www.sciencemag.org/content/357/6358/1350/suppl/DC1



# Supplementary Material for

## **Reducing antimicrobial use in food animals**

Thomas P. Van Boeckel, Emma E. Glennon, Dora Chen, Marius Gilbert, Timothy P. Robinson, Bryan T Grenfell, Simon A. Levin, Sebastian Bonhoeffer, Ramanan Laxminarayan

Email: ramanan@cddep.org

Published 29 September 2017, *Science* **357**, 1350 (2017) DOI: 10.1126/science.aao1495

#### **This PDF file includes:**

Materials and Methods Figs. S1 to S9 Tables S1 to S3 References

## **Materials and Methods**

### Data used in this paper can be found at

### [https://www.dropbox.com/sh/9k4oojy1fu8hsbw/AABoobcb\\_8GPM48BHpjsCQgLa?dl=0](https://www.dropbox.com/sh/9k4oojy1fu8hsbw/AABoobcb_8GPM48BHpjsCQgLa?dl=0)

#### Protocol S1. Antimicrobials sales data

We conducted systematic online search for sales data on veterinary antimicrobials from government sources and scientific publications. The procedure for the online search is identical to Van Boeckel et al 2015 (*1*), but novel data sources were incorporated in this study (Table S1). Reports of antimicrobials sales volumes (Tons) were obtained for 38 countries (Fig S1). The countries where antimicrobial sales could be obtained represent 47% of the estimated global biomass of livestock standing and slaughtered each year (FAOSTAT 2013). In this study, only medically important antimicrobials were considered; ionophores and coccidiostats were excluded from the analysis. Reports of sales were obtained using the year 2013 as reference, or the most recent year for which data broken down by species or classes of compounds were available. In 17 countries, sales were broken down by at least two groups of animals. If two countries have the same relative proportion for different types of livestock, their respective consumption can nonetheless differ because of local disease prevalence, climate, market, legislations and implantation of drug manufacturers. In order to account for these differences we adapted the methodology from Van Boeckel et al. 2015, to estimate the consumption of antimicrobials by classes of compounds (see Statistical Procedure) and by species.

All bird species were pooled in a single poultry category (chicken and ducks) as well as small ruminants (sheep and goats). For New Zealand reports of sales of antimicrobial were pooled together for horse and sheep. We made the assumption that antimicrobial use in horse could be neglected compared with sheep, particularly given the large size of this sector in New Zealand and have assumed that sheep represent the total consumption reported. In Belgium, antibiotic sales per species were obtained for 2009 and adjusted for 2013 using the overall volume of antimicrobial. We checked for systematic correlation (drug used in combination treatment) or inverse correlation (substitution of drugs) for all the non-tetracycline drugs (Pearson coefficients <0.6). In France antimicrobial consumption in cattle and small ruminants was reported in a single pooled category. We distributed the total using a ratio of 1/3.575, which corresponds the mean ratio in countries that had reported animal specific data for both sheep and cattle.



**Fig S1.** Reported sales of veterinary antimicrobials. Consumption levels in milligrams per population correction unit for 10 classes of compounds (Table S1).

#### Protocol S2. Livestock Census

This study includes four categories of animals: chicken, cattle, pigs and small ruminants (sheep and goats, hereafter referred as 'sheep'), which together account for the overwhelming majority of terrestrial animals raised for food (*2*). Sheep are important sources of animal-protein in Africa and Asia –two regions where meat consumption is growing rapidly. In each country (or self-governing dependency, hereafter referred to as 'Country'), we estimated the total biomass of animals using population correction units (PCU). PCU represent the number of kilograms of animal alive or slaughtered each year. This metric is used to standardize estimates of biomass between countries that have variations in average weight of the animals or number of production cycles per year. Livestock census disaggregated by production systems (extensive vs intensive) were obtained from Robinson et al (*3*) and projected for the year 2013.

The total PCUs in any country (or pixel) for livestock type  $k$  in the production system  $s$ were defined as follows:

$$
PCU_{k,s} = An_{k,s} \cdot \left(1 + n_{k,s}\right) \cdot \left(\frac{Y_k}{R_{CW,k}}\right)
$$

where  $An_{k,s}$  is the stock of the animal of type 'k' raised in the production systems 's' (extensive or intensive) that is alive in a country/pixel,  $n_{k,s}$  is the number of production cycles from animals 'k' in each production system 's' in the corresponding country, *Y* is the quantity of meat per animal obtained for each country, and  $R_{CW/LU}$  is the killing-out percentage (or dressing percentage)—that is, the ratio of the carcass weight that result from partial butchering and removing all the less desirable parts (organs, tail, feet) to live weight of an animal—obtained from literature estimates (*4*). The last term of this equation can be interpreted as the animal weight reconstructed from country-specific productivity figures. All parameters were obtained from FAOSTAT for the year 2013.

