# Code Manual for the AHHME Tool for Antibiotic Resistance

This version of the AHHME App was to pilot the skeleton code for (a) a basic microeconomic evaluation model that incorporates impacts of antibiotic usage scenarios and (b) the app, to test functionality and feasibility of such a model.

This manual provides details on the assumptions made to get roughly acceptable parameter values in order to parameterise a pilot of the model in the absence of a specific case study. This model will then be tested in specific case studies to give more robust estimates.

## Code functions

### app.R

* All code functionality for the web application is available in the “app.R”
* For the model without the ShinyApp user interface is available in “
* The structure is a compartmental model based on annual transition probabilities.
* Currently just works for a base-case deterministic analysis, using many pre-specified values from the input file in the “data/” folder
* The next iteration should incorporate probabilistic analyses as well as deterministic analyses, and will build on the deterministic analysis model code to increase robustness within an applied specific case study.
* Antibiotic usage scenarios are modelled through their impact on cost (currently labelled “cost of implementation”) and their impact on resistance – future iterations may want to also incorporate other changes (e.g. to profit or to susceptible infection incidence).

## Data Inputs

* The input.csv hosts all of the parameters used within the model before alterations of the user inputs through the AHHME app.
* The “scenario” column indicates which scenario the parameters belong to.
  + Those ending with “\_0” are used throughout the different scenarios. For example, “human\_0” relates to parameters used for humans irrespective of the scenario chosen; such as background mortality rates.

## Current Test Example - UK

* The current example roughly parameterised (i.e. these figures are not robust and do not represent usable results as they currently stand) is:
  + Resistance to at least one antibiotic in *Escherichia coli* bloodstream infections (BSI) in England for adult humans
  + Resistance to at least one antibiotic in *Escherichia coli* in England in cattle, sheep and pigs. [Ended up being mostly reflective of cattle herds I think].
  + The base year is 2018, with costs and rewards in 2018 Great British Pounds and Quality Adjusted Life Year values, at the national level.
  + General intervention that reduces resistance.
* See “notes” tab for discussion of how values were chosen and/or estimated, but extra information given below where more discussion was needed.
* Background mortality and birth are the routes of humans entering and leaving the model (have not incorporated migration impacts, these could be included through an annual immigration and emigration rate). We have taken birth rate as entry into the model, but should be really tied to proportion of new 18 year olds entering through demographic data.
* To work out annual probability of transitioning to susceptible and resistant BSI states:
  + 76.0 cases per 100,000 population in 2018 from ESPAUR 2019 report; <https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/843129/English_Surveillance_Programme_for_Antimicrobial_Utilisation_and_Resistance_2019.pdf>
  + From the same report & my thesis: <https://spiral.imperial.ac.uk/bitstream/10044/1/70879/1/Naylor-N-2019-PhD-Thesis.pdf>

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| Antibiotic | Resistance in 2011/12 (my thesis) | Resistance in 2018  (ESPAUR 2019) | Difference (%) |
| ciprofloxacin | 13% | 19.4% | 49.23076923 |
| third generation cephalosporin | 6% | 14.1% | 135 |
| gentamicin | 7% | 10.2% | 45.71428571 |
| Carbapenem | 0.1% | 0.1% | 0 |
| Piperacillin/  tazobactam | 6% | 8.9% | 48.33333333 |
| Average increase |  |  | 55.65567766 |

* + From my thesis levels of “resistant to atleast 1 antibiotic” = 19% in 2011/12
  + Applying same difference = 29.6%
  + Apply to 76.0 cases per 100,000: Resistant cases are p=0.000022496 annually occurring in our population, and susceptible cases are p=0.000053504
  + Noticed subsequently that the downloadable AMR Fingertips data do have 2018 quarterly data for “Rolling quarterly average proportion of E. coli blood specimens resistant to any 1 of the key antimicrobials; by quarter” including lower and upper 95% confidence interval estimates and event count/denominator data.
* For cost of different healthcare states:
  + Excess length of stay for susceptible and resistant cases were 3.71(95% CI: 3.52 – 3.89) days and 4.63 (4.12 – 4.95) respectively. These were multiplied with the 201/2018 reference cost of a bed day (£346) [2018/19 costings changed due to overall costing guidance changes]-<https://improvement.nhs.uk/documents/1972/1_-_Reference_costs_201718.pdf>
* We have taken the QALY loss from the HRQOL COVID-19 QALY Tool, with a rough age distribution similar to that used in my thesis (eyeballed and kept same for now, could sample using specified distributions and input). The total is already discounted at 3.5% for base year – but need to think about then using that same average over multiple years in terms of discounting. <https://github.com/LSHTM-CHIL/COVID19_QALY_App> Didn’t include QALY loss for within hospital state for now.
  + I have just used this for the QALY loss for all deaths, but in reality should apply different age distributions for background mortality and for infection-related mortality over time, need to do in next iteration of the model.
* For animal on-farm background mortality: “The average monthly mortality rate of 0.27% in the province of Bolzano was very close to the national average of 0.28%, while the average monthly mortality rate in the province of Trento was more than double (0.58%).” In Italy cattle was all that was available from a quick Google search: <https://core.ac.uk/download/pdf/38620929.pdf> . Using the formula to get the annual probability of transition : 1-EXP(-0.0028\*12).
* For animal likelihood of getting resistant and susceptible infections the following was done:
  + From One Health report – 23% level of susceptible infections in 2016/17. That’s a 20% reduction from 2015/16, applying the same reduction gives 18.4% levels of susceptibility, so 81.6% resistant to at least one. From [doi:10.1017/S0950268817002151]; mean herd-level prevalence of *E. coli* in cattle 0.236 (95% CI; 0.116 – 0.325) [for now just going to say this is incidence per herd per year but this is not robust and needs converting appropriately for future use, taking into account illness duration etc.] – multiplied these together. Though this was for cattle, another reference stated that E. coli was present in around 10 – 33% of pigs, which falls within the realms of the above 95% Confidence interval -<https://www.ed.ac.uk/files/atoms/files/cs4_pigs.pdf>
* For “general cost per animal kept” Using £100 guestimate - see<https://www.agriland.ie/farming-news/actually-cost-keep-suckler-cow-year/> means likely higher value but as is currently structured we wanted a starting point of a cost per production cycle < income per production cycle to ensure at least some baseline profitability (which we see in the reports cited in this manual). – for now selected a general cost per animal kept but in next iteration would want to look at cost of purchase vs keeping and include cost of purchase in new transitions into the state (transition costs vs state costs).
* Income; average farm income £50,400 [DEFRA, 2019, Farm Business Income by type of farm in England, 2018/19] divided by average number of livestock [DEFRA, 2019, Numbers of commercial holdings and land areas / livestock numbers by size group: England (a)] ;

