated that LAIV has the potential to reduce resistance-attributable disability-adjusted life years (DALYs) by 642, cases by 432, and deaths by 22 per year in England and Wales (Table 2); averted DALYs were spread relatively evenly across the 7 causative pathogens analyzed (Figure 2, panel A). We estimated a yearly cost saving of £224,000 for averted resistant infections. Compared with the projected incremental cost (program cost minus healthcare saving) of pediatric LAIV at £63.6 million, and its projected effect of saving 27,475 quality-adjusted life years and averting 799 deaths yearly (3), accounting for resistance will not substantially increase the cost-effectiveness of pediatric LAIV in this setting. Our uncertainty analysis (Figure 2, panel B) identified the consultation rate as having the greatest influence over the effect of LAIV on resistance-associated adverse health outcomes.

Conclusions

Our estimates for the foreseeable reduction in antibiotic prescribing from the LAIV program in England and Wales might seem surprisingly low, given that sore throat, cough, and sinusitis together account for 53% of all inappropriate prescribing, which in turn accounts for at least 9%–23% of all prescribing in England (1). However, many viral and bacterial pathogens cause these symptoms. By

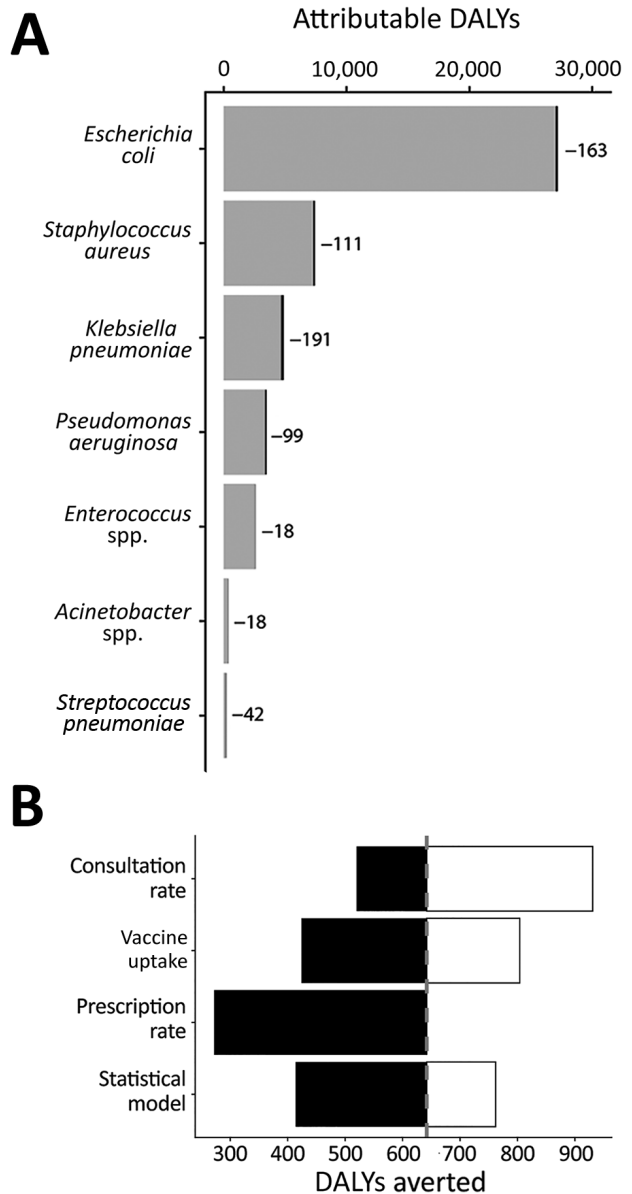


Figure 2. Effect of pediatric LAIV on adverse health outcomes attributable to antibiotic-resistant bacterial strains, England and Wales. A) Estimated DALYs attributable to resistant infections averted by pediatric LAIV, stratified by causative pathogen. The entire width of each bar is the current number of DALYs; potential reductions are highlighted in black and reported next to each bar. B) One-way uncertainty analysis, showing the effect on DALYs averted, of alternative assumptions concerning the rate of influenza-attributable general practitioner consultations, the pediatric uptake of LAIV, the rate of antibiotic prescribing per general practitioner consultation, and how the effect of prescribing on adverse health outcomes associated with resistance is attributed (additional details in Methods and Appendix, <https://wwwnc.cdc.gov/EID/article/25/12/19-1110-App1.pdf>). DALYs, disability-adjusted life years; LAIV, live attenuated influenza vaccine.

one estimate, influenza causes only 11% of GP consultations for acute respiratory illness in England (4), so it might be optimistic to expect influenza vaccination to substantially reduce antibiotic use in this setting.

