Global and regional burden of attributable and associated bacterial antimicrobial resistance avertable by vaccination: modelling study

Chaelin Kim 1, Marianne Holm 2, Isabel Frost 3, Mateusz Hasso-Agopsowicz 3, Kaja Abbas 4

ABSTRACT

Introduction Antimicrobial resistance (AMR) is a global health threat with 1.27 million and 4.95 million deaths attributable to and associated with bacterial AMR, respectively, in 2019. Our aim is to estimate the vaccine avertable bacterial AMR burden based on existing and future vaccines at the regional and global levels by pathogen and infectious syndromes.

Methods We developed a static proportional impact model to estimate the vaccination impact on 15 bacterial pathogens in terms of reduction in age-specific AMR burden estimates for 2019 from the Global Research on Antimicrobial Resistance project in direct proportion to efficacy, coverage, target population for protection, and duration of protection of existing and future vaccines.

Results The AMR burden avertable by vaccination in 2019 was highest for the WHO Africa and South-East Asia regions, for lower respiratory infections, tuberculosis, and bloodstream infections by infectious syndromes, and for Mycobacterium tuberculosis and Streptococcus pneumoniae by pathogen. In the baseline scenario for vaccination of primary age groups against 15 pathogens, we estimated vaccine-avertable AMR burden of 0.51 (95% UI 0.49–0.54) million deaths and 28 (27–29) million disability-adjusted life-years (DALYs) associated with bacterial AMR, and 0.15 (0.14–0.17) million deaths and 7.6 (7.1–8.0) million DALYs attributable to AMR globally in 2019. In the high-potential scenario for vaccination of additional age groups against seven pathogens, we estimated vaccine-avertable AMR burden of an additional 1.2 (1.18–1.23) million deaths and 37 (36–39) million DALYs associated with AMR, and 0.33 (0.32–0.34) million deaths and 10 (9.8–11) million DALYs attributable to AMR globally in 2019.

Conclusion Increased coverage of existing vaccines and development of new vaccines are effective means to reduce AMR, and this evidence should inform the full value of vaccine assessments.

INTRODUCTION

Since the discovery of penicillin in 1928, antimicrobials have been used to treat bacteria, fungi, parasites and viruses, saving countless lives. However, antimicrobial resistance (AMR) is a growing global public health threat in the 21st century. Resistance occurs through pathogen evolution, either naturally over time or acquired by the use of antimicrobial drugs, which render these drugs ineffective and increase the risk of morbidity and mortality. While access to antimicrobial drugs in low-income and midle-income countries...
to treat infections continues to be a challenge, misuse and overuse of antimicrobials along with lack of access to clean water, sanitation and hygiene and effective infection prevention and control measures have fuelled the emergence and spread of AMR globally. The UK government commissioned review on AMR in 2014 projected that if AMR is not controlled, it would lead to significant impact on health with 10 million AMR-related deaths annually and macroeconomic consequences with a cumulative economic loss of US$100 trillion by 2050.7

Vaccination, when used in conjunction with other preventive measures, has the potential to significantly reduce AMR transmission through several pathways.4–5 First, vaccination has a direct influence on the health burden of AMR by preventing the emergence and transmission of drug-resistant and drug-sensitive infections, and the associated antibiotic use. Second, vaccines have an indirect influence by reducing resistant infections in unvaccinated populations through herd immunity. Third, vaccination can prevent infections where antimicrobials are not indicated but often wrongly prescribed, such as primary viral infections, thereby reducing misuse and overuse of antimicrobials. Fourth, vaccines can also reduce the use of antimicrobials to treat secondary bacterial infections caused by viral diseases. Finally, vaccines can give longer-term health benefits in preventing infections and resistance to vaccines is rarely observed.6

The Global Research on Antimicrobial Resistance (GRAM) project estimated the deaths and disability-adjusted life-years (DALYs) attributable to and associated with resistance by replacing all drug-resistant infections with susceptible infection or no infection, respectively. It estimated that 1.27 (95% UI 0.91–1.7) million deaths and 47.9 (35–64) million DALYs were attributable to bacterial AMR and 4.95 (3.6–6.6) million deaths and 192 (146–248) million DALYs were associated with bacterial AMR in 2019.7 Despite the significant potential impact of vaccination in lowering AMR, evidence is limited due to the methodological difficulties and challenges in obtaining data on the health burden associated with AMR in order to calculate this impact.8–10 Such evidence will be valuable to inform improvements in the coverage of existing vaccines and prioritise research and development of new vaccines.

To address this evidence gap, our aim is to analyse the findings from the GRAM project and estimate the vaccine-avoidable bacterial AMR burden based on the profiles of existing and future vaccines by pathogen and infectious syndromes at the regional and global levels in 2019. Such pan-pathogen analyses using standardised approaches are critical to inform vaccine development, funding, introduction and use. They also inform the WHO-led value attribution framework for vaccines against AMR,11 which includes five criteria: (1) vaccine averted AMR health burden, (2) vaccine averted AMR economic burden, (3) vaccine averted antibiotic use, (4) sense of urgency to develop antimicrobial approaches and (5) pathogen impact on equity and social justice. Our study contributes to the first criterion—vaccine-avoided AMR health burden.