### Protocol S3. Extrapolation of Antimicrobial Consumption

We used a five step statistical procedure adapted from Van Boeckel et al (*1*), to extrapolate antimicrobial consumption from countries reporting sales (n=38) to all other countries. The methodology was adapted to include sheep, and 10 different classes of compounds (Protocol S1). The objective of this procedure is to calculate coefficients for the consumption for each class of antimicrobials  $(c=10)$  in each country (i=228) for each group of livestock species (k=4) and in each production system (s = extensive *or* intensive).

**Step 1: Consumption Intensity** We used a multivariate regression model including the 38 reporting countries to establish a statistical relationship between the overall antimicrobial consumption and the PCU of chicken and pigs raised in intensive systems. This relationship was subsequently used to predict overall intensity of antimicrobial use in intensive systems (mg/PCU) in all other countries (n=190).

**Step 2: Tetracyclines use vs Consumption Intensity.** We used a univariate regression model including all reporting countries to establish a relationship between the consumption intensity in intensive systems  $(mg/PCU_{int})$  and the percentage tetracycline  $\pi_{\text{TET}}$  as part of the total antimicrobial consumption (Fig. S2). This relationship was subsequently used to predict the proportion of tetracycline used in each country according to its consumption intensity (step 1). This reflected the fact that tetracyclines are proportionally overused in high-consuming countries. The respective proportions of nontetracycline compound were derived from the mean proportions of each of those compounds in all reporting countries (no significant relationship between intensity and overuse of other compounds was found). All proportions were adjusted to sum up to one, and replaced by original data for the reporting countries.



**Fig S2.** Share of tetracycline in a country vs antimicrobial consumption per kilogram of animal. Circles are proportional to the log10 of the PCU in each country.

**Step 3: Species-specific consumption.** We used countries where species-specific data could be obtained to compute species-specific relative proportions for different compounds  $(\pi_{k,c})$ . For countries where consumption by species was provided by class of compound (SCB), these values were used directly to compute coefficients of consumption for intensive system. For countries where species consumption levels were aggregated across compounds (SB), this overall volume was disaggregated in 10  $\alpha_{\rm c,i,k,s}$ coefficients, according to the mean proportions  $\pi_{c,k}$  computed in SCB countries. Finally, in every country the value of the species-specific consumption for tetracycline  $(\pi_{\text{TET,k}})$ , was adjusted to reflect the increased tetracycline consumption in high-consuming countries (Step 2) and the consumption for other compounds was modulated accordingly. Finally, in the countries were species-specific coefficient were available from the collected data the  $\alpha_{c,i,k,s}$  coefficients were scaled to match the reported values (Fig S8).

**Step 4: Extensive vs intensive production systems.** In agreement with Van Boeckel et al. 2015 (*1*), we assumed that intensive systems consume on average four times the amount extensive systems per kilogram of livestock produced. Finally, estimates of the global consumption by species, production systems, and countries were obtained by multiplying the coefficients of consumption by the number of PCU in each corresponding livestock system. Confidence intervals on the total consumption were calculated as 1.96 times the standard deviation associated with the coefficients of consumption per species (step 3). Negative predictions for the lower bound were ceiled to zero. Thus the global consumption of antimicrobial and its associated confidence interval (95% C.I.) was estimated as,

Global Consumption = 
$$
\sum_{j}^{228} \sum_{c}^{10} \sum_{k}^{4} \sum_{s}^{2} (\alpha_{c,j,k,s} \pm 1.96 \cdot sd(\alpha_{c,j,k,s})) \cdot PCU_{2013,c,j,k,s}
$$

where  $sd(\alpha_{c,j,k,s})$ , is the standard deviation on the estimated coefficient from step 3. In 2013, the global consumption of antimicrobials in food animals was 131,109 tons (95% C.I. [100,812 - 190,492]). Based on future trends for consumption of livestock products (see next section), the global consumption of antimicrobials in food animals is projected to reach 200,235 tons in 2030 (95% CI [150,848 - 297,034]). Fig S6 shows the breakdown of the global antimicrobial consumption by drug-class, species and production systems.

