SUPPLEMENTARY INFORMATION

The Scope of the Antimicrobial Resistance Challenge and the Need for Sustainable Access to Effective Antibiotics

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Text S1: Extended Methods

The figures in this review present data and analyses from previously published sources. We have collated that data to provide a complete perspective on antimicrobial resistance, and in some cases have conducted minimal analyses to make the data comparable. Below, we detail the data gathered and data visualization techniques as well as ancillary analyses.

Data and Visualization

We required both estimates of mortality from various high-level causes over time and the burden of antimicrobial resistance (AMR) from specific pathogens for the most recent year available, by age group. These two datasets enabled a comparison of mortality from AMR and specific causes by year (**Figure 2**) and direct characterization of the burden of specific pathogens (**Figures S2** and **3**).

Mortality rates from syndromic causes

Mortality rates by high-level cause and age were obtained from the Global Burden of Disease (GBD) study.[1] We tracked global estimates of neonatal all-cause, neonatal sepsis, and under-five all-cause mortality from 2000 to 2019 (the last year for which estimates are available). GBD reports the absolute number of deaths, percent of all deaths in an age group attributable to a given cause, and mortality rate per 100,000 population for individuals in a given age group by cause. Our analyses used estimated mortality rates by age group because this measure can be compared across years while still informing the absolute magnitude of mortality from a specific cause. We normalized reported mortality rates by year to mortality rates in the year 2000, pegging values from the year 2000 to 1 or 100%. This enabled us to compare changes in the rates of sepsis among neonates and children under five with all-cause childhood mortality with respect to the United Nations Sustainable Development Goals mortality targets (data shown in **Figure 2A** and **2B** under "Overall isolates").[2]

We conducted a similar analysis to show changes in the burden of bacterial infections in older populations. There are no reliable estimates of sepsis in adult populations, so we instead tracked bacteria-attributable mortality by aggregating over all modeled GBD mortality causes that can be traced to bacteria. This included bacterial respiratory infections and tuberculosis, enteric infections, sexually transmitted infections (excluding HIV), measles, pertussis, meningitis, diphtheria, encephalitis, and tetanus. We tracked mortality rates for these diseases from 2000 to 2019 among individuals over and under 65 years of age (data shown in **Figure 2C**). Note that nearly identical results were obtained (R^2 = 99%) when using GBD estimates of mortality from specific bacterial etiologies regardless of the syndromic cause. We assumed that the gathered GBD data serve as a reliable proxy for the rates of death from the causes we seek to measure – namely neonatal sepsis, childhood all-cause, and overall bacteria-attributable mortality – even if the absolute values are not necessarily correct. We addressed this issue by assessing mortality relative to the year 2000.

Mortality rates from AMR pathogens by age group

To obtain estimates of the burden of specific AMR pathogens by age group, we used two data sets: for individuals over 65, we used data from the Global Burden of Disease antimicrobial resistance sub-study,[3] and for neonates, we expanded on the work of Kumar et al. (2023).[4] For individuals over 65, we obtained estimates of resistance-attributable deaths from the GBD AMR sub-study using the GBD counterfactual scenario "drug-susceptible infection", meaning that the values we report correspond to AMR-attributable infections. Concretely, AMR-attributable infections are lives that would have been saved had the infection been from a drug-susceptible infection. In this case, the death was caused by AMR and not the infection itself. GBD reports AMR-attributable infections by pathogen-antibiotic class combination to stratify the antibiotic class to which the pathogen is resistant: we aggregate over the antibiotic class to consider pathogens that were resistant to at least one antibiotic.