METHODS

AMR burden data

We used the bacterial AMR burden estimates from the GRAM project which provided data for age-specific deaths and DALYs associated with and attributable to AMR by pathogen, infectious syndrome and region for 2019.7 12 These comprehensive estimates of bacterial AMR burden were based on statistical predictive modeling of data from systematic reviews, surveillance systems, hospital systems and other sources to generate estimates for 23 pathogens and 88 pathogen-drug combinations for 204 countries in 2019. The AMR burden estimates for Neisseria gonorrhoeae include only morbidity and no mortality.

Two sets of estimates are presented—burden attributable to AMR, that is, deaths and DALYs that could be averted if all drug-resistant infections would be replaced by drug-sensitive infections; and burden associated with AMR, that is deaths and DALYs that could be averted if all drug-resistant infections would be replaced by no infections. As vaccines prevent drug-resistant and drug-susceptible burden, we infer that the associated AMR burden is the appropriate metric for measuring the impact of vaccination on AMR burden.

Vaccine profiles

We focused our analysis on 15 pathogens—Acinetobacter baumannii, Enterococcus faecium, Escherichia coli, Group A Streptococcus, Haemophilus influenzae, Klebsiella pneumoniae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, non-typhoidal Salmonella, Pseudomonas aeruginosa, Salmonella paratyphi, Salmonella typhi, Shigella spp, Staphylococcus aureus and Streptococcus pneumoniae. We selected pathogens that are part of the WHO evaluation of the value of vaccines in preventing AMR. We used vaccine profiles (see table 1), which comprise the vaccine target population, efficacy, coverage, duration of protection and disease presentation prevented. For the existing vaccines against H. influenzae type b, S. pneumoniae and S. typhi, the vaccine profiles expand coverage of the current vaccines in order to meet the strategic priority on coverage and equity of Immunisation Agenda 2030.13 For vaccines that are not yet available, hypothetical profiles were developed based on preferred product characteristics (PPCs), target product profiles (TPPs), attributes of advanced vaccine candidates and expert consultations with WHO working groups, PATH and pathogen experts. Some pathogens have multiple disease presentations and would require different vaccines to prevent different disease presentations. As such, these pathogens have more than one vaccine profile.