Our base-case estimate of 726 antibiotic prescriptions per 1,000 influenza-attributable consultations is more than double what electronic health records suggest (7). One explanation is that our estimate, derived from statistical attribution of antibiotic prescriptions to influenza circulation during 1995–2009 (5), feasibly includes prescribing for secondary infections such as otitis media, sinusitis, and pneumonia. Moreover, electronic health records might not reliably reflect antibiotic prescribing rates for influenza: in 1 study, only 8% of consultations for ILI resulted in influenza or ILI being medically recorded (6). Conversely, antibiotic use in England has declined since 1995 (by 22% during 1998–2016) (11). Accordingly, our base-case results should be interpreted as the maximum potential reduction by LAIV of antibiotic use.

In randomized trials, the direct effect of influenza vaccines on vaccinated children has ranged from a 44% reduction (Italy) to a 6% increase (United States) in antibiotic prescriptions over the 4-month period following vaccination, whereas estimates of the effect over entire populations (all ages, vaccinated and unvaccinated) range from 11.3 fewer prescriptions per 1,000 person-years in Ontario, Canada, to 3.9 fewer in South Africa and Senegal (Appendix). This variability might arise from differences in vaccine efficacy and coverage, population risk factors, influenza circulation, or existing patterns of antibiotic use, which make generalizing estimates across settings challenging.

The adverse health outcome estimates that we adopt (9) assume that resistant infections add to, rather than replace, nonresistant infections. Relaxing this assumption would further reduce the projected effect of LAIV, because some prevented resistant infections would be replaced by nonresistant infections (12).

Our framework estimates the effect of influenza vaccination on antibiotic resistance by using the relationship between influenza circulation and antibiotic use in England and Wales, and can be adapted to other settings for which this relationship can be quantified. An alternative approach would be to correlate LAIV uptake, rather than influenza circulation, directly with antibiotic use. Challenges with that approach include appropriately controlling for confounding factors in the relationship between vaccine uptake and antibiotic use and quantifying

herd immunity. However, consistent with our approach, UK-specific empirical estimates have suggested little or no effect of LAIV uptake on prescribing: a self-controlled case-series study found that 2–4-year-old LAIV recipients took 13.5% fewer amoxicillin courses in the 6 months after vaccination (13), whereas an LAIV pilot study detected no difference in prescribing rates for respiratory tract infections between treatment groups (14). No single vaccine is likely to substantially reduce inappropriate antibiotic use in the United Kingdom.

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EID SPOTLIGHT TOPIC: Antimicrobial Resistance

Antibiotics and similar drugs, together called antimicrobial agents, have been used for the past 70 years to treat patients who have infectious diseases. Since the 1940s, these drugs have greatly reduced illness and death from infectious diseases. However, these drugs have been used so widely and for so long that the infectious organisms the antibiotics are designed to kill have adapted to them, making the drugs less effective.

Each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections.



EMERGING INFECTIOUS DISEASES <http://wwwnc.cdc.gov/eid/page/resistance-spotlight>

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Appendix

Influenza-attributable GP consultations

Base-case estimate

This estimate is derived from Table 2 of Fleming et al. (1), giving consultations for respiratory disease broadly defined attributable to either influenza A or B. Age groups reported by Fleming et al. differ from those used in this study, so we adapt estimates of Fleming et al. by assuming that reported rates are constant within an age group, and that half of children under 12 months old are under 6 months old.

Fleming et al. do not directly report confidence intervals in measured rates (instead, variation between flu seasons is reported), so we assume that uncertainty in the influenza-attributable GP consultation rates follows a normal distribution. We assume that the standard deviation of any consultation rate derived from this source is always S times the mean rate, where S is estimated from Figure 2 of Fleming et al. (1) by assuming that the width of the 95% confidence intervals on this figure are equivalent to 1.96 times the standard deviation of an associated normal distribution, and that the standard deviation of influenza-attributable GP visits is $(a^2 + b^2)^{1/2}$ where a is the standard deviation of influenza A-attributable consultations and b is the standard-deviation of influenza B-attributable consultations. S is then the mean relative standard deviation, calculated in this manner, across all study years.