## Protocol S4. Projections for antimicrobial use in 2030

We projected the future consumption of antimicrobials under four scenario corresponding to different targets for antimicrobial use.

*Business as usual target (BAU***).** Current levels of antimicrobials consumption were projected in 2030. First, trends for total number of PCUs in 2030 were derived from future consumption levels of livestock products as predicted the Food and Agriculture Organization of the UN (*5*). The number of PCU in 2030 was projected in each country according to national growth rate. If national rates were not available the average continental growth rate was applied. Second, the proportions of animals that are raised in extensive and intensive production systems were projected based on Gilbert et al. (*6*) using forecasts of GDP per capita (PPP) from the *International Monetary Fund.* Forecast from 1980 to 2021 were extended to 2030 using linear regression models. Third we obtained the number of PCU in each production system (extensive vs intensive) in 2030, based on the future proportion of animals raised in each system.

**Target 1. Imposing global regulations on antimicrobial use.** Recent reports have shown that several high-income countries have highly productive livestock sectors while using less than 50 mg per PCU per year, and suggested this threshold as a 'broadly reasonable target' to limit antimicrobial consumption in the short term (*7*). First we estimate that by 2030 a cap on antimicrobial consumption at 50mg/PCU could be imposed in all countries currently exceeding this threshold (target 1A). Second, we consider the more realistic eventuality that these targets would only be enforced in the countries of the *Organisation for Economic Co-operation and Development* (OECD), as well as China (target 1B).

**Target 2. Reduction in meat consumption.** We estimated the total reduction in antimicrobial consumption that would be associated with a hypothetical decrease in meat consumption worldwide. First we consider that global meat consumption could be reduced to 40 g of meat/day (target 2A) as recently recommended in the revised Chinese nutritional guidelines (*8*). Second, we consider a more plausible target for reduction of meat consumption with the following conditions (target 2B):

- In countries with growing meat consumption per capita, the increase could be reduced twofold by 2030.
- In countries with decreasing meat consumption per capita, this decrease could be increased twofold by 2030.
- In all countries, total meat consumption should not exceed the median projected consumption in Europe in 2030.

We accounted for difference in productivity and population growth in each country; and calculated the ratio of PCU produced to the current levels of meat consumption. We scaled the number of PCU that would be produced under those consumption targets.

**Target 3. User fee on veterinary antimicrobials.** We followed a three-step procedure to evaluate the impact of imposing a user fee on antimicrobial use in animals. We estimated the shift in demand for veterinary antimicrobials, and the corresponding revenues associated with this policy. Five situations were considered to reflect a range of assumptions on fee rates and price elasticity of demand.

Step 1. Retail prices of veterinary antimicrobials.

Data on retail prices  $(P^*)$  of products containing antimicrobials used in food animals were collected in 22 countries (Table S3), for 1,418 unique country-products combinations. Online searches for veterinary supply stores retailers were conducted in English, Mandarin Chinese, and Spanish using the following terms: 'veterinary supplies', 'antimicrobial purchase online', 'livestock antibiotics' and 'food animal antibiotics'. In addition, we obtained expert opinion estimates of prices of antimicrobials through contacts (phone and e-mail) with national branches of *veterinarians without borders*, as well as veterinarians in academic institutions. All price estimates were obtained between June and December 2016. All prices were expressed in US\$ per kilogram of active ingredient.

In the 22 countries where information of retail prices of veterinary antimicrobial could be obtained, we calculated the median price for each class of antimicrobial in each county by aggregating the retail price of all products that contained a specific class of compound.

In the countries where information of retail prices of veterinary antimicrobial could not be obtained, the prices estimates were extrapolated from the 22 countries where data was available using the following procedure:

- i) First, we classified countries in income groups (high-income *vs* low- and middle-income) based on a GNI per capita of 12,475 US\$/year, as estimated by the World Bank for the fiscal year 2013.
- ii) For each income group, we calculated the median price of each class of antimicrobial within that group. Median prices in high-income countries were calculated from 302 country-products samples, and median prices in low- and middle-income countries were based on 1,107 country-products samples.
- iii) For the residual category 'other compounds', the price assigned was the median of the median price calculated for the 9 other classes of compounds.

We used this approach to extrapolate retail prices of antimicrobials worldwide in order to reflect potential variations in the relative prices of veterinary antimicrobials according to income. We used only two groups for the extrapolation of retail prices because of the limited number of countries were prices data could be obtained did not allow fine-scale regional extrapolations.