Modelling process

We developed a static proportional impact model (see figure 1) to estimate the vaccination impact in terms of
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease presentation</th>
<th>Vaccine</th>
<th>Efficacy (%)</th>
<th>Coverage (%)</th>
<th>Duration of protection</th>
<th>Baseline scenario</th>
<th>High-potential scenario</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter baumannii—BSI*</td>
<td>BSI</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
<td>6 weeks, elderly age group with highest burden</td>
<td>All age groups</td>
<td>Hypothetical vaccine based on expert opinion</td>
<td></td>
</tr>
<tr>
<td>A. baumannii—all</td>
<td>All (Bacterial skin infections, BSI, cardiac infections, LRI and thorax infections, UTI)</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
<td>6 weeks, elderly age group with highest burden</td>
<td>All age groups</td>
<td>Hypothetical vaccine based on expert opinion</td>
<td></td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>All (bone and joint infections, BSI, cardiac infections, intra-abdominal infections, UTI)</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
<td>6 weeks, elderly age group with highest burden</td>
<td>All age groups</td>
<td>Hypothetical vaccine based on expert opinion</td>
<td></td>
</tr>
<tr>
<td>Enterotoxigenic Escherichia coli</td>
<td>Diarrhoea</td>
<td>60</td>
<td>70</td>
<td>5 years</td>
<td>6 months</td>
<td>–</td>
<td>WHO Preferred Product Characteristics and Expert opinion and Advanced candidate</td>
<td></td>
</tr>
<tr>
<td>Extraintestinal Pathogenic E. coli (ExPEC)—BSI*</td>
<td>BSI</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
<td>6 weeks, elderly age group with highest burden</td>
<td>All age groups</td>
<td>Hypothetical vaccine based on expert opinion</td>
<td></td>
</tr>
<tr>
<td>ExPEC—UTI*</td>
<td>UTI</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
<td>6 weeks, elderly age group with highest burden</td>
<td>All age groups</td>
<td>Hypothetical vaccine based on expert opinion</td>
<td></td>
</tr>
<tr>
<td>E. coli—non diarrheagenic</td>
<td>Bacterial skin infections, bone and joint infections, BSI, cardiac infections, CNS infections, intra-abdominal infections, LRI and thorax infections and UTI</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
<td>6 weeks, elderly age group with highest burden</td>
<td>All age groups</td>
<td>Hypothetical vaccine based on expert opinion</td>
<td></td>
</tr>
<tr>
<td>Group A Streptococcus</td>
<td>All (bacterial skin infections, bone and joint infections, BSI, cardiac infections)</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
<td>6 weeks</td>
<td>–</td>
<td>WHO Preferred Product Characteristics and Expert opinion</td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae type B</td>
<td>All (CNS infections, LRI and thorax infections)</td>
<td>59; 92; 93† (69 for LRI)</td>
<td>90</td>
<td>5 years</td>
<td>6, 10, 14 weeks</td>
<td>–</td>
<td>Existing vaccine</td>
<td></td>
</tr>
<tr>
<td>Klebsiella pneumoniae—BSI</td>
<td>BSI</td>
<td>70</td>
<td>70</td>
<td>6 months</td>
<td>0 weeks (maternal)</td>
<td>–</td>
<td>Hypothetical vaccine based on expert opinion</td>
<td></td>
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<tr>
<td>K. pneumoniae—all</td>
<td>All (bacterial skin infections, bone and joint infections, BSI, cardiac infections, CNS infections, intra-abdominal infections, LRI and thorax infections, UTI)</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
<td>6 weeks, elderly age group with highest burden</td>
<td>All age groups</td>
<td>Hypothetical vaccine based on expert opinion</td>
<td></td>
</tr>
<tr>
<td>Mycobacterium tuberculosis—M72*</td>
<td>Tuberculosis</td>
<td>50</td>
<td>70</td>
<td>10 years</td>
<td>10 years + boost every 10 years</td>
<td>–</td>
<td>WHO Preferred Product Characteristics and Expert opinion and Advanced candidate</td>
<td></td>
</tr>
<tr>
<td>M. tuberculosis—Improved</td>
<td>Tuberculosis</td>
<td>80</td>
<td>70</td>
<td>10 years</td>
<td>0 weeks (at birth) + boost every 10 years</td>
<td>–</td>
<td>WHO Preferred Product Characteristics and Expert opinion</td>
<td></td>
</tr>
<tr>
<td>Pathogen</td>
<td>Disease presentation</td>
<td>Efficacy (%)</td>
<td>Coverage (%)</td>
<td>Duration of protection</td>
<td>Baseline scenario</td>
<td>High-potential scenario</td>
<td>Justification</td>
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<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>Gonorrhoea</td>
<td>70</td>
<td>70</td>
<td>10 years</td>
<td>15 years</td>
<td>–</td>
<td>WHO Preferred Product Characteristics and Expert opinion</td>
<td></td>
</tr>
<tr>
<td>Non-typhoidal <em>Salmonella</em></td>
<td>All (BSI, cardiac infections, diarrhoea, typhoid, paratyphoid and iNTS)</td>
<td>80</td>
<td>70</td>
<td>5 years</td>
<td>6 weeks, 9 months</td>
<td>–</td>
<td>Hypothetical vaccine based on expert opinion</td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>BSI, LRI and thorax infections</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
<td>6 weeks, elderly age group with highest burden</td>
<td>All age groups</td>
<td>Hypothetical vaccine based on expert opinion</td>
<td></td>
</tr>
<tr>
<td><em>Salmonella paratyphi</em></td>
<td>Typhoid, paratyphoid and iNTS</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
<td>9 months</td>
<td>–</td>
<td>Hypothetical vaccine based on expert opinion</td>
<td></td>
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<tr>
<td><em>Salmonella typhi</em></td>
<td>All (BSI, cardiac infections, typhoid, paratyphoid and iNTS)</td>
<td>85</td>
<td>70</td>
<td>15 years</td>
<td>9 months</td>
<td>–</td>
<td>Existing vaccine and Expert opinion</td>
<td></td>
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<tr>
<td><em>Shigella</em></td>
<td>All (diarrhoea)</td>
<td>60</td>
<td>70</td>
<td>5 years</td>
<td>6 months</td>
<td>–</td>
<td>WHO Preferred Product Characteristics and Expert opinion</td>
<td></td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>All (Bacterial skin infections, bone and joint infections, BSI, cardiac infections, CNS infections, intra-abdominal infections, LRI and thorax infections, UTI)</td>
<td>60</td>
<td>70</td>
<td>5 years</td>
<td>6 weeks, elderly age group with highest burden</td>
<td>All age groups</td>
<td>Hypothetical vaccine based on expert opinion</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>BSI, CNS infections, cardiac infections, LRI</td>
<td>29; 58, 58†</td>
<td>58† (27 for LRI)</td>
<td>90 years</td>
<td>6, 10, 14 weeks</td>
<td>6, 10, 14 weeks, elderly age group with highest burden</td>
<td>Existing vaccine</td>
<td></td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>Improved*</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
<td>6 weeks</td>
<td>6 weeks, elderly age group with highest burden</td>
<td>Hypothetical vaccine based on expert opinion</td>
<td></td>
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</tbody>
</table>

Product characteristics for efficacy and duration of protection for vaccine-derived immunity, and coverage and target population (age of vaccination) for current and future vaccines against bacterial pathogens. The baseline scenario includes 15 pathogens, and the high-potential scenario includes a subset of 7 pathogens.

*The effects of these vaccines were not added to the aggregated impact of vaccination on AMR burden by region and by infectious syndrome.
†Efficacy corresponding to first, second and third doses respectively.
AMR, antimicrobial resistance; bacterial skin infections, bacterial infections of the skin and subcutaneous systems; Bone and joint infections, infections of bones, joints, and related organs; BSI, bloodstream infections; cardiac infections, endocarditis and other cardiac infections; CNS, central nervous system; CNS infections, meningitis and other bacterial central nervous system infections; intra-abdominal infections, peritoneal and intra-abdominal infections; iNTS, invasive non-typhoidal Salmonella spp; LRI, lower respiratory infection; LRI and thorax infections, lower respiratory infections and all related infections in the thorax; typhoid, paratyphoid, and iNTS, typhoid fever, paratyphoid fever, and invasive non-typhoidal Salmonella spp; UTI, urinary tract infections and pyelonephritis; UTI, urinary tract infection.
reduction in age-specific AMR burden estimates for 2019 from the GRAM project. We estimated a counterfactual prevaccination scenario for diseases with current vaccinations and adjusted for disease type specification before applying the vaccine impact. We calculated the reduction in prevaccine AMR burden after vaccination in direct proportion to efficacy, coverage, target population for protection, and duration of protection of existing and potential future vaccines.15

For ages that lie within the duration of protection since the time of vaccination:

AMR burden averted at age $i = $AMR burden at age $i$ prevaccination $\times$ vaccine efficacy $\times$ vaccine coverage.