Low estimate

Rates of PCR confirmed influenza are estimated from Tables S2 and S3 of Hayward et al. (2), taking the mean over the five winter flu seasons reported (i.e., excluding the Summer 2009 pandemic flu period). We assume that the reported rates of PCR confirmed influenza in the form B (A – C) represent a triangular distribution with B as the peak (mode) and A – C as the 95% highest density interval (using a triangular distribution rather than a normal distribution allows us

to account for skew). Then, the probability of a GP visit given PCR-confirmed illness is taken from Table S6 of the same source. We correct for low numbers by assuming a “base proportion” of 12/82 as the measured proportion of PCR confirmable influenza episodes resulting in a GP visit, which comes from the overall number of reported GP visits for 5–64-year-olds with PCR-confirmed influenza. To account for uncertainty in measurement, we draw the “base rate” of GP consultation given PCR-confirmable influenza for 5–64-year-olds from a beta distribution with parameters $\alpha = 12 + 1$, $\beta = 82 - 12 + 1$ (i.e., assuming a uniform prior); to account for the observation that this rate is higher in young children and the elderly (Table S6 of Hayward et al.), we add 0.12 to this rate for under-5s and over-65s. The annual influenza-attributable rate of GP consultation for a given age group is then the product of the PCR-confirmable influenza incidence and the rate of GP consultation given PCR-confirmable influenza.

High estimate

These are taken from Table 4 of Cromer et al. (3), assuming that reported 95% confidence intervals represent 1.96 times the standard deviation of a normal distribution.

Rate of antibiotic prescribing given an influenza-attributable GP consultation

Base-case estimate

This estimate is derived from Table 2 of Fleming et al. (1), by dividing the rate of antibiotic prescribing by the rate of influenza-attributable GP consultations, assuming a normal distribution for the final rate with the same relative standard deviation derived above (see “Base-case estimate” under “Influenza-attributable GP consultations”).

Low estimate

This estimate is derived from Table 3 of Pouwels et al. (4), which reports that 48% of consultations for acute cough and 29% of consultations for influenza-like illness result in a systemic antibiotic prescription within 30 days. We assume that 88.1% of influenza-attributable consultations are for ILI (hence having a 29% prescription rate) and the rest are for acute respiratory infection without fever (2) (hence having a 48% prescription rate), which yields an overall (crude) prescribing rate of 31.3%.

To calculate age-stratified values, we assume prescribing for under-5s is around 20% less, and for over-45s is around 20% more, than prescribing in 5–44-year-olds, consistent with

the results of Fleming et al. (1), Meier et al. (5), and Pitman et al. (6). That is, we draw a value d from a normal distribution with mean 0.2 and standard deviation 0.05, and assume that the relative prescribing rate for under-5s is $(1 - d)$ times the rate for 5–44-year-olds, while the relative prescribing rate for over-45s is $(1 + d)$ times the rate for 5–44-year-olds.

Impact of LAIV on rates of GP consultation

We use fitted models from Baguelin et al. (7) projecting the impact of LAIV on influenza cases in different age groups, assuming either a 50% vaccine uptake (base-case estimate), 30% uptake (low estimate), or 70% uptake (high estimate).

Age-stratified rates for uncertainty analysis

We summarize the base-case and uncertainty-analysis estimates of age-stratified consultation rates, prescription rates, and overall LAIV effectiveness in the Appendix Table.

Prediction of prescription rate impact on resistance-associated health burdens

Defined daily doses per prescribed antibiotic course

We assume that each prescription comprises 7 defined daily doses (DDD), as 7 days is the typical duration of antibiotic treatment for upper respiratory tract infections (8).

Main scenario

We use total primary care antibiotic consumption (ATC code J01C) for European countries for 2015 from the ECDC (9) as the predictor variable, and per-country median health burden (DALYs, cases, or deaths) attributed to each of 16 resistant strains analyzed by Cassini et al. (10) as the outcome variable, in a series of country-level linear regressions from which we separately predict the impact of reducing overall prescribing by a defined amount. For each country, we normalize each resistant-strain-specific health burden to the total number of bloodstream infections caused by the species in question before performing the regression to control for differences in the population and the per-capita incidence of infection between countries.