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| Average herd size across animals 2018 |
| 97 |
| 27 |
| 135 |
| 196 |
| 392 |
| 71 |
| 564 |
| 494 |
| (mean = 247) |

* + Mean: 50400/247 = £204, Standard Error: 50400/182 = £. Applied this to “well” group and to “sold” group currently, would want to likely differentiate between the 2 in the next iteration. Additionally, this may be double counting for cost if net profit not revenue.
* Birth rate; averaged these values across livestock; (n( <1 year old) / n(total)) where available and took the highest value (as pigs thought to be even higher, >1 due to high slaughter rate) [from <https://www.gov.uk/government/statistical-data-sets/structure-of-the-livestock-industry-in-england-at-december>]; 0.49
* To get a proportion of herd size that are sold for meat (and therefore leave well) – took the proportion of fattening pigs and proportion of beef cattle out of all (very weak proxy but otherwise herds would become large quickly). Range was 0.37 – 0.89, but wanted to keep below birth rate so 0.37 used.
* For cost of treating resistant infections versus susceptible infections, and the outcomes of these (recovery to well, or death) – as couldn’t find much after a quick Google search applied a uniform distribution impact of [0% - 50%, base case value 25%] worse outcomes in resistant infection within animals, comparative to susceptible ones. Although the figures used for susceptible costs could also include resistant cases (and therefore this is double counting).
* Cost for susceptible cases, used the following data points (based on just sheep & cattle, and included non-bacterial infections/illness and also includes things like herd replacement for sick animals so double counting but to give proxy of animal healthcare treatment costs) - <http://beefandlamb.ahdb.org.uk/wp-content/uploads/2013/04/Economic-Impact-of-Health-Welfare-Final-Rpt-170413.pdf> -

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| --- | --- |
|  | 6 |
|  | 4.4 |
|  | 12.3 |
|  | 122 |
|  | 90 |
|  | 58 |
|  | 45 |
|  | 82 |
|  | 58 |
|  | 90 |
| mean | 56.77 |
| sd | 40.19304 |

* For cost per fallen stock used the one provided for ewes in Economic Impact of Health and Welfare Issues in Beef Cattle and Sheep in England - available: <https://projectblue.blob.core.windows.net/media/Default/Research%20Papers/Beef%20&%20Lamb/Economic-Impact-of-Health-Welfare-Final-Rpt-170413.pdf>
* For “change in resistance in humans from reduction in antibiotic usage in animals” we used the Tang et al review [<https://pubmed.ncbi.nlm.nih.gov/29387833/>];
  + Proportion of farmers in population 1.17% -<https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/848641/AUK_2018_09jul19a.pdf>
  + Weighted average of difference in infection across farmers and non-farmers;
  + 0.017\*(-0.29) + (1-0.017)\*(-0.09)
  + Did some rough back calculations to get an estimate of the standard error (not robustly).
* The impact of a reduction in usage in terms of resistance in humans and animals is taken from Tang et al [<https://pubmed.ncbi.nlm.nih.gov/29387833/>] but there is no then interaction across the resistance levels (it is not dynamic). Additionally, the figures taken are absolute risk difference; however we cannot minus these directly from our current probability (as then p<0) so have just taken as relative to 1 for now (which is not correct). Have taken this to be reduction in drug resistant infections (not accounted for susceptible strain replacements, where infection levels stay the same but the proportion of resistance changes – you can adapt for this fairly easily).
* To get number of farms, took; number of small holdings;

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| <https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/848641/AUK_2018_09jul19a.pdf> | number of holdings for 2017 |

* and removed proportion in line with: “Percentage share of the value of total livestock output in 2019” (which again is not correct as this is output proportions – not input - but to get a smaller % than total for all farms as we didn’t include chickens etc. and hasn’t accounted for crop farms); 217000\*0.29 + 217000\*0.14 + 217000\*0.11 + 217000\*0.07
* Need to adjust for multiple agricultural production cycles : 1 production cycle in human healthcare system