**Scenarios**

We estimated vaccine avertable deaths and DALYs attributable to and associated with AMR by region, infectious syndrome and pathogen with 95% uncertainty intervals (UIs) for two scenarios—baseline scenario (for 15 pathogens) for primary vaccination of specific age groups, and high-potential scenario (for a subset of 7 pathogens) that includes additional age groups at risk of infection based on expert opinion.

Vaccine profiles with the corresponding product characteristics for efficacy and duration of protection for vaccine-derived immunity, and coverage and target population for the baseline and high-potential scenarios are described in table 1. In the baseline scenario, we estimated the vaccine avertable burden from the age of vaccination under the assumption that vaccine-derived immunity would sustain for the duration of protection of the corresponding vaccines. We did not consider vaccine waning dynamics due to limited evidence. For pathogens with a highly uncertain vaccine target population or feasibility of vaccine delivery, we estimated an additional high-potential scenario which assumed that individuals at risk (including additional age groups at risk) would be vaccinated to protect against corresponding disease presentations. This was applicable to vaccines against *A. baumannii*, *E. faecium*, Extraintestinal Pathogenic *E. coli* (ExPEC), *K. pneumoniae (all syndromes)*, *P. aeruginosa* and *S. aureus*. For *S. pneumoniae*, we explored the high-potential scenario by administering a vaccine to an elderly population with the highest disease burden.

**Uncertainty analysis**

We conducted a Monte Carlo simulation of 400 runs (sufficient for results to converge) to propagate the uncertainty in the AMR burden, vaccine efficacy and coverage through the model simulations to estimate the uncertainty in our projected outcomes of vaccination impact. We provide summary estimates in terms of vaccine-avertable deaths and DALYs attributable to and associated with AMR by region, infectious syndrome and pathogen with 95% UIs for the baseline and high-potential scenarios. Additional details on the modelling process, scenarios and uncertainty analysis are provided in online supplemental appendix A1.

**Patient and public involvement**

We analysed anonymised secondary data in our study. The data analysed originated from the GRAM project, and they were analysed in aggregate. As a result, it was not appropriate or possible to involve patients or the
public in the design, or conduct, or reporting, or dissemination plans of our research. The public will benefit from the findings of our study as our model-based projections facilitate evidence-based decision-making for scaling up of existing vaccines to regions in most need with higher AMR burden and prioritise development of new vaccines with high potential for lowering AMR burden by pathogen, infectious syndrome and region.

Data availability and code repository
We conducted our analysis using the R (version 4.2.3) programming language for statistical computing, and the repository for the data and software code of this modelling study are publicly accessible at https://github.com/vaccine-impact/vaccine_amr and Dryad open data publishing platform.

RESULTS
Vaccine impact on global AMR burden
At the global level in 2019 for the baseline scenario, we estimated that vaccines against the 15 pathogens (analysed in this study) could avert 0.51 (95% UI 0.49–0.54) million deaths and 28 (27–29) million DALYs associated with AMR, and 0.15 (0.14–0.17) million deaths and 7.6 (7.1–8.0) million DALYs attributable to AMR. In the high-potential scenario, we estimated that vaccines against a subset of 7 pathogens could avert an additional 1.2 (1.18–1.23) million deaths and 37 (36–39) million DALYs associated with AMR, and 0.33 (0.32–0.34) million deaths and 10 (9.8–11) million DALYs attributable to AMR globally in 2019.

Vaccine impact on AMR burden by pathogen
Figure 2A and table 2A present the vaccine avertable burden attributable to and associated with AMR in 2019 for each of the pathogen-specific vaccine profiles at the global level for the baseline scenario. For pathogens with licensed vaccines, we estimated that vaccination against S. pneumoniae at 2019 coverage levels averted 44 (37–52) thousand deaths and 3.8 (3.3–4.5) million DALYs associated with AMR in 2019. By reaching the WHO recommended coverage level of 90% globally, 59 (50–69) thousand deaths and 5.1 (4.5–5.9) million DALYs associated with AMR could have been averted in 2019. Expanding the coverage to elderly populations would increase the vaccination impact to aver 71 (63–81) thousand deaths. We estimated that vaccination against H. influenzae at 2019 coverage levels averted 11 (9.7–13) thousand deaths and 0.98 (0.85–1.2) million DALYs associated with AMR in 2019. At 90% coverage globally, 13 (11–15) thousand deaths and 1.1 (0.96–1.3) million DALYs associated with AMR could have been averted. We estimated that wider introduction and scale-up of vaccination against S. typhi could have averted 34 (26–44) thousand deaths and 2.8 (2.2–3.6) million DALYs associated with AMR in 2019.