To estimate the total number of bloodstream infections caused by a given species in a given country, we begin by taking the maximum of the number of total tested isolates recorded by the ECDC for that country and species. Then we correct that figure according to the estimated population coverage for that country and species to the ECDC (i.e., an estimate of what fraction of the population is covered by the hospitals submitting resistance testing data to national surveillance programs which then report their data to the ECDC). For example, for *S. pneumoniae* infections in the United Kingdom in 2015, 1095 isolates were tested for penicillin non-susceptibility, 1077 isolates were tested for macrolide non-susceptibility, and 1060 isolates were tested for combined non-susceptibility to both penicillins and macrolides. Additionally, these isolates were reported as covering an estimated 21% of the entire population of the UK. Accordingly, we estimated the total number of bloodstream infections by *S. pneumoniae* in the UK as $\max(1095, 1077, 1060) / 0.21 = 1095 / 0.21 \approx 5214$.

An alternative method whereby health burdens were normalized to the population of each country produced similar results (a mean reduction of 714 instead of 642 DALYs, 362 instead of 432 cases, and 24 instead of 22 deaths).

Alternative scenario 1

Rather than using the overall antibiotic consumption for each country as the sole predictor in the regression model, we also built a separate series of models where we used as predictors each country's consumption of tetracyclines (J01AA), extended spectrum penicillins (J01CA), β -lactamase sensitive penicillins (J01CE), and macrolides (J01FA), as these four classes comprise the majority of antibiotics prescribed for sore throat and cough (11). We assume that for a given reduction in the overall prescription rate x , there is a reduction $0.0620x$ in tetracycline prescribing, $0.4752x$ in extended spectrum penicillin prescribing, $0.2793x$ in β -lactamase sensitive penicillin prescribing, and $0.1835x$ in macrolide prescribing. This predicted a smaller impact upon resistance than the main scenario (4.1) and comprises the "low-effect" statistical model for the uncertainty analysis (Figure 2B, main text).

Alternative scenario 2

We follow the same procedure as in 4.2, but if any predictor variable is negatively correlated with a resistance related health burden (i.e., the best fitting linear model suggests that decreasing use of that antibiotic would increase resistance), we remove it from the linear

regression and rerun the model, continuing this process until all predictors are positively associated with the outcome variable. If more than one variable has a negative association in a given round, all negative-association variables are removed for the next round. This predicted a larger impact upon resistance than the main scenario (4.1) and comprises the “high-effect” statistical model for the uncertainty analysis (Figure 2B, main text).

Economic calculations

To convert between U.S. and UK healthcare expenditures, we use hospital-service price level indices for health care purchasing power parity published by the OECD (12) (see their Figure 1).

Secular trends in antibiotic prescribing rates

Data from NHS Digital show that community antibiotic use in England has decreased by $\approx 2.5\%$ per year from 2012 to 2018 (Appendix Figure).

The impact of influenza vaccination on antibiotic use in different settings

A systematic review (13) found that in randomized trials, the direct effect of influenza vaccines on vaccinated children has ranged from a 44% reduction in antibiotic prescriptions in Italy (14) to a 6% increase in the United States (15), both over the 4-month period following vaccination. Published estimates of the impact over entire populations (all ages, vaccinated and unvaccinated, i.e., incorporating both direct and indirect protection) range from 11.3 fewer prescriptions per 1000 person-years in Ontario, Canada (16) to 3.9 fewer in South Africa and Senegal (17).