Assuming that resistance-attributable deaths by pathogen in individuals over the age of five (i.e., numbers that are publicly reported) are dominated by deaths in individuals over the age of 65, we evaluated resistance-attributable deaths by bacteria by geographic GBD super regions – where we are referencing the income-based GBD regions by their geographic locations, the Oceania region has been grouped with Australasia, Southern Latin America with the rest of Latin America and the Caribbean, and high-income Asia Pacific has been renamed "East Asia" (data shown in **Figure 3**). **Figure 3A** presents estimated numbers of AMR-attributable deaths in individuals over 65, taking the reported values for individuals over five and scaling by the population fraction of over 65 individuals compared to individuals over five. **Figure 3B** presents the estimated percent of over 65 deaths that are attributable to AMR, calculated by dividing the number of AMR deaths in individuals over 65 by the number of all-cause mortality as estimated from the GBD base study from 2019 (the GBD AMR substudy reports values as of 2019).

For neonates, we expanded on previous work by Kumar et al. (2023) that modeled the number and percent of neonatal deaths that were attributable to sepsis by pathogen and the antimicrobial resistance of those sepsis isolates. That work used underlying data from the Child Health and Mortality Prevention Surveillance (CHAMPS),[5] Burden of Antibiotic Resistance in Neonates from Developing Societies (BARNARDS),[6] and Global Neonatal Sepsis Observational Study (NeoObs)[7] groups: all three provide surveillance on the etiologies causing neonatal sepsis from various locations in low- and middle-income countries (LMICs) with NeoObs also providing surveillance in select high-income countries (HICs). Only the latter two (BARNARDS and NeoObs) conducted antimicrobial resistance susceptibility testing of bacterial isolates from neonates. Using the same source data and a nearly identical methodology (we adjust the error bars for correlated probabilistic sampling, described below), we expanded on the estimates published in the work of Kumar et al. (2023) to report the percentage of neonatal deaths that are attributable to bacterial sepsis from the four leading etiologies (*Klebsiella pneumoniae, Acinetobacter baumannii, Escherichia coli,* and *Staphylococcus aureus*) that are resistant to at least one of the

main antibiotics used to treat neonatal sepsis (ampicillin, piperacillin-tazobactam, gentamicin, ceftazidime, amikacin, meropenem, ciprofloxacin, levofloxacin, and, specific to *S. aureus*, vancomycin) (results shown in **Figure S1** and **Figure S2**).[8]

Changes in mortality rates across AMR pathogens

Although we had mortality rates from AMR pathogens for just one year (2019 for the GBD AMR study and individuals over 65 and 2018 for the work of Kumar et al. (2023) and neonates), we sought to estimate the rate of change in AMR for comparison to global progress in reducing mortality (**Figure 2A** and **2B**). We limited this analysis to neonates and children, and we required estimates of AMR mortality for these age groups for additional points in time. We supplemented the GBD AMR data (estimates also available for children under five and neonates) and the expanded work from Kumar et al. (2023) with the Delhi Neonatal Infection Study (DeNIS)[9] – which conducted surveillance on antimicrobial-resistant neonatal sepsis in 2012 – and the work of Ingle et al., (2016, 2018)[10, 11] – which conducted surveillance on *Escherichia coli* infection among children under the age of five in 2009. To estimate rates of antimicrobial resistance in children under five for all bacteria (i.e., not just *E. coli*), we multiplied the reported rates for *E. coli* by scale factors derived from comparing the resistance rates in *E. coli* to other pathogens from the data reported in Kumar et al., (2023). For both studies, we extracted the proportion of tested isolates that were multidrug resistant – defined akin to Sievert et al., (2013)[12] to mean resistance to the majority of common first-line treatments at the time of data gathering (**Figure 2B**). This gave us two point estimates in different years of the rates of multidrug resistance in infectious pathogens for both neonates and children under five. For neonates, we had data from DeNIS and Kumar et al. (2023); for children under five, we had data from Ingle et al., (2016, 2018) and the GBD AMR study. Note that the estimates of multidrug resistance present in Kumar et al. (2023) utilize source data only from the BARNARDS group.