For pathogens with hypothetical vaccine profiles (developed by experts or provided in PPCs), we estimated that a vaccine against M. tuberculosis that meets WHO’s PPC criteria of 80% efficacy, given to infants, with lifelong immunity or boosting, would have averted 0.12 (0.11–0.13) million deaths and 4.5 (4.1–5.0) million DALYs associated with AMR. An improved vaccine against S. pneumoniae (70% efficacy against bloodstream infections (BSI), meningitis and other bacterial central nervous system infections, 50% efficacy against lower respiratory infection (LRI) and all related infections in the thorax, given to 90% of infants at 6 weeks of life) would have a relatively highest impact by averting 99 (86–115) thousand deaths and 8.6 (7.5–10) million DALYs associated with AMR in 2019. An M72-like vaccine against M. tuberculosis given to adolescents and older populations with lifelong immunity or boosting would aver 71 (64–78) thousand deaths and 2.6 (2.3–2.8) million DALYs associated with AMR. A vaccine against all disease presentations of K. pneumoniae infection given to infants and elderly populations would avert 64 (59–72) thousand deaths and 3.7 (3.3–4.1) million DALYs associated with AMR.

In the high-potential scenario (see table 2B), we estimated that vaccination of at-risk individuals across all age groups against E. coli—non-diarrheogenic could aver 0.39 (0.37–0.40) million deaths and 13 (12–13) million DALYs associated with AMR in 2019. Vaccination of at-risk individuals against K. pneumoniae could aver 0.32 (0.31–0.34) million deaths and 14 (13–15) million DALYs associated with AMR, and vaccination against S. aureus could aver 0.32 (0.31–0.33) million deaths and 11 (10–11) million DALYs associated with AMR.

Vaccine impact on AMR burden by infectious syndrome
Figure 2B shows the vaccine avertable deaths and DALYs attributable to and associated with bacterial AMR for the different infectious syndromes in 2019 at the global level in the baseline scenario. We estimated vaccine avertable mortality associated with bacterial AMR to be highest for LRIs at 0.16 (0.14–0.17) million deaths and 11 (9.6–11) million DALYs for the baseline scenario, followed by tuberculosis (TB) at 0.12 (0.11–0.13) million deaths and 4.5 (4.1–5.0) million DALYs and bloodstream infections at 0.11 (0.10–0.12) million deaths and 5.6 (5.1–6.3) million DALYs in 2019. In the high-potential scenario, vaccine avertable deaths and DALYs were highest for LRIs, BSIs and intra-abdominal infections.

For each infectious syndrome, we stratified the vaccine avertable AMR burden for deaths and DALYs by pathogen in the baseline scenario, as shown in figure 3 and online supplemental figure A1. S. pneumoniae, S. aureus and K. pneumoniae account for most of the vaccine avertable AMR burden associated with LRIs. K. pneumoniae, A. baumannii and E. coli account for most of the vaccine avertable AMR burden associated with BSIs.

Vaccine impact on AMR burden at the regional level
Table 3 and figure 2C show the vaccine avertable deaths and DALYs attributable to and associated with bacterial AMR at the regional levels in 2019 for the baseline scenario. We estimated the vaccine avertable burden
Figure 2  Continued
associated with bacterial AMR to be highest in the WHO Africa region at 0.17 (0.15–0.18) million deaths and 12 (11–13) million DALYs, followed by the WHO South-East Asia region at 0.16 (0.15–0.18) million deaths and 7.5 (6.8–8.5) million DALYs in 2019. The vaccine avertable AMR burden for the WHO Africa and South-East Asia regions accounts for around two-thirds of the vaccine avertable AMR burden globally in 2019. In the high-potential scenario, we estimated that vaccines would avert an additional 0.19 (0.18–0.20) million deaths and 9.6 (8.8–11) million DALYs associated with AMR in the WHO Africa region, and 0.32 (0.30–0.33) million deaths and 11 (10–11) million DALYs associated with AMR in the WHO South-East Asia region.

**DISCUSSION**

We estimated vaccine avertable disease burden attributable to and associated with AMR for existing and new vaccines in the pipeline by pathogen, infectious syndrome and region based on the most recent, comprehensive estimates of the global burden of AMR. The AMR burden avertable by vaccination in 2019 was highest for the WHO Africa and South-East Asia regions, for LRIs, TB and BSIs by infectious syndrome, and for *M. tuberculosis* and *S. pneumoniae* by pathogen.

Our estimates show the impact of existing vaccines for pneumococcal conjugate vaccine, *H. influenzae* type b (Hib) and typhoid conjugate vaccine (TCV) on reducing AMR burden attributable to and associated with *S. pneumoniae*, *H. influenzae* and *Salmonella typhi*, respectively. We highlight the critical need to scale up existing vaccines to high and equitable immunisation coverage, and the acceleration of TCV introductions in high burden countries. Also, we show that vaccines can contribute towards preventing a significant proportion of the AMR burden for pathogens which have vaccines in late-stage clinical development with clear attributes or published PPCs or TPPs, such as for ExPEC and *M. tuberculosis*. Novel regulatory and policy mechanisms should be developed to accelerate the approval and use of these vaccines to prevent AMR. Based on the estimated high vaccine avertable burden associated with AMR for *K. pneumoniae*, *S. aureus* and *A. baumannii*, we urgently call for studies to enhance biological understanding and improve the