We performed an analysis of variance and multiple comparison test (Tukey) to study prices variations between classes and income groups (Fig. S3). This includes all classes that were represented by a least 10 price estimates (this excludes polymyxins and pleuromutilins). Prices of veterinary antimicrobial showed considerable variation within each class of compounds and income groups. For the categories of antimicrobials where at least 10 estimates could be collected, significant prices differences were observed between those classes in high-income (p-value  $= .01$ ) but not in low- and middle-income countries (p-value  $= .09$ ). In high-income countries cephalosporins were significantly more expensive than penicillin, tetracycline and sulfonamides.



**Fig. S3.** Retail prices of one kilogram of active ingredient for 10 classes of veterinary antimicrobial in low- and middle-income countries (left) and high-income countries (right).

#### Step 2. Elasticity of Demand of Veterinary Antimicrobials.

Price elasticity of demand (PED) is percentage change in quantity of veterinary antimicrobials demanded (Q) in response to a change in price (P); in this analysis, this is after imposing a user fee on current prices.

$$
PED = \frac{dQ/Q}{dP/P} \quad (\text{Eq. 1})
$$

Country-specific estimates of PED were calculated to estimate the global shift in demand for veterinary antimicrobials under a user fee imposed on current retail prices. Import data on the volume and sales value of tetracycline derivatives were obtained from the UN COMTRADE database (commodity code 294130). We used a log-log linear regression model (Eq 1) between yearly prices and imports volumes to estimate the PED (Fig S5).

$$
\log P = \alpha \cdot \log Q + \log C \quad (Eq. 2)
$$

Where C is a constant and  $\alpha$  is the regression coefficient to be estimated, such as:  $PED = \frac{1}{\infty}$ . In each country, if a statistically significant estimate could not be obtain for  $\alpha$ , than the median PED of the corresponding income group was considered for that country.

Overall, we obtained statistically significant estimates of PED for 67 countries that had 8 years (or more) of imports reported (Fig S4).



**Fig. S4.** Probability density of elasticity of demand (PED) by income groups.

We performed an analysis of variance (weighted by total antimicrobial consumption) – and excluding China- to identified a significant difference in elasticity (p-value  $< 0.05$ ) between high-income countries and low-income countries. In low- and middle-income countries, the average demand was more elastic (PED  $= -1.75$ ) than in high-income countries (PED =  $-1.43$ ) with the notable exception of China (PED =  $-0.68$ ).

#### Step 3. Shift in demand and associated revenues.

Taking the natural logarithm of Eq. 1 we obtain the relationship between price (P) and quantity  $(Q)$ . At equilibrium  $(*)$  this can be rewritten:

$$
P^* = Q^{*^{\alpha}} \cdot \exp(C) \quad \text{(Eq. 3)}
$$

Applying an ad-valorem user fee of *TR* percent on the current prices of antimicrobials correspond to shift of in the demand curve (Fig. 4) given by:

$$
P_t = Q_t^{\alpha} \cdot \exp(C) - TR \cdot P^* \text{ (Eq. 4)}
$$

Where  $P_t$  and  $Q_t$  are the new price and quantity of antimicrobial demanded following the imposition of the user fee on the original price P\*. In first approximation, we assumed a constant returns to scale in manufacturing, resulting in a horizontal supply curve such that,  $P^* = P_t$ . Combining Eq 2, 3 & 4, the quantity of antimicrobial demanded after imposing a user fee was given by:

$$
Q_t = Q^* \cdot (1 + TR)^{PED} \qquad \text{(Eq. 5)}
$$

The revenues associated with the user fee in each country was given by quantity demanded  $Q_t$  times the different between the price paid by the consumer  $P_c = (1 + TR) \cdot P^*$ -including the fee- and the original price  $P_t = P^*$ .



**Fig. S5.** Regression models for estimation of elasticity of demand (PED) in Ethiopia (A), and in the United States (C). Shift in demand curve and associated revenues from imposing a 50% user fee on veterinary antimicrobials in Ethiopia (B) and the United States (D).

