SUPPLEMENTARY INFORMATION

Ensuring Progress on Sustainable Access to Effective Antibiotics at UNGA 2024: A Target-Based Approach

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Text S1: Methods – Development of antibiotic use targets.
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In order to estimate burden-appropriate targets for a global reduction in total antibiotic use, we estimated country-specific appropriate antibiotic use in defined daily doses (DDD) / 1000 inhabitants / day (DID) under several different scenarios using 2018 baseline data. Antibiotic use estimates in DID (with associated uncertainty intervals) were extracted from the Global Burden of AMR (GRAM study) for 2018.[1] Using infection mortality and infection incidence (per 100,000 people) extracted from Global Burden of Disease 2019 for the year 2018 for all available infections where guidelines indicate Anatomical Therapeutic Code J01 antibiotics are indicated:[2] syphilis, chlamydia, gonococcal infection, trichomoniasis, LRTI, URTI, otitis media, typhoid and paratyphoid, diarrhoeal disease, cellulitis. We defined two benchmark countries for high income countries (HIC) and low-and-middle-income countries (LMIC) separately based on infection mortality <40/100,000 and DID between 9.7 DID (lowest HIC) and 18 DID (global median DID in 2018): Sweden for HIC (DID = 10.8) and Morocco for LMIC (DID = 14.9). We used the point estimates from GRAM for the purposes of these estimates **(Table S1).** The ratio of DID / infection incidence (both using the point estimates) for Morocco and Sweden were calculated as the benchmark to estimation of burden-adjusted DID.

Table S1. Benchmark countries for low-and-middle-income countries (Morocco) and high-income countries (Sweden). Selected based on infection mortality and DID. Ratio of DID and infection incidence point estimates used to estimate burden-adjusted expected antibiotic use.

	DID (UI)	Infection mortality (UI)	Infection incidence (UI)	Ratio of DID and infection incidence (point estimates)
Morocco	14.9 (14.3 – 15.3)	23.1 (16.7 – 31.6)	276348.4 (24197.2 – 315918.8)	0.00005
Sweden	10.8 (10.8 – 10.8)	35.9 (29.9 – 40.3)	267832.7 (241523.4 – 298318.0)	0.00004

Using point estimates and 95% confidence intervals for country-specific DID in 2018 estimated from the GRAM project, we took 10,000 draws from the DID distribution for each country from the normal distribution assuming country-specific point estimate as mean and standard error (calculated from 95% CI) as the standard deviation.

Using the same process, we also took 10,000 draws from the distributions of infection incidence per 100,000 people for each country using the point estimate and 95% CI from Global Burden of Disease study. Point estimates and 95% CIs for each infection in 2018 were summed to get the total infection incidence from which the draws were taken.

We illustrate estimated actual antibiotic use from the GRAM study, a hypothetical blanket 20% reduction (not a suggested actual target) and three scenarios accounting for varying infection burden.

Scenario 1
We estimated what global antibiotic use would look like if all countries above the income-specific benchmark reduced by 20% or to the benchmark (if the benchmark was <20% reduction) and if all countries below the benchmark increased antibiotic use to the benchmark. This would mean for HIC, that all countries higher than 10.8 DID decreased antibiotic use by 20% (never further than 10.8 DID). For LMIC, this would mean that all countries higher than 14.9 DID decreased antibiotic use by 20% (never further than 14.9 DID) and that all countries using less than 14.9 DID would increase to 14.9.

Scenario 2
Using the benchmark DID/infection incidence ratio, we estimated the expected antibiotic use for any country's disease burden if all of those patients were to be treated in the benchmark countries. This has been done previously and allows for estimation of expected antibiotic use if patients from high (or too low) countries were treated in a country with relatively low DID and low infection mortality (indicating the antibiotic use levels may be "safe").[3,4]

This ratio was applied to each draw (10,000 draws per country) in the distribution matrix of infection incidence for each country, using the ratio for Sweden for all HIC and the ratio for Morocco for all LMIC. After estimating burden-adjusted DID using this benchmark ratio, any draw estimated to be below the actual DID in the benchmark country (10.8 in Sweden or 14.9 in Morocco) were replaced with the DID value of the respective benchmark country. Expected DID for each country was summarized as the mean and 95% CI (from 2.5 and 97.5 quantile) of the 10,000 draws. Absolute (DID) and percentage changes were calculated from 2018 observed estimates (GRAM) for 190 countries.