**Figure 2** Vaccine impact on AMR burden by (pathogen-specific) vaccine profile, infectious syndrome, and region. The estimates (median and 95% uncertainty intervals) of the vaccine avertable deaths attributable to and associated with bacterial antimicrobial resistance in 2019 were aggregated by (pathogen-specific) vaccine profile, infectious syndrome, and WHO region in the baseline scenario. (Bone+ = infections of bones, joints, and related organs; BSI = bloodstream infections; cardiac = endocarditis and other cardiac infections; CNS = meningitis and other bacterial CNS infections; intra-abdominal = peritoneal and intra-abdominal infections; LRI+ = lower respiratory infections and all related infections in the thorax; skin = bacterial infections of the skin and subcutaneous systems; TF–PF–INTS = typhoid fever, paratyphoid fever, and invasive non-typhoidal Salmonella spp; UTI = urinary tract infections and pyelonephritis).
Table 2  Vaccine impact on AMR burden by vaccine profile

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease presentation</th>
<th>Vaccine avertable deaths (median and 95% UI)</th>
<th>Vaccine avertable DALYs (median and 95% UI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Associated with resistance</td>
<td>Attributable to resistance</td>
<td>Associated with resistance</td>
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<tr>
<td>(A) Baseline scenario</td>
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</tr>
<tr>
<td>Acinetobacter baumannii—BSI</td>
<td>BSI</td>
<td>18 060 (13 305–25 668)</td>
<td>5 723 (4 142–8 442)</td>
</tr>
<tr>
<td>A. baumannii—all</td>
<td>All (bacterial skin infections, BSI, cardiac infections, LRI and thorax infections, UTI)</td>
<td>34 327 (28 241–43 094)</td>
<td>10 799 (8 651–14 129)</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>All (bone and joint infections, BSI, cardiac infections, intra-abdominal infections, UTI)</td>
<td>13 933 (12 268–16 025)</td>
<td>3 641 (3 094–4 689)</td>
</tr>
<tr>
<td>Enterotoxigenic Escherichia coli</td>
<td>Diarrhoea</td>
<td>2 779 (2 043–4 136)</td>
<td>784 (545–1 094)</td>
</tr>
<tr>
<td>Extraintestinal Pathogenic Escherichia coli (ExPEC)—BSI</td>
<td>BSI</td>
<td>15 316 (11 794–19 992)</td>
<td>3 938 (3 060–5 348)</td>
</tr>
<tr>
<td>ExPEC—UTI</td>
<td>UTI</td>
<td>6 727 (5 659–7 934)</td>
<td>1 787 (1 469–2 172)</td>
</tr>
<tr>
<td>E. coli—non-diarrheagenic</td>
<td>All (bacterial skin infections, bone and joint infections, BSI, cardiac infections, CNS infections, intra-abdominal infections, LRI and thorax infections)</td>
<td>62 424 (56 454–68 555)</td>
<td>16 405 (15 090–18 344)</td>
</tr>
<tr>
<td>Group A Streptococcus</td>
<td>All (bacterial skin infections, bone and joint infections, BSI, cardiac infections)</td>
<td>792 (643–998)</td>
<td>82 (55–130)</td>
</tr>
<tr>
<td>Haemophilus influenzae type B</td>
<td>All (CNS infections, LRI and thorax infections)</td>
<td>13 027 (11 058–15 180)</td>
<td>2 946 (2 412–3 622)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae—BSI</td>
<td>BSI</td>
<td>27 333 (22 045–34 905)</td>
<td>8 116 (6 508–10 273)</td>
</tr>
<tr>
<td>K. pneumoniae—all</td>
<td>All (bacterial skin infections, bone and joint infections, BSI, cardiac infections, CNS infections, intra-abdominal infections, LRI and thorax infections)</td>
<td>64 484 (58 747–72 028)</td>
<td>19 397 (16 971–21 761)</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis — M72</td>
<td>Tuberculosis</td>
<td>70 704 (64 053–77 951)</td>
<td>31 040 (26 956–37 850)</td>
</tr>
<tr>
<td>M. tuberculosis—improved</td>
<td>Tuberculosis</td>
<td>118 316 (107 061–130 567)</td>
<td>51 675 (45 223–61 401)</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>gonorrhoea</td>
<td>not applicable</td>
<td>not applicable</td>
</tr>
<tr>
<td>Non-typhoidal Salmonella</td>
<td>All (BSI, cardiac infections, diarrhoea, typhoid, paratyphoid, and INTS)</td>
<td>1 820 (1 412–2 624)</td>
<td>396 (290–618)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>BSI, LRI and thorax infections</td>
<td>20 700 (18 148–23 443)</td>
<td>5 314 (4 633–6 801)</td>
</tr>
<tr>
<td>Salmonella paratyphi</td>
<td>Typhoid, paratyphoid and INTS</td>
<td>1 463 (853–2 793)</td>
<td>301 (149–637)</td>
</tr>
<tr>
<td>Salmonella typhi</td>
<td>All (BSI, cardiac infections, typhoid, paratyphoid and INTS)</td>
<td>34 478 (26 029–44 037)</td>
<td>6 630 (5 022–8 959)</td>
</tr>
<tr>
<td>Shigella</td>
<td>All (diarrhoea)</td>
<td>4 133 (2 765–6 132)</td>
<td>860 (545–1 557)</td>
</tr>
</tbody>
</table>