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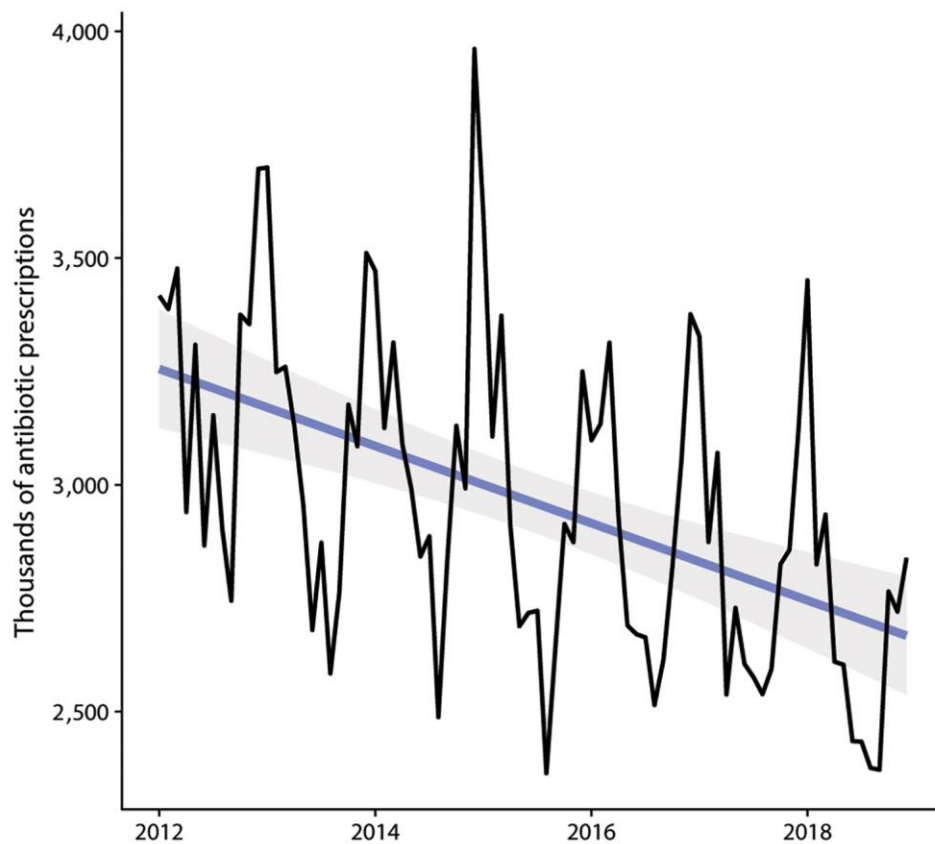
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Appendix Table. Summary of base-case and alternative estimates for uncertainty analysis for the influenza-attributed GP consultation rate (per 1,000 person-years in England and Wales), prescriptions per influenza-attributable GP consultation, and reduction in influenza cases owing to rollout of LAIV

Age group	Influenza-attributed consultation rate			Prescriptions per consultation		Overall LAIV effectiveness		
	Low	Base	High	Low	Base	Low	Base	High
0–6 m	32.2 (17.4–48.4)	29.7 (23.7–35.9)	73.6 (70.6–76.7)	0.238 (0.203–0.273)	0.597 (0.474–0.719)	0.390 (0.330–0.447)	0.574 (0.501–0.651)	0.694 (0.616–0.767)
6m–4 y	32.2 (17.4–48.4)	29.7 (23.7–35.9)	60.9 (59.2–62.6)	0.238 (0.203–0.273)	0.597 (0.474–0.719)	0.469 (0.433–0.517)	0.663 (0.618–0.714)	0.779 (0.739–0.821)
5–14 y	21.0 (9.87–33.3)	22.1 (17.6–26.7)	38.7 (37.7–39.8)	0.238 (0.203–0.273)	0.588 (0.466–0.708)	0.552 (0.507–0.591)	0.754 (0.709–0.794)	0.855 (0.828–0.885)
15–44 y	10.6 (4.99–16.9)	12.8 (10.2–15.4)	18.8 (18.4–19.1)	0.298 (0.290–0.305)	0.676 (0.536–0.814)	0.280 (0.247–0.321)	0.446 (0.394–0.502)	0.585 (0.526–0.655)
45–64 y	6.68 (3.16–10.6)	12.4 (9.84–14.9)	18.3 (18.0–18.6)	0.357 (0.336–0.377)	0.805 (0.639–0.970)	0.262 (0.227–0.298)	0.423 (0.374–0.484)	0.562 (0.497–0.632)
≥65 y	8.45 (4.06–13.2)	12.2 (9.67–14.7)	5.82 (5.56–6.08)	0.357 (0.336–0.377)	0.857 (0.680–1.03)	0.306 (0.250–0.368)	0.477 (0.397–0.561)	0.608 (0.516–0.692)
Overall	11.8 (6.68–17.3)	14.7 (11.7–17.7)	21.4 (20.9–21.9)	0.313 (0.313–0.313)	0.726 (0.576–0.875)	0.323 (0.289–0.358)	0.494 (0.446–0.549)	0.626 (0.572–0.686)



Appendix Figure. Antibiotic use in England has fallen by $\approx 2.5\%$ each year from 2012 to 2018.