Scenario 3
Reducing the burden of disease where antibiotics are prescribed (appropriately and inappropriately) would also decrease antibiotic use and generally improve public health as illustrated in paper 2 of this *Lancet* series.[5] Using the burden-expected antibiotic use estimates for each country, we estimated the potential for further reductions when accounting for the potential reductions to

antibiotic use in children <5 years through water, sanitation and hygiene improvements and increased vaccination coverage (paper 2 of this *Lancet* series).[5] We estimated these further reductions in antibiotic use by reducing disease burden for LMIC. For HIC, we assumed that WASH and vaccination coverage were high, thus no further reductions in antibiotic use would be seen in these countries on top of reduction in scenario 2.

Expected AWaRe Antibiotic use methods

In order to compare observed Watch antibiotic use to infection-burden expected Watch antibiotic use, we extracted estimates of AWaRe antibiotic use from the GRAM project for 71 countries.[1] These percentages of AWaRe were applied to total DID estimates and their 95% CI interval from GRAM for the available countries to get observed AWaRe use in DID. Using these point estimates and 95% CI we took 10,000 draws from the distribution of observed Watch antibiotics assuming a normal distribution where the mean was the point estimate and the standard deviation was the standard error.

The AWaRe Antibiotic Book provides recommendations for antibiotic prescribing for common clinical infections in primary care and hospital setting include recommended dose and duration.[6] We selected common infections outlined in the AWaRe Book for which Watch antibiotics are recommended where infection incidence (per 100,000) estimates were available in the Global Burden of Disease 2019 repository. We used country-specific estimates of incidence for 2018 for lower respiratory tract infections (community-acquired and hospital-acquired pneumonia in the AWaRe book), typhoid and paratyphoid from GBD. We estimated the case count for dysentery (bloody diarrhoea) using the aetiology-specific case counts for diarrhoeal disease from Global Burden of Disease;[2] we defined dysentery as cases of *Shigella* spp., non-typhoidal *Salmonella* spp., Enterotoxigenic *Escherichia coli*, and *Campylobacter* spp. per the common bacterial causes listed in the AWaRe Book Infectious-aetiology. Sepsis incidence rate was extracted from Global Burden of Disease 2017 paper;[7] we assumed incidence in 2018 was the same as 2017, and used absolute case count from this paper. All other estimates of incidence were converted to absolute case counts using World Bank population estimates from 2018.[8]

For each infection, we extracted the recommended Watch antibiotics, their dosage and duration and used WHO ATC recommended DDD for each antibiotic[9] to calculate the total DDDs needed for a treatment course. We then used a conservative estimate of the highest number of DDDs for each infection for severe cases to calculate the estimated DDDs needed to treat the burden of infections in each country. This means for example for lower respiratory tract infections, we used the DID for hospital-acquired pneumonia (HAP) rather than mild community acquired pneumonia which illustrates the conservativeness of our estimates. DDDs used are summarised in **Table S2**.

Table S2. Antibiotic treatment courses from the AWaRe Book for the select infections of interest used to estimate expected infection-burden DDDs. These are conservative estimates using the highest number of DDDs for a treatment course for the severe infections.