Methods

Counterfactual scenario for child deaths with no antimicrobial resistance

We required two parameters to construct a counterfactual scenario for child deaths with no antimicrobial resistance: the mortality rate of childhood deaths that are attributable to AMR in a given year (i.e., the same quantity that we plot for neonatal/under-five all-cause mortality but for antimicrobial-resistant deaths only), and the rate of change in that number (source data described above). The GBD AMR substudy directly estimates the number and rate of childhood deaths (for both neonates and children under five) that are attributable to AMR in 2019. Graphically, this informs the shift between the counterfactual and real scenarios. Concretely:

$$\textit{no AMR counterfactual} = \textit{all-cause mortality} - \textit{AMR mortality} \qquad (1)$$

Secondly, we required estimates of the rate of change in AMR-attributable deaths. Though determining the factors that drive a childhood death is challenging, we assume that such mortality varies with AMR proportions. This may be through an indirect relationship because, for instance, AMR proportions may reflect a hospital's sanitary measures, which is the causal driver of childhood deaths. Previous work has supported this assumption.[13-15] We calculated the rate of change of AMR in infectious pathogens afflicting each age group from the two sets of surveillance estimates of multidrug resistance with data gathered in different years described above. We fit log-linear models to estimate the yearly percent change in the multidrug resistance fraction from these data. Assuming this was the rate of change in AMR-attributable deaths, we produced an exponential rate of change curve for the number of AMR-attributable neonatal and under-five deaths. Concretely:

$$\textit{AMR mortality(year)} = \textit{AMR mortality(2019)} \,/\, (\textit{yearly rate of change}^{\textit{year - 2019}})$$

In line with Eqn. 1, this quantity is subtracted from the yearly neonatal all-cause and under-five all-cause curves to obtain the counterfactual scenario (**Figure 2A**).

Estimating the burden of antimicrobial resistant neonatal sepsis on neonatal all-cause mortality

We followed the methods described in Kumar et al., (2023) and with the same underlying source data to jointly estimate the percentage of neonatal deaths associated with *Klebsiella pneumoniae, Acinetobacter baumannii, Escherichia coli, Staphylococcus aureus,* and other pathogens. Although Kumar et al. (2023) provide estimates of these quantities in their extended data, they estimated each quantity independently. This poses an issue for our analysis because adding these independent estimates and their error bars results in overestimated uncertainty intervals. Concretely, the error bars calculated by Kumar et al. (2023) have a contribution associated with both pathogen-specific uncertainty (i.e., what is the proportion of sepsis associated with a specific pathogen?) and overall neonatal-sepsis uncertainty (how many deaths are from neonatal sepsis?). As we sum across all percentages to estimate the total burden of neonatal sepsis, the uncertainty from the second term (overall neonatal-sepsis uncertainty) is added repeatedly, even though it should only be included once because each pathogen represents a portion of the fixed total neonatal-sepsis mortality. We address this issue by applying a Gaussian correlated errors correction[16] when propagating the uncertainty by scaling the summed error bars by $1/\sqrt{n}$ where n is the number of pathogens over which we are summing.

We calculated antimicrobial-resistant neonatal sepsis from this estimate of the percentage of neonatal deaths that are attributable to sepsis by location by multiplying by a location- and pathogen-specific fraction that reflects the proportion of isolates that were resistant to at least one of the five drugs most commonly used to treat neonatal sepsis (ampicillin, gentamicin, ceftazidime, amikacin, meropenem).[8] For locations where we did not have underlying antimicrobial-resistance data, we multiplied by the proportion of

resistance for that pathogen across the other locations, following evidence that AMR proportions among neonates are relatively homogenous across world regions (**Figure S1**).

