Supplementary for: Who takes antibiotics when they're ill? Antibiotic usage in Flusurvey

Contents

Data cleaning

32,746 unique episodes were recorded in the 2012-2017 UK Flusurvey data. To clean this data, several variables where ambiguous answers were recorded were removed:

- Visit: only those episodes where the participant had responded to the medical visit question were kept for analysis (no visit, appointment made or specified visit type). This removes 571 episodes.
- Health score: only those episodes with a finite health score, between 0 and 100, were kept. This removes 15 episodes. Those episodes with infinite or missing health scores had their health score set to be "NA".
- Vaccine status: any episode where the participant had responded with a "don't know" to whether they had been vaccinated that year was removed. This removed 45 episodes.
- ILI and fever: if an NA was entered for this status then the episode was removed. This removes 94 episodes.
- Age: if an NA was entered for age then this episode was removed. This removes 237 episodes.

This left a total of 31,784 episodes to be analysed (97% of all possible episodes). These episodes came from 6,667 unique participants. Participants reported receiving antibiotics in 1,441 (4.5%) episodes.

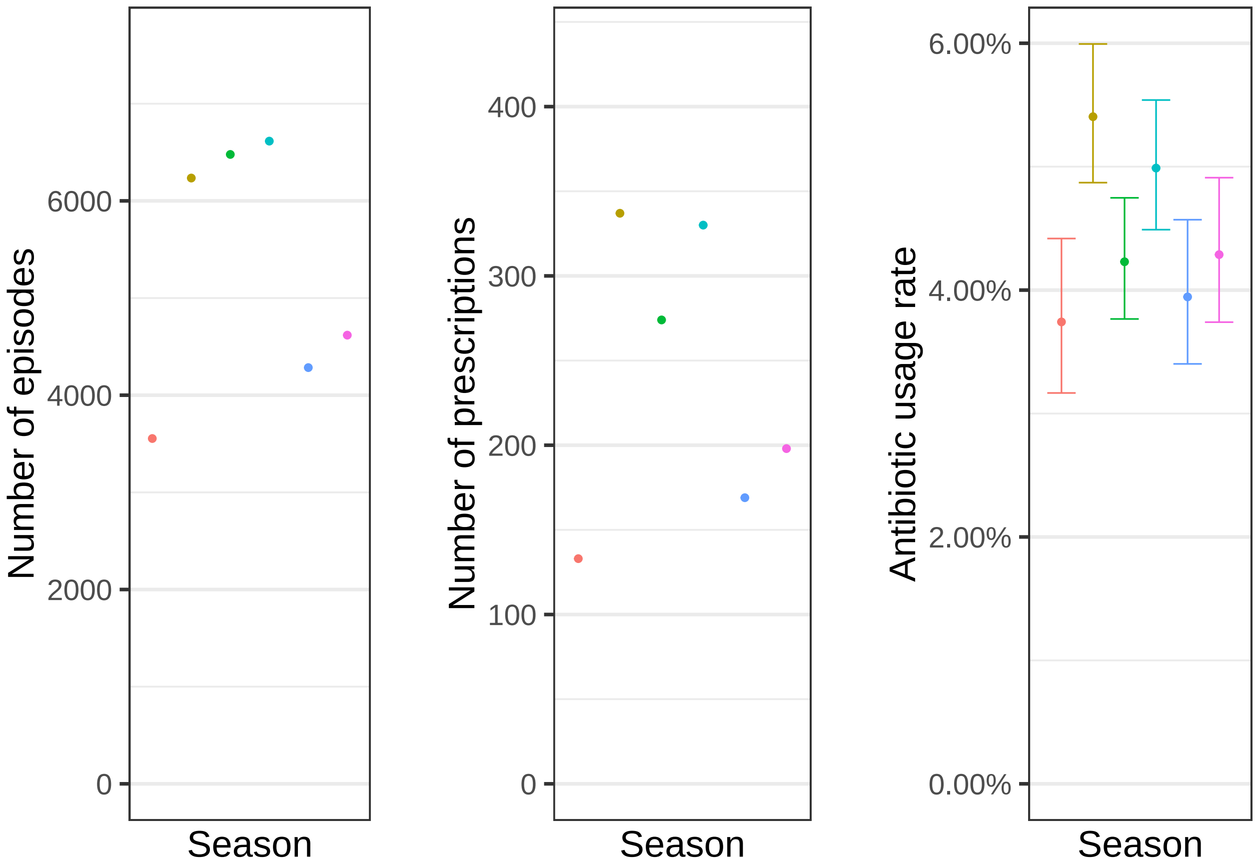

Figure 1: Comparing baseline data across seasons

Univariate analysis

Compare seasons

Over 3,554 episodes were recorded for each season, ranging from a total of 3,554 - 6,615 episodes per season (Figure 1). The number of antibiotic prescriptions per season ranged from 133 - 337, suggesting that analysis of prescriptions per individual season may be inappropriate (Figure 1). The mean overall prescription rate was similar for each season at 3.7 - 5.4% (Figure 1). This equates to participants receiving antibiotics in 4.5% of the episodes of illness.