Infection	Antibiotic	Treatment course from AwaRe book	WHO DDD for oral administration	Total DDDs for a treatment course
Dysentery	Azithromycin	500mg on day 1 + 250mg once daily for 3 days	0.3g	4.2 DDDs
Clinical sepsis of unknown origin	Cefotaxime	2g every 8 hours for 7 days	4g	10.5 DDDs
Lower respiratory tract infections (Hospital acquired pneumonia)	HAP Cefotaxime	2g every 8 hours for 7 days	4g	10.5 DDDs
Typhoid	Low risk Fluoroquinolone resistance (severe cases) Ciprofloxacin	500mg twice daily for 10 days (severe)	1g for oral	10 DDDs
	High risk fluoroquinolone resistance (severe cases) Ceftriaxone	2g every 24 hours for 10 days	2g	10 DDDs

We used the infection case count point estimate and 95% CI for each infection of interest to take 10,000 draws from the distribution for each country-infection total cases using the normal distribution with point estimate as mean and standard error as standard deviation. These draws were multiplied by the DDDs per case for each infection to get the distribution of expected DDDs for each infection. These DDDs were summed across all infections to get total infection-expected DDDs. These infection-expected DDD draws for each country were converted to DID using the 2018 World Bank population estimate.

To account for additional necessary Watch antibiotic use that is not covered in these infections of interest (other infections, second- and third-line treatment recommendations, etc), we compared the difference between observed Watch use (in DID) in HIC with the expected infection burden Watch DID. We used HIC as they have relatively low infection mortality overall (illustrated in **Figure S1**) therefore current antibiotic use levels are assumed to be generally safe. Using the distribution of

observed Watch DID as observed, we subtracted the expected Watch DID from observed to get the distribution of additional Watch DID. To account for some countries using a large excess of Watch antibiotics, we took the 25th percentile of this distribution across all HIC as the extra allotment of Watch antibiotics for each country. The 25th percentile of extra Watch antibiotics was 3.5 DID which was similar to that of Australia. Therefore, we used Australia total Watch DID (4.5 DID) as the benchmark level of total Watch antibiotics. Any country with observed Watch DID below 4.5 DID, were expected to remain at current Watch antibiotic levels and not increase given current patterns of Watch use may be appropriate for burden, resistance and other factors. For countries above this benchmark, we estimated expected Watch DID using the burden-expected DID + 3.5 extra DID of additional Watch to account for other needs.

Considerations/limitations

We rely on imperfect estimates of current antibiotic use and infection burden from modelled estimates from limited data sources particularly for LMIC settings. Much the underlying data for the modelled infection burden estimates is from hospital infections. Given the majority of antibiotic use are oral antibiotics used in the primary care setting[10–12] for which the AWaRe Antibiotic Book provides clear guidance on when not to prescribe antibiotics, better data of the frequency, aetiology and severity of infections in primary care would improve model estimates of burden-adjusted antibiotic use. Even if the estimates of infection burden would be perfect, we may still overestimate appropriate increases in antibiotic use in LMIC if a substantial proportion of antibiotics used in these countries might come from informal providers not captured in data informing the estimates of current antibiotic use across the globe. It is possible that the countries these estimates show as below benchmark may not actually be if informal antibiotic use volumes are not captured in the GRAM estimates.[13]

We recognise that many of our scenarios may not be feasible, either for LMIC countries to dramatically increase antibiotic use to burden-adjusted levels or for some HICs to decrease antibiotic use more than 20% in the next 6 years. Improvements in following local treatment guidelines (like the AWaRe book) particularly in primary care, may contribute to further decreases in observed antibiotic use. Our estimates of reductions in antibiotic use in scenario 3 based on reductions in burden from WASH & vaccines are potentially an underestimate as these ignore any benefits of these interventions on infection burden and related antibiotic use in those aged 5 years or older or improvements that could be made in uptake of these interventions in high-income countries.
We model estimates of antibiotic use focusing on reducing potential overuse and expansion of access to antibiotics at the national level. While there is inequity between countries in different income groups and regions, there are also inequities in antibiotic use at a sub-national level. In India for example, a patient in New Delhi or Mumbai is far more likely to receive antibiotics than a patient in rural Bihar or Madhya Pradesh. Care should be taken when implementing national targets to ensure access is maintained for those who require antibiotics within a country and don't further exacerbate inequalities.
Our analysis of Access / Watch use also has some limitations. Firstly, it was applied only to generally HIC and upper-middle-income countries, which may have lower burden of these infections than lower middle income and low-income countries. We didn't account for resistance prevalence in these countries; however, we took a very conservative estimate of estimated Watch DDDs and added additional levels of Watch use. Most infections and total antibiotic use are in the primary care setting in a country for which the AWaRe Book outlines majority for these infections can be treated with Access antibiotics. Watch antibiotics are important second line antibiotics and for hospital infections, however prevalence of infection is generally lower in that setting.