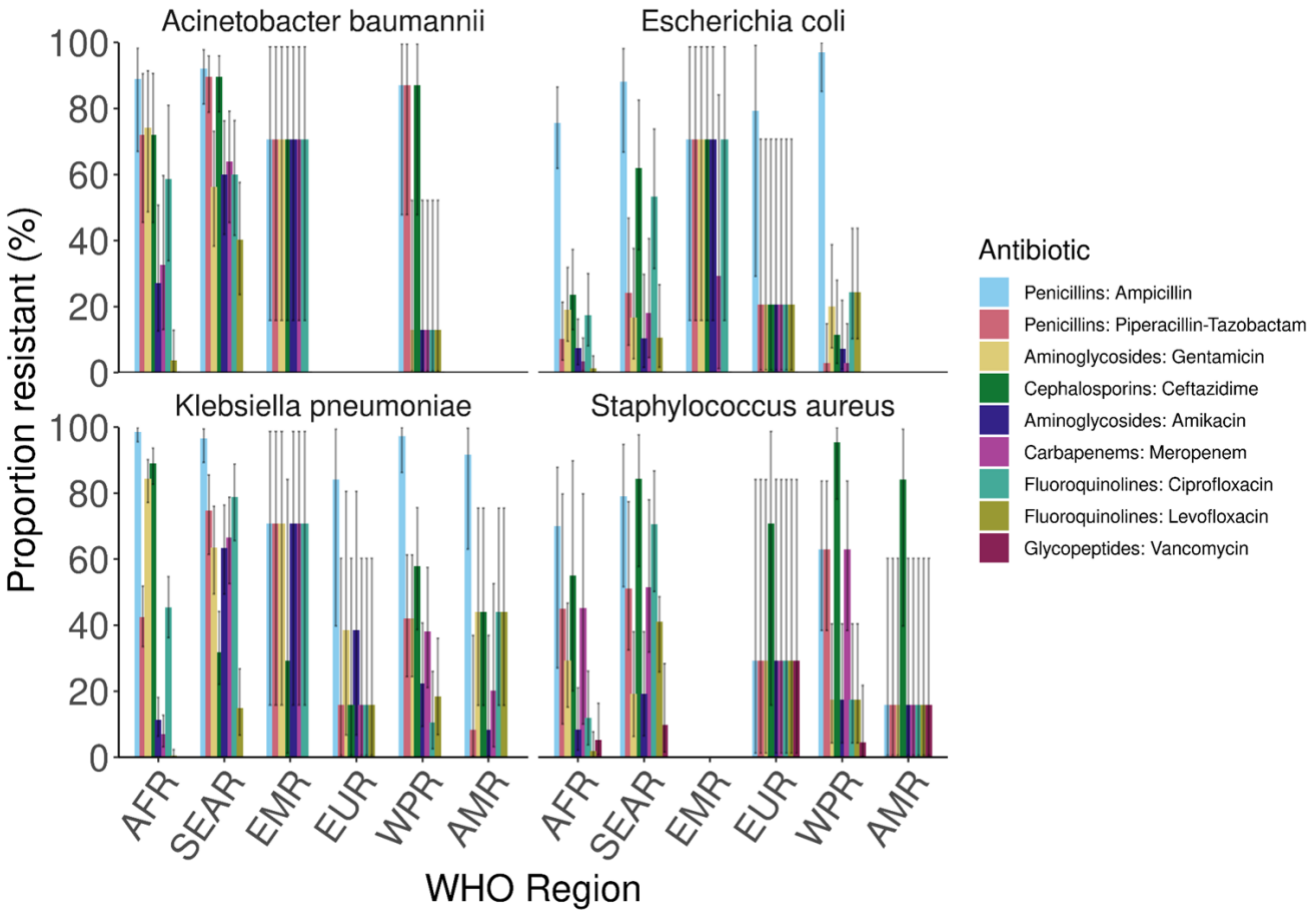

Figure S1. Neonatal sepsis cases show high drug resistance against the most common antibiotic treatments. Proportion of bacterial isolates resistant to antibiotics prescribed to treat clinical hospital-acquired neonatal sepsis by World Health Organization region (AFR = Africa; SEAR = South-East Asia; EMR = Eastern Mediterranean; EUR = Europe; WPR = Western Pacific; AMR = Americas). Data as of 2020. A Bayesian beta distribution is used to aggregate data from multiple sources and estimate the credible intervals, as described in Kumar et al. (2023). The source data are from the BARNARDS group (Sands et al., 2021) and NeoObs study (Russell et al., 2023).