Season was not included in the multivariate analysis as there was too little data and little difference by season.

By age and season

Antibiotic prescription rates are higher for children (age <18yrs) and the elderly (>65 yrs) (see Main paper Figure). This is consistent with previous data. The same pattern can be seen across the seasons.

Age was included in the multivariate analysis.

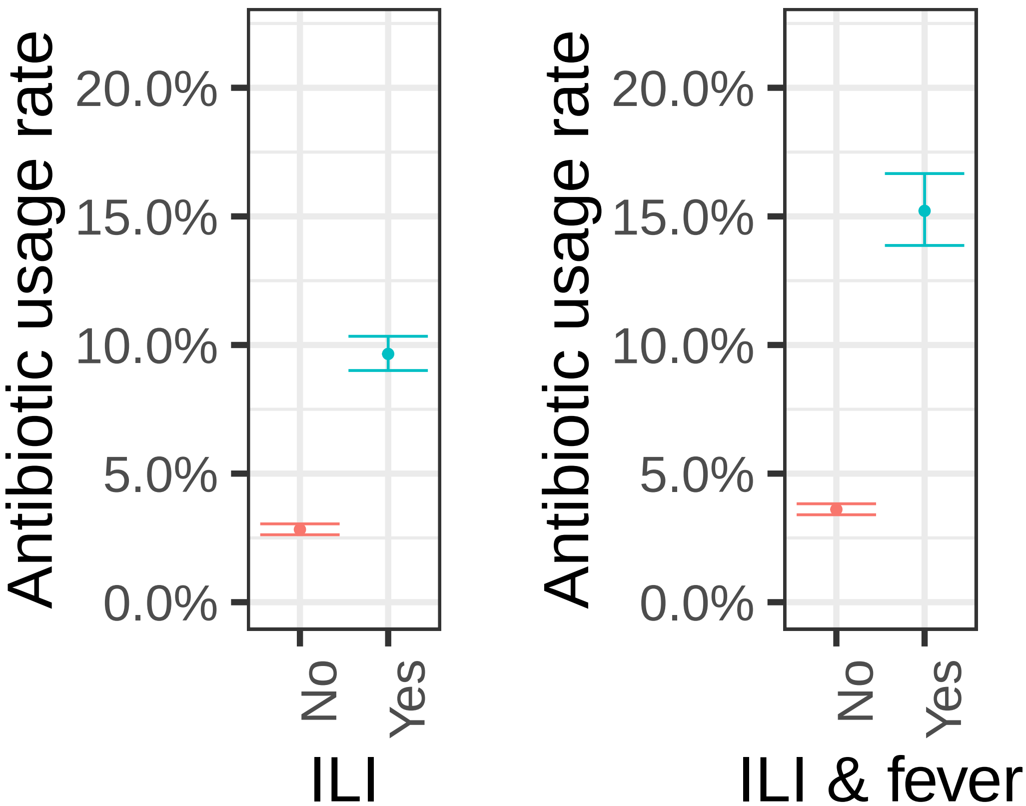

Figure 2: Comparing antibiotic prescription rate by ILI status (ECDC standards)

Influenza like illness

Episodes could be split into those where participants reported symptoms that, under the ECDC standards (Disease Prevention and (ECDC) 2015), could be defined as an Influenza like illness (ILI) or not. Moreover, there was the option to report if a participant suffered fever during an episode. Considering antibiotic prescriptions by ILI (Figure 2), shows that episodes where participants experienced ILI were much more likely to receive antibiotics than those without ILI: 2.8% vs. 9.7% (Figure 2). This difference is significant (under a Pearson's chi-squared test statistic at the 0.05 significance level). The addition of fever to the symptoms increased the percentage of episodes that involved an antibiotic prescription and the difference in rates between them: 3.6% vs. 15.2% (Figure 2). This difference is significant (under a Pearson's chi-squared test statistic at the 0.05 significance level).

ILI plus fever was included in the multivariate analysis as it provided a better differentiation of prescribing rates and is known to track the 'flu season well [SEB personal communication - any ref?].

Region

Analysis of prescription rate by region shows little variation from the approximately 4% mean rate per episode (Figure 3). The Channel Islands and the Isle of Man had very few reports leading to large confidence intervals in rates (N = 24 or 11 respectively).

Region was not included in the multivariate analysis as there was not much difference in usage between regions and too little data.

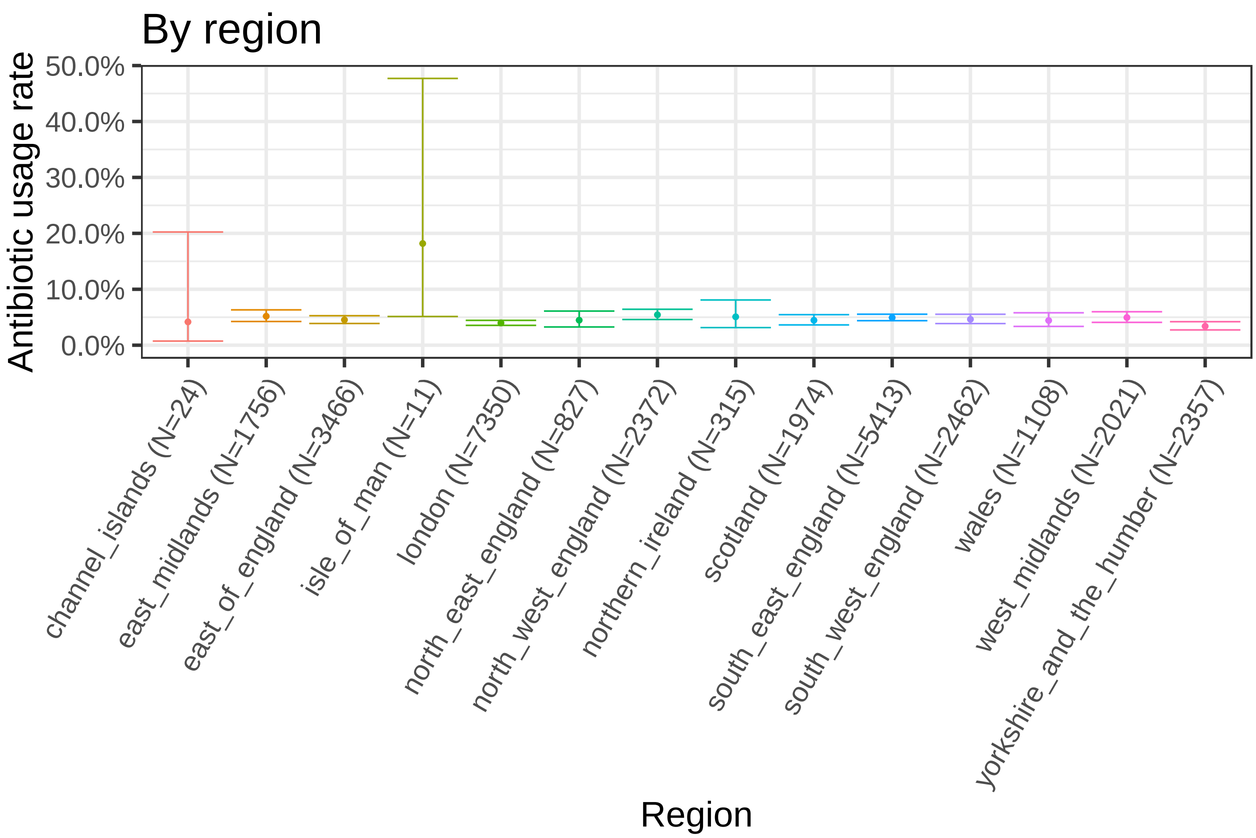

Figure 3: Data by region.

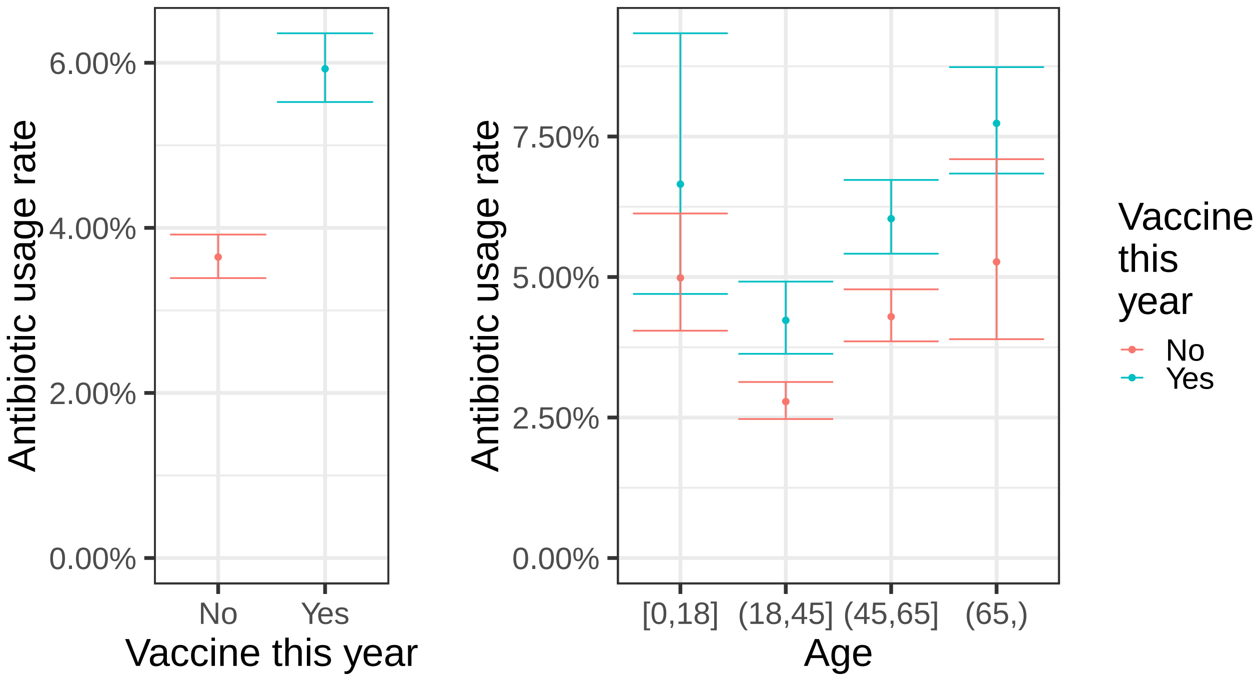

Figure 4: Data by influenza vaccination status

Influenza vaccine status

Participants were asked to state whether they had received the influenza vaccine that year. Grouping by vaccine status, revealed that those who had been vaccinated in the current season were more likely to receive antibiotics per episode (5.9% vs. 3.6%) (Figure 4). This difference was significant (under a Pearson's chi-squared test statistic at the 0.05 significance level). This difference may be due to increased access to care for those who are vaccinated.

If we consider prescription rate by vaccine status and age (Figure 4), it can be seen that those in the risk factor age for vaccination (children and elderly), do not have a difference in prescription rate by vaccine status. However, adults (18-65yo) are more likely to receive antibiotics if they have had the influenza vaccine suggesting that there is a link to care behaviour.

Influenza vaccine status alongside **age** needs to be included in the multivariate analysis.

Visit or contact with a medical service during an episode

Participants were asked if they had visited any medical services due to their symptoms. [SEB?] All visits in a single episode were grouped together. If we consider antibiotic prescription rate by any medical service visit (Figure 5), we can see that rates are much higher if a visit to a medical service was recorded (0.5% vs. 32.9%). The difference between reporting or not reporting a health visit was significant (under a Pearson's chi-squared test statistic at the 0.05 significance level). This is as would be expected as antibiotics should only be available by prescription in the UK.

Participants were also asked if they had had contact with a medical services due to their symptoms. [SEB?] All contacts in a single episode were grouped together. Visits to, or contact with, a medical service were made in 2917 and 2297 episodes respectively. 1281 episodes reported both contact and a visit. 44.2% of episodes which reported a contact only had contact and did not report visiting a medical service.

If we consider antibiotic prescription rate by any contact with a medical service (Figure **??**), we can see that rates are much higher if any contact to a medical service was recorded (27.9% vs. 2.7%). This difference was significant (under a Pearson's chi-squared test statistic at the 0.05 significance level). Visiting a medical service was a bigger driver than contact.

In those who reported no contact or visit with a medical service, antibiotic reporting rates were 0.5% of episodes.

As "contact" is ambiguous as to whether a prescription could have been received, we conservatively assumed that any contact or visit with a medical service could have resulted in a valid opportunity for a prescription. Hence the main analysis used visit or contact as a grouped variable.

Looking at the type of medical service visited or contacted shows some variation in usage rates. However, this further breakdown meant that few episodes were linked to each type of medical visit or contact behaviour. Considering only those that had >100 episodes ("*" indication, Figure 5), suggests that higher prescription rates were found for those who visited or contacted a GP or the Hospital than visiting "Other" medical services.

Visit to or contact with a medical service was grouped to indicate whether anyone had contacted or visited any medical service in an episode and this was included in the multivariate analysis. However, the individual services visited or contacted, due to the small numbers, was not included.

Higher education and main activity

Analysing prescription rates by highest education status or main daily activity (Figure 6), shows that these may have a significant impact. Those with lower levels of education ("gcse") vs. the highest ("msc"), had large differences in rates (7.8% vs. 3.7%) (Figure 6). 96% of episodes had information on education status.

Age may account for some of the trends by main activity as well as underlying health (Figure 6), with those on long term leave and retired having high levels of antibiotic prescriptions. There was less of a trend visible here.

Highest education was not included as 4% of episodes have no information on this. All episodes have data on **Main activity**; however this is likely to be confounded by age and other health issues and so was not included in the multivariate analysis.

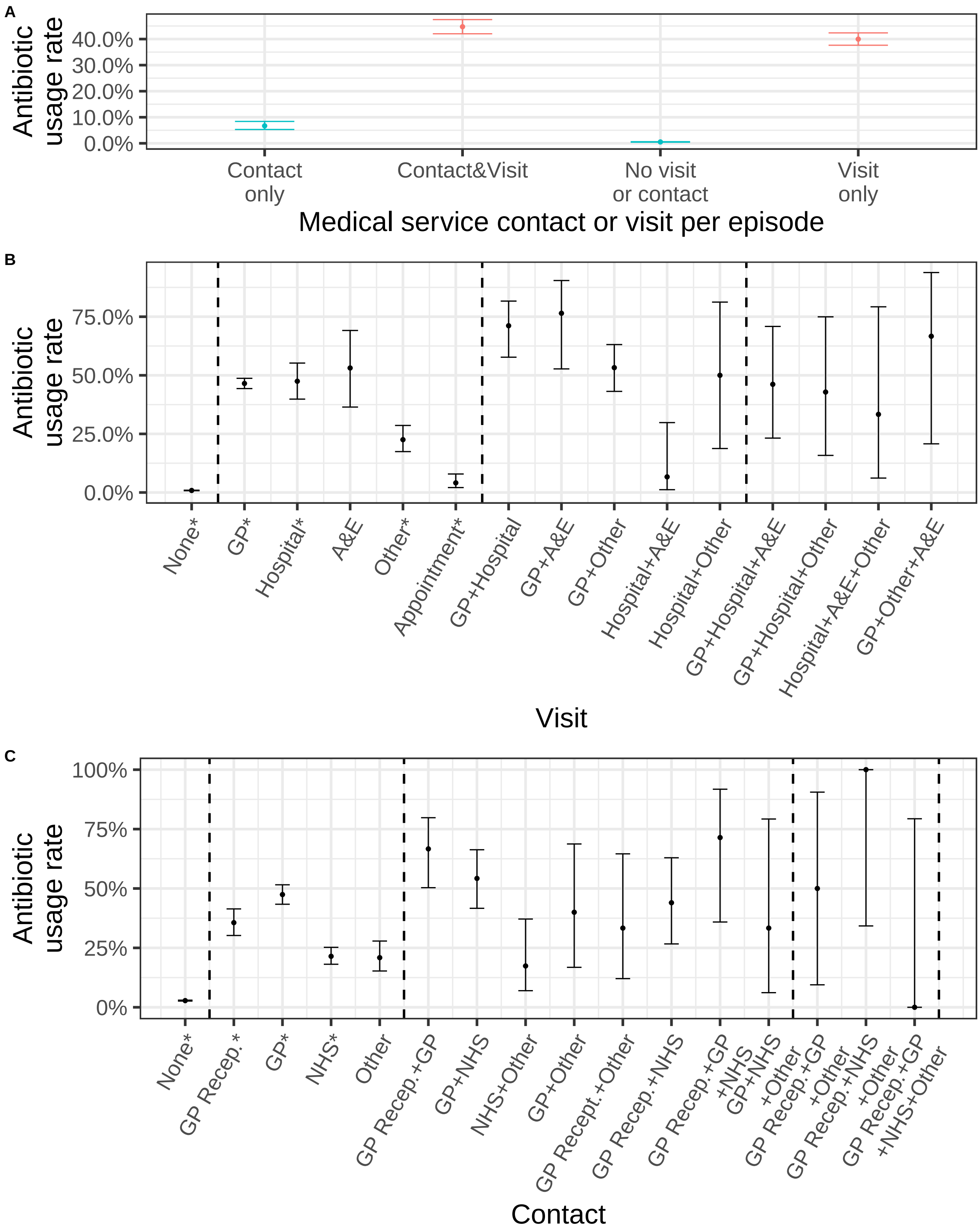

Figure 5: Data by visit to or contact with a medical service. For the lower two figures, those on the left of the first dashed line did not visit or contact a medical service during the episode (None). Those in the next section only reported visiting or contacting one medical service, whilst those sections to the right indicate rates in those who visited multiple services in an episode. A * indicates that more than 100 episodes had this visit behaviour recorded.

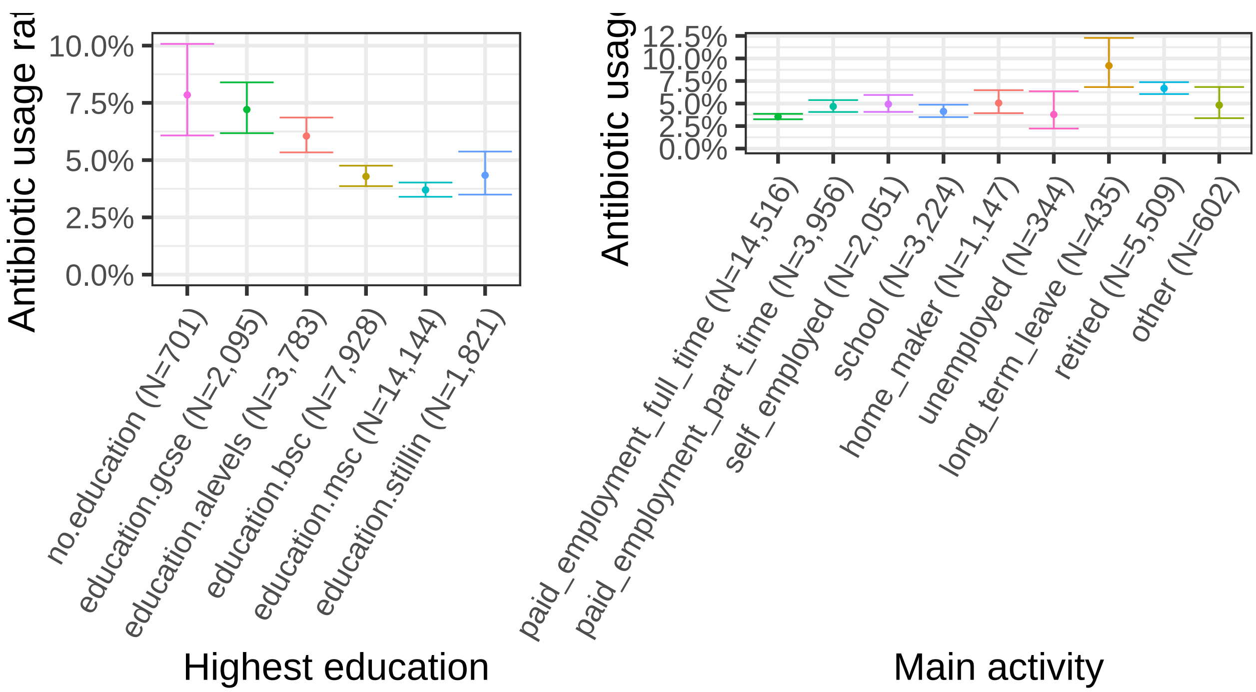

Figure 6: Data by education level and main activity

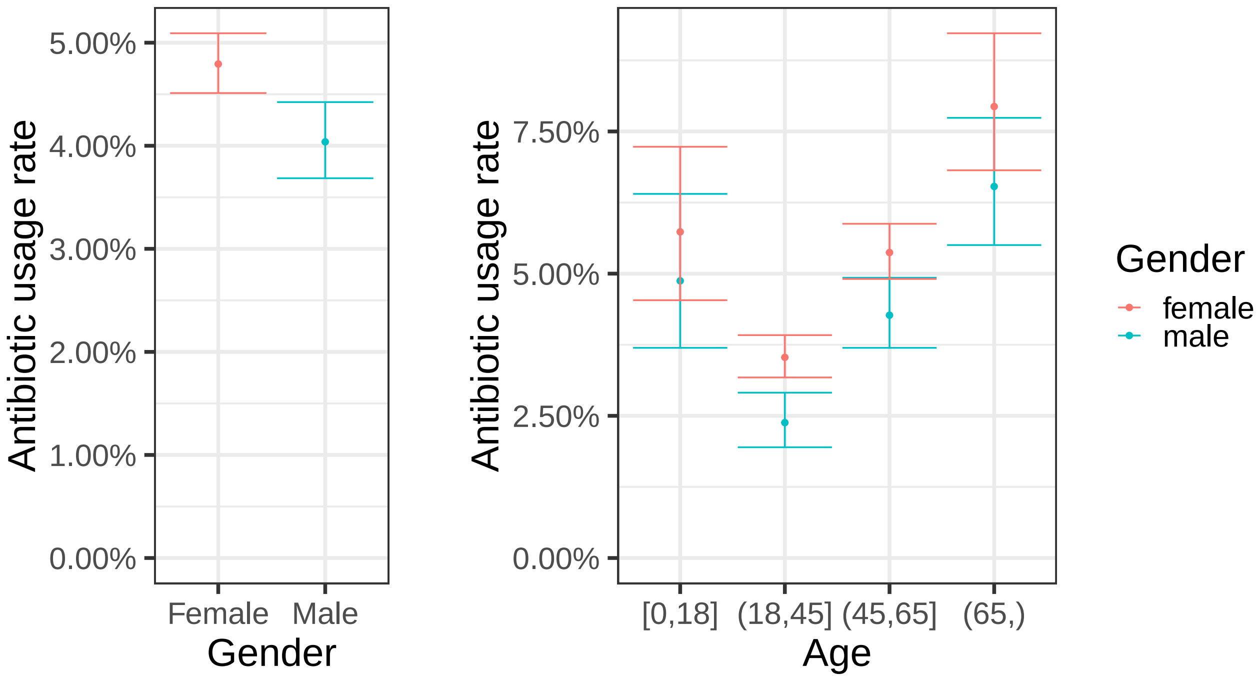

Figure 7: Data by gender, and age

Gender

Women are more likely to be prescribed antibiotics (Shallcross et al. 2017). This trend is seen in the Flusurvey data (Figure 7): 4% vs. 4.8%. This difference is significant (under a Pearson's chi-squared test statistic at the 0.05 significance level).

If age is factored into the analysis it is not seen for all age groups except for young adults (18-45yo) (Figure 7).

Gender was included, alongside **age**, in the multivariate analysis.

Contact with children

Those with frequent contact with children might be expected to be ill more often and hence may receive antibiotics more often. This is supported by this data (Figure 8): 4.4% vs. 5.2%. This difference is significant (under a Pearson's chi-squared test statistic at the 0.05 significance level).

Frequent contact with children was included in the multivariate analysis.

Contact with the elderly

As the elderly have higher rates of antibiotic usage, those with frequent contact may also do the same. This is supported by this data (Figure 9): 4.4% vs. 5.8%. This difference is significant (under a Pearson's chi-squared test statistic at the 0.05 significance level).

Frequent contact with elderly was included in the multivariate analysis.

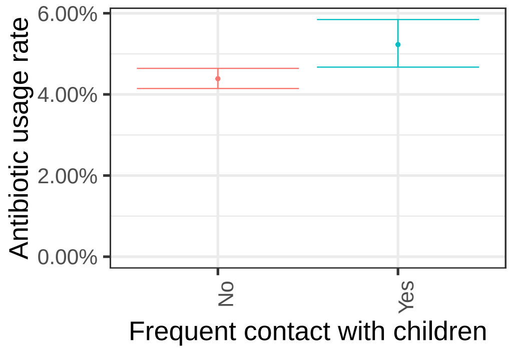

Figure 8: Data by whether participants had 'frequent contact with more than 10 children'.

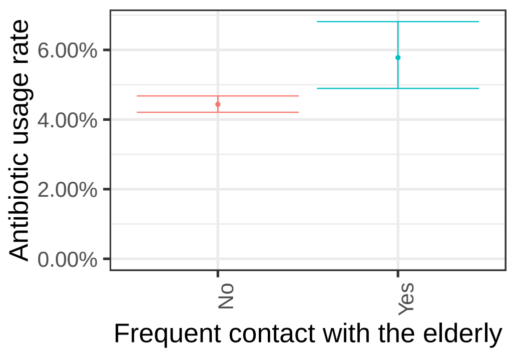

Figure 9: Data by whether participants had 'frequent contact with elderly'.

Health score

Health score is a self-reported, weekly value between 0 and 100. The baseline health score is the median health score (?) when a participant is not ill. This changes by season. An episode health score gives the mean health score over the episode. Health score is not recorded well. Out of the 31,784 episodes, 39.7% (12,621 episodes) have no reported minimum or baseline health score. These were removed for this univariate sub-analysis.

We first explored whether the minimum health score recorded in an episode was linked to antibiotic usage (Figure 10). There seemed to be some correlation - as those who received antibiotics appeared to have a slightly lower minimum health score (seen by comparing medians). This would be as we might expect.

We then explored whether stratified baseline or minimum episode health score was correlated with antibiotic consumption rate, as well as the difference between the two (to take into account that people start at different health score levels) (Figure 11). This showed a distinct correlation between episode health score and antibiotic usage rate: those with lower health scores had higher antibiotic usage rates. However, this may be affected by some people having a baseline higher health score.

Health score was not included in the multivariate analysis as there was a lot of missing data (39.7% of episodes).

Underlying health issue

Flusurvey participants are asked if they have an underlying health issue that may affect their risk of becoming ill. This included diabetes and asthma. Of those episodes where antibiotics were prescribed, 956 (66%) were from participants who had an underlying health issue.

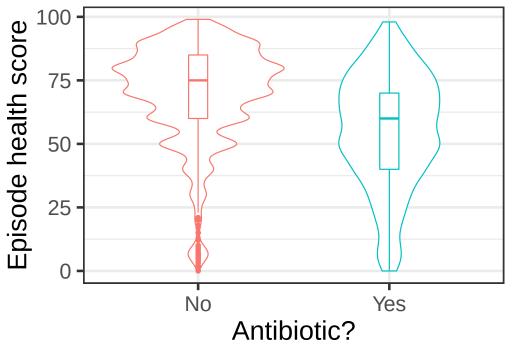

Figure 10: Data by episode health score. Within this violin plot the boxplot shows median and interquartile range.