There are major limitations with surveillance of antibiotic use as noted in paper 1 of this *Lancet* series, with over reliance on a limited number of data sets with significant limitations. For setting broad policy goals, we consider that formulation can be used as a proxy for location of use, with oral antibiotics in primary care and IV formulation in hospital care providing reasonable estimates to enable future goals of total and relative AWaRe use to be focussed in different settings. Based on clearly explicit parameters, targets of appropriate national levels of AWaRe antibiotic use could be developed at a country level through a UN-administered process, with local responsibility for agreeing this allocation and subsequent method of implementation of future targets. This longer-term goal would require considerable improvement in data quality and the ability to attribute country specific levels of AWaRe use and relate that to high-quality data on (sub)national estimates of infectious disease burden, going beyond information about resistance rates alone.

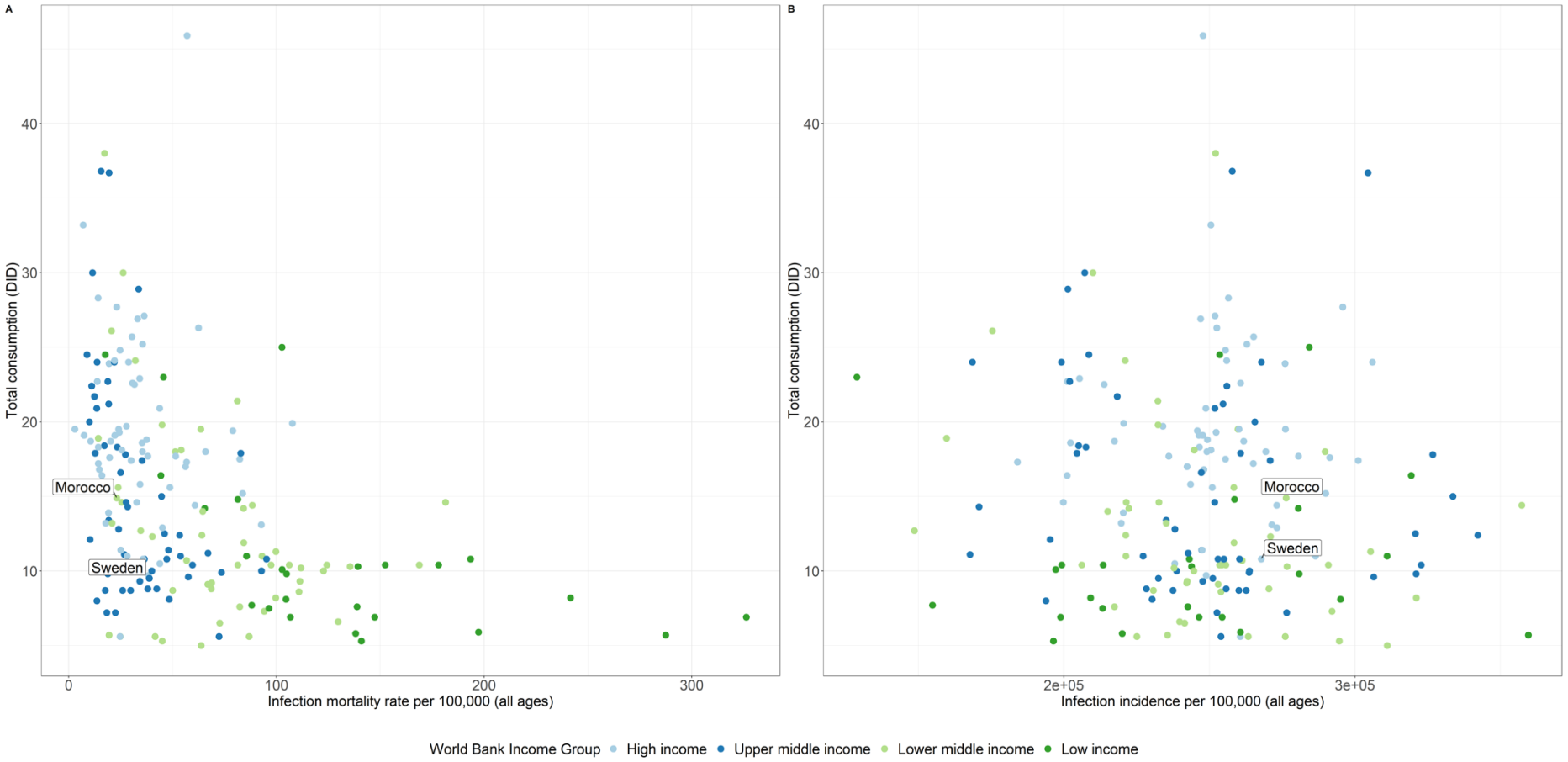

Figure S1. Infection mortality (A) and infection incidence (B) per 100,000 people for available infections in Global Burden of Disease (syphilis, chlamydia, gonococcal infection, trichomoniasis, LRTI, URTI, otitis media, typhoid and paratyphoid, diarrhoeal disease, cellulitis) and total daily defined doses/1000 inhabitants per day (DID). Countries used for benchmarking (Sweden for high income countries and Morocco for low- and middle-income countries) are shown.