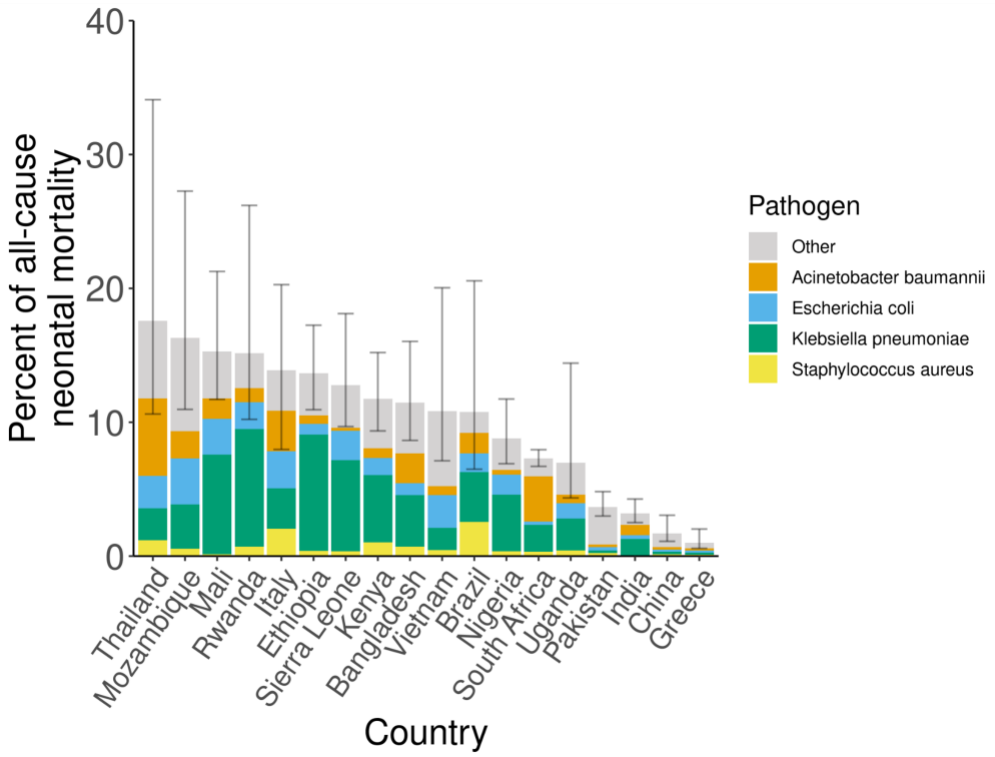

Figure S2: Drug-resistant pathogens drive neonatal deaths. The total height of each bar represents the percent of all-cause neonatal mortality attributable to drug-resistant pathogens (i.e., pathogens resistant to at least one of the five most common antibiotics prescribed to treat clinical neonatal sepsis of ampicillin, gentamicin, ceftazidime, amikacin, and meropenem). The colored portion of each bar represents the percent associated with a specific drug-resistant pathogen. Data as of 2020. A Bayesian beta distribution is used to aggregate data from multiple sources and estimate the credible intervals, as described in Kumar et al. (2023). Uncertainty bars represent 95th percentile credible intervals on the percent of all-cause neonatal mortality attributable to drug-resistant pathogens. Source data are from the BARNARDS group (Sands et al., 2021), NeoObs study (Russell et al., 2023), and CHAMPS study (Taylor et al. 2020). Estimates reflect the situation in 2018.

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