In this study, the retail prices collected  $P^*$  were scaled such as the total sales of antimicrobial would correspond to the reported size of the global market for veterinary antimicrobials. This price-scaling procedure maintains relative differences in prices across countries and compounds. The global animal health market, has been evaluated at 30 billion \$US (HealthforAnimals.org, 2015). In 2007, the global market for antiinfective and medicated feed additives was estimate at 27% of the animal health market (*9*). However, in the absence of public information on the current share of antimicrobials in the animal health market, we hypothesize that antimicrobials could represent between 15% (4.5 billions) to 40% (12 billions) of the current market. This generates a lower and upper bound on the estimates of revenues associated with a user fee policy for this study. The reference scenario (3C) used for the user fee policy assumed a rate of 50% and PED estimates derived from imports. In addition we conducted a sensitivity analysis on the

rate of the user fee (scenario 3D and 3E) as well as on the estimates of PED derived from import data (scenario 3A and 3B).

## **Combined interventions (Targets 1, 2 & 3).**

The three intervention policies were also considered in combination. In the absence of information on potential synergetic (or antagonist effect) between the scenario we assumed that the effect interventions strategies to be additive if applied sequentially. The hypothetical reduction in meat consumption was applied first (Scenario 2B), followed by either imposing a user fee directly (Scenario 2B+3C), or imposing a cap on consumption at 50mg/PCU in OECD countries and China (Scenario 2B+1B). We also considered all three interventions together (Scenario 2B+1B+3C). In this case, meat consumption was decreased first, and the user fee was applied on the residual consumption of antimicrobials after imposing the regulation cap.



**Fig S1.** Reported sales of veterinary antimicrobials. Consumption levels in milligrams per population correction unit for 10 classes of compounds (Table S1).



**Fig. S2.** Share of tetracycline in a country vs antimicrobial consumption per kilogram of animal. Circles are proportional to the size of the livestock sector within each country.



Fig. S3. Retail prices of one kilogram of active ingredient for 10 classes of veterinary antimicrobial in low- and middle-income countries (left) and high-income countries (right).



**Fig. S4.** Probability density of elasticity of demand (PED) by income groups..



animal (C).



**Fig. S7.** Antimicrobial consumption in largest consumers in 2013 and 2030.



**Fig. S8.** Antimicrobial consumption per population correction unit (PCU) by class of antimicrobials.



**Fig. S9.** Antimicrobial consumption for food animal production by country, in 2013 (light red) and projected for 2030 (dark red).

### Table S1. Reported antimicrobial sales in (Kg)



Individual reports for each country are accessible at (https://www.dropbox.com/sh/fsht4fp0qsquf2u/AADCArtJJCk2ovrKPh\_wHEbga?dl=0)



#### **Table S2. Projected tons of antimicrobials by country 2013 (+%Growth by 2030)**









### Table S3 Retail prices of antimicrobials per kilogram of active ingredient in 2016 (SUS)





## **References**

- 1. T. P. Van Boeckel *et al.*, Global trends in antimicrobial use in food animals. *Proc. Natl. Acad. Sci.* **112**, 5649–5654 (2015).
- 2. M. Herrero *et al.*, Biomass use, production, feed efficiencies, and greenhouse gas emissions from global livestock systems. *Proc. Natl. Acad. Sci. U. S. A.* **110**, 20888– 20893 (2013).
- 3. T. P. Robinson *et al.*, Mapping the Global Distribution of Livestock. *PLoS ONE*. **9**, e96084 (2014).
- 4. P. D. Warriss, *Meat science: an introductory text* (Cabi, 2010; http://books.google.com/books?hl=en&lr=&id=ExEOboVw\_KUC&oi=fnd&pg=PP6 &dq=Warriss,+P.D.+2010+Meat+Science:+an+introductory+text&ots=p5qKmpcO3J &sig=mKv0xmKBW0rhimOXyD\_8pRO6k3s).
- 5. T. P. Robinson, F. Pozzi, Mapping supply and demand for animal-source foods to 2030. *Anim. Prod. Health Work. Pap.*, 164 (2011).
- 6. M. Gilbert *et al.*, Income Disparities and the Global Distribution of Intensively Farmed Chicken and Pigs. *PLOS ONE*. **10**, e0133381 (2015).
- 7. J. O'Neill, Tackling drug-resistant infections globally: Final report and Recommandations (2016), (available at http://amrreview.org/sites/default/files/160525\_Final%20paper\_with%20cover.pdf).
- 8. Y. Yang, X. Yang, F. Zhai, Y. Cheng, Dietary Guidelines for Chinese (2016). *J. Acad. Nutr. Diet.* **116**, A37 (2016).
- 9. S. W. Page, P. Gautier, Use of antimicrobial agents in livestock. *Rev. Sci. Tech.-OIE*. **31**, 145 (2012).