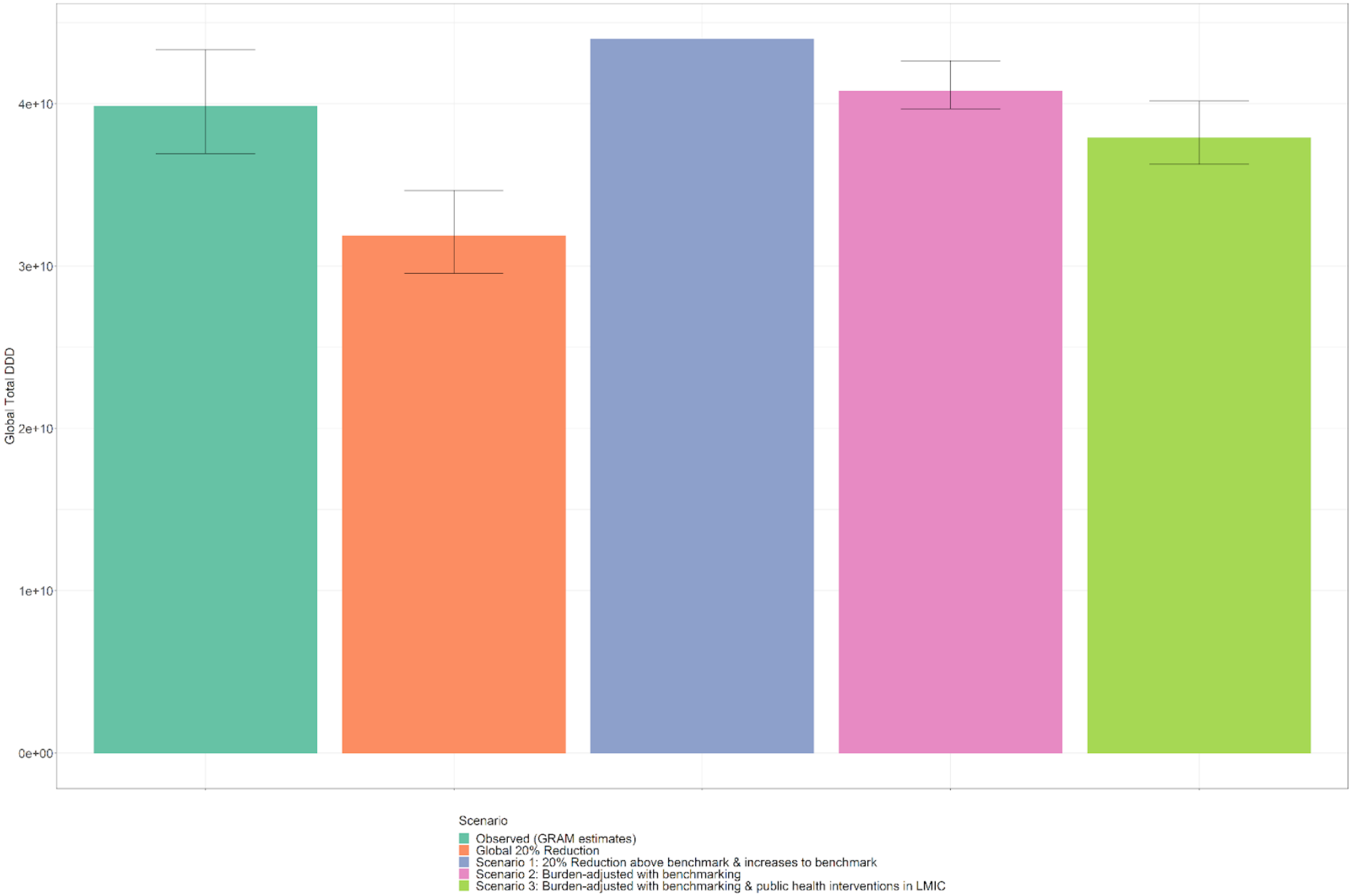

Figure S2. Global Total defined daily doses under different scenarios.

Table S3. Summary of estimated defined daily doses and defined daily doses/1000 inhabitants/day globally under different scenarios.

Scenario	**Defined daily doses (DDD)**	**Defined daily doses / 1000 inhabitant / day**	**% Change in DDD (sign indicates direction of change)**
Observed (GRAM estimates)[1]	39,853,032,452 (95% CI: 36922642700 - 43318150970)	14.3 (95% CI: 12.3 - 15. 6)	
Global 20% reduction	31,882,425,962 (95:% CI: 29538114160 - 34654520776)	11.5 (95% CI: 10.6 - 12.5)	-20% (-20% to -20%)
Scenario 1: 20% Reduction above benchmark & increases to benchmark	43,987,127,611 (point estimate only)	15.8 (point estimate only)	10.4% (point estimate only)
Scenario 2: Infection burden-adjusted with benchmarking	40,793,898,938 (95% CI: 39680464801 - 42640466764)	14.7 (95% CI: 14.3 - 15.3)	+2.3% (- 1.6% to +7.4%)
Scenario 3: Infection burden-adjusted with benchmarking and public health interventions in LMIC	37,934,685,886 (95%CI: 36288417463 - 40181431403)	13.7 (95% CI: 13.1 - 14.5)	-4.8% (-7.2% to - 2%)

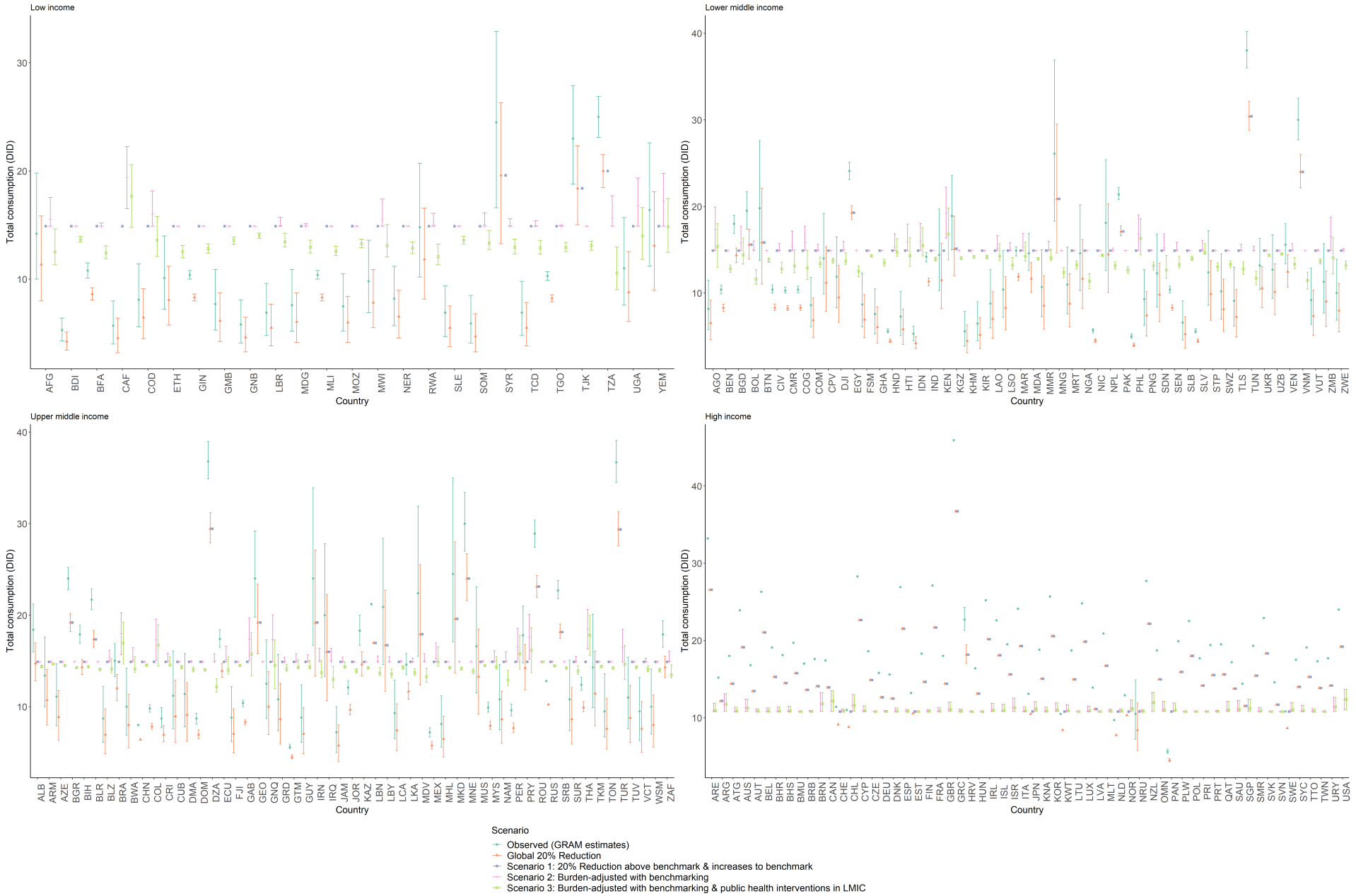

Figure S3. Total estimated antibiotic use in DID under different scenarios for countries by income group **A.** Low-income countries, **B.** Lower middle income countries (UMIC), **C.** Upper middle income countries (LMIC), **D.** High income countries

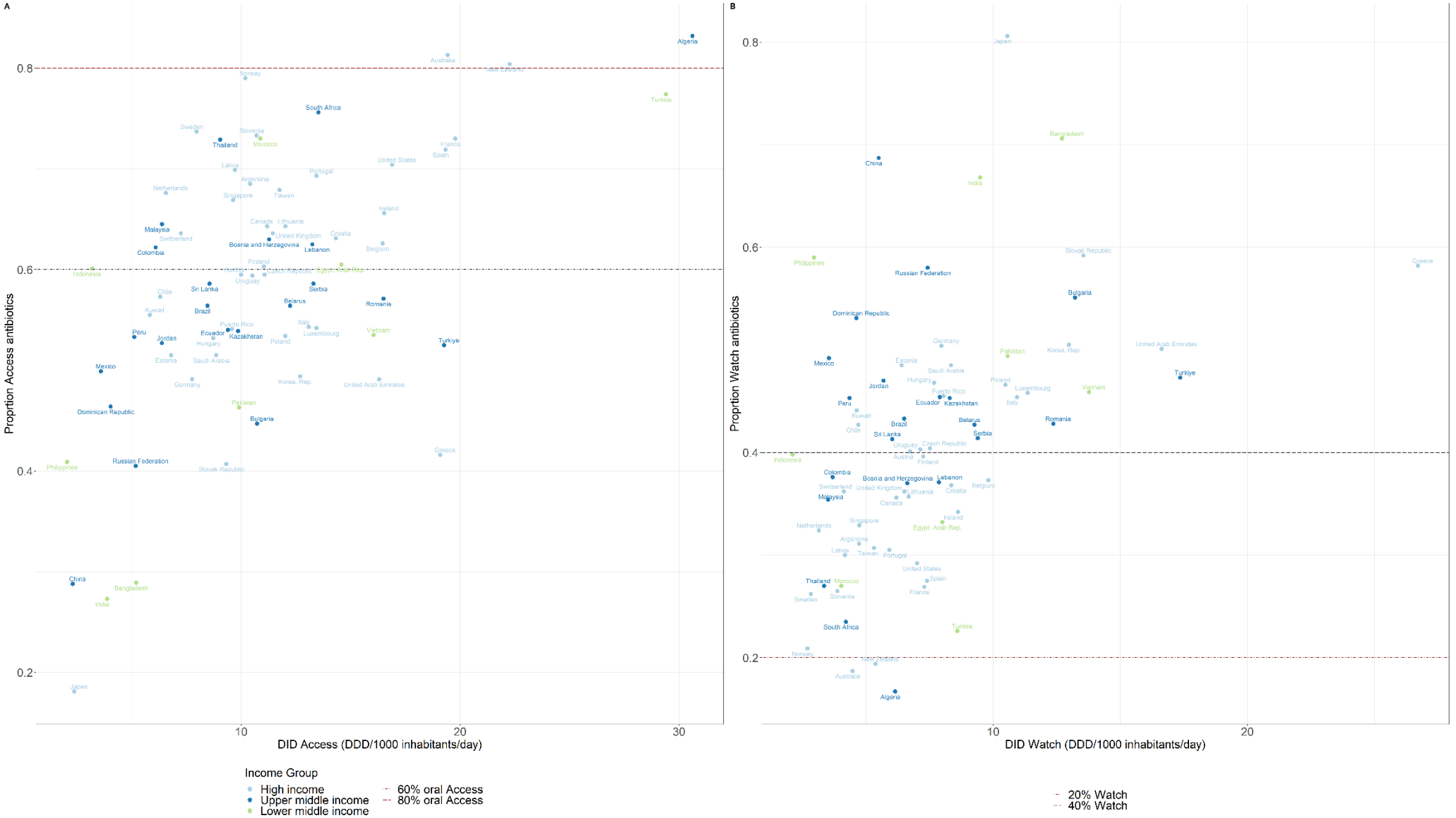

Figure S4. Plots illustrating total defined daily doses (DDD) / 1000 inhabitants / day (DID) of **A.** Access antibiotics and **B.** Watch antibiotics compared to relative percentage of total DID. Dashed lines on **A** (Access) indicates currently 60% target and a higher 80% target and on **B** (Watch) indicates the inverse - 40% maximum and lower 20% maximum Watch target.

Supplemental References

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