Continued
Pathogen | Disease presentation | Vaccine avertable deaths (median and 95% UI) | Vaccine avertable DALYs (median and 95% UI) |
--- | --- | --- | --- |
| | Associated with resistance | Attributable to resistance | Associated with resistance | Attributable to resistance |

**Staphylococcus aureus**
- All (bacterial skin infections, bone and joint infections, BSI, cardiac infections, CNS infections, intra-abdominal infections, LRI and thorax infections, UTI)
- 56141 (50768–62454) 13322 (11924–15169)
- 2544277 (2287576–2854546) 601157 (529162–697354)

**Streptococcus pneumoniae**
- BSI, CNS infections, cardiac infections, LRI
- 58922 (50170–69048) 12179 (10178–14772)
- 5138513 (4453672–5943041) 1069634 (892728–1256886)

**S. pneumoniae—improved**
- BSI, CNS infections, cardiac infections, LRI
- 98987 (86231–115406) 20415 (17330–24803)
- 8606730 (7457713–9953947) 1781930 (1511883–2089464)

(B) High-potential scenario

**Acinetobacter baumannii**
- BSI
- 116141 (105342–128342) 36641 (33081–41272)
- 3463881 (3167174–3769823) 1081836 (992261–1201335)

**A. baumannii—all**
- All (bacterial skin infections, BSI, cardiac infections, LRI and thorax infections, UTI)
- 216584 (201748–231987) 67905 (63384–73535)
- 6018518 (5653363–6337590) 1854005 (1728332–1985653)

**Enterococcus faecium**
- All (bone and joint infections, BSI, cardiac infections, intra-abdominal infections, UTI)
- 100814 (95339–105798) 26342 (24611–28209)
- 2727684 (2594918–2873565) 699956 (657337–742297)

**ExPEC—BSI**
- BSI
- 103016 (93650–114889) 26551 (24078–29292)
- 2664329 (2471634–288329) 698896 (648274–764365)

**ExPEC—UTI**
- UTI
- 49669 (46732–52824) 13003 (12189–13885)
- 1079376 (1029529–1140334) 287866 (271982–306681)

**E. coli—non-diarrhoeic**
- Bacterial skin infections, bone and joint infections, BSI, cardiac infections, CNS infections, intra-abdominal infections, LRI and thorax infections and UTI
- 389043 (373393–404859) 102352 (97917–106919)
- 12648212 (12044182–13489274) 3375286 (3163077–3641542)

**Klebsiella pneumoniae—all**
- All (bacterial skin infections, bone and joint infections, BSI, cardiac infections, CNS infections, intra-abdominal infections, LRI and thorax infections and UTI)
- 321242 (308878–335698) 97026 (92013–102088)
- 13709546 (12834214–1723484) 4068201 (380569–4425285)

**Pseudomonas aeruginosa**
- BSI, LRI and thorax infections
- 118966 (113054–125950) 30495 (28728–32634)
- 4821442 (4495845–525746) 1237497 (1149086–1347794)

**Staphylococcus aureus**
- All (bacterial skin infections, bone and joint infections, BSI, cardiac infections, CNS infections, intra-abdominal infections, LRI and thorax infections, UTI)
- 319112 (307397–331431) 76796 (73583–80782)
- 10579419 (10085244–1164417) 2499704 (235737–2664681)

**S. pneumoniae**
- BSI, CNS infections, cardiac infections, LRI
- 71343 (62610–68314) 14728 (12661–17487)
- 5324115 (4648050–6118739) 1107245 (930760–1296970)

**S. pneumoniae—improved**
- BSI, CNS infections, cardiac infections, LRI
- 118645 (103983–135056) 24471 (20943–28957)
- 8980361 (7882947–10255670) 1848190 (1559623–2190715)

The estimates (median and 95% UI) of the vaccine avertable deaths and DALYs attributable to and associated with bacterial AMR in 2019 were aggregated by vaccine profile for the baseline (A) and high-potential (B) scenarios.
feasibility of developing vaccines for these pathogens. For the remaining pathogens that have vaccine candidates in the early stages of clinical development or no vaccines in the pipeline, we recommend investing in vaccine development to resolve biological challenges as well as feasibility in terms of product development, market access and product implementation.

Our analysis included a baseline and high-potential scenarios. In the baseline scenario, we model vaccine delivery based on known vaccine attributes, including a defined target age group that has been immunised with a vaccine in the past, during clinical trials or identified in vaccine TPPs. In contrast, the high-potential scenario makes no assumptions about vaccine delivery and target age group and shows the highest probable vaccine impact, should there be a policy recommendation and feasibility of delivery to all who would benefit from a vaccine. We recognise that the high-potential scenario includes multiple challenges that need overcoming such as immunisation of adults and the elderly, timely immunisation to prevent nosocomial infections, vaccine efficacy in patients who are immunocompromised and with comorbidities, vaccine demand and financing.

Pan-pathogen analyses with standardised methodologies are critical to inform vaccine funding and development and should be followed up with detailed vaccine-specific analyses, considering pathogen biology and transmission, and accounting for varied disease burden patterns across the spatial and temporal scales. *H. influenzae* type b (Hib), rotavirus, pneumococcal, typhoid and influenza vaccines have been directly associated with reduction of resistance, antibiotic use and related clinical complications,9 18–25 while Fu et al modelled the global burden of drug-resistant TB avertable by a future TB vaccine.26

Our study has limitations. First, since we included the direct effect of vaccination but excluded indirect effect and transmission dynamics of AMR pathogens, our vaccine impact estimates on averted AMR burden are conservative. Second, our analysis focused on 15 bacterial pathogens and additional pathogens included in the GRAM project such as Enterobacter spp, Group B Streptococcus, *E. faecalis*, Proteus spp, *Citrobacter* spp and *Morganella* spp were excluded. However, inclusion of these pathogens appears unlikely to significantly affect our overall inferences considering that the included 15 pathogens are responsible for the majority of the AMR burden. Third, while our analysis was based on the estimates generated by the GRAM project, which represents the most comprehensive estimates of bacterial AMR burden to date, limited input data to the GRAM project especially from low-income and middle-income countries

![Figure 3](image-url)

**Figure 3** Vaccine avertable AMR burden by infectious syndrome and pathogen. Vaccine avertable deaths associated with AMR by infectious syndrome and pathogen in the baseline scenario. (“Others” include infections of bones, joints, and related organs, bloodstream infections, endocarditis and other cardiac infections, meningitis and other bacterial CNS infections, peritoneal and intra-abdominal infections, lower respiratory infections and all related infections in the thorax, bacterial infections of the skin and subcutaneous systems, typhoid fever, paratyphoid fever, and invasive non-typhoidal Salmonella spp, and urinary tract infections and pyelonephritis)
The value of vaccines in preventing AMR should be systematically considered in the decision-making process during scale-up of existing vaccines and introduction of new vaccines. Vaccines should be explicitly incorporated as tools to combat AMR into National Action Plans on AMR\(^3\) and National Immunisation Strategies.\(^3\) For new vaccines in the pipeline and future vaccines, we recommend vaccine avertable burden of AMR to be included in the full value of vaccine assessments.\(^3\) This evidence can support stakeholders in their decision-making process and priority setting throughout the end-to-end continuum from discovery and clinical development to investment, development, introduction and sustainability of new vaccines with equitable access.

### Table 3

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Vaccine avertable deaths (median and 95% UI)</th>
<th>Vaccine avertable DALYs (median and 95% UI)</th>
<th>Attributable to resistance</th>
<th>Attributable to resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Africa</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1,184,307,681(1,092,629–1,250,636)</td>
<td>296,226(259,907–321,201)</td>
</tr>
<tr>
<td><strong>Americas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>32,901(30,029–35,892)</td>
<td>882,4(7,949–9,939)</td>
<td>1,197,042(727,42–1,459,954)</td>
<td>88,241(36,920–149,240)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18,408,608(1,062,629–1,250,636)</td>
<td>295,18(1,023,025–1,258,309)</td>
</tr>
<tr>
<td><strong>Eastern Mediterranean</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>32,901(30,029–35,892)</td>
<td>882,4(7,949–9,939)</td>
<td>1,197,042(727,42–1,459,954)</td>
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</tr>
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<td></td>
<td>18,408,608(1,062,629–1,250,636)</td>
<td>295,18(1,023,025–1,258,309)</td>
</tr>
<tr>
<td><strong>Europe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18,408,608(1,062,629–1,250,636)</td>
<td>295,18(1,023,025–1,258,309)</td>
</tr>
<tr>
<td><strong>South-East Asia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>32,901(30,029–35,892)</td>
<td>882,4(7,949–9,939)</td>
<td>1,197,042(727,42–1,459,954)</td>
<td>88,241(36,920–149,240)</td>
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<td></td>
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<td>295,18(1,023,025–1,258,309)</td>
</tr>
<tr>
<td><strong>Western Pacific</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td>882,4(7,949–9,939)</td>
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<td>88,241(36,920–149,240)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>18,408,608(1,062,629–1,250,636)</td>
<td>295,18(1,023,025–1,258,309)</td>
</tr>
<tr>
<td><strong>Global</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18,408,608(1,062,629–1,250,636)</td>
<td>295,18(1,023,025–1,258,309)</td>
</tr>
</tbody>
</table>

The estimates (median and 95% UI) for vaccine avertable disease burden attributable to and associated with bacterial AMR in 2019 is presented in terms of deaths and DALYs avertable by vaccination in the baseline scenario.

is a significant data gap that necessitates newer surveillance data and platforms to inform the updates, validity and confidence in the estimates of the GRAM project. In particular, estimates from the GRAM project for TB do not include TB associated with HIV. Fourth, we did not consider the impact of viral vaccines on reducing the AMR drivers of antibiotic misuse and overuse.\(^2\) Finally, we did not consider geographic and socioeconomic clustering of vaccination coverage, which could lead to heterogeneity in vaccination impact on lowering AMR burden with relatively less impact among subpopulations with higher risk of disease while also facing lower healthcare access including access to vaccination services.\(^2\)
article, and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated. All authors had full access to all the data in the study and final responsibility for the decision to submit for publication.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the ethics committee (Ref 26896) of the London School of Hygiene & Tropical Medicine.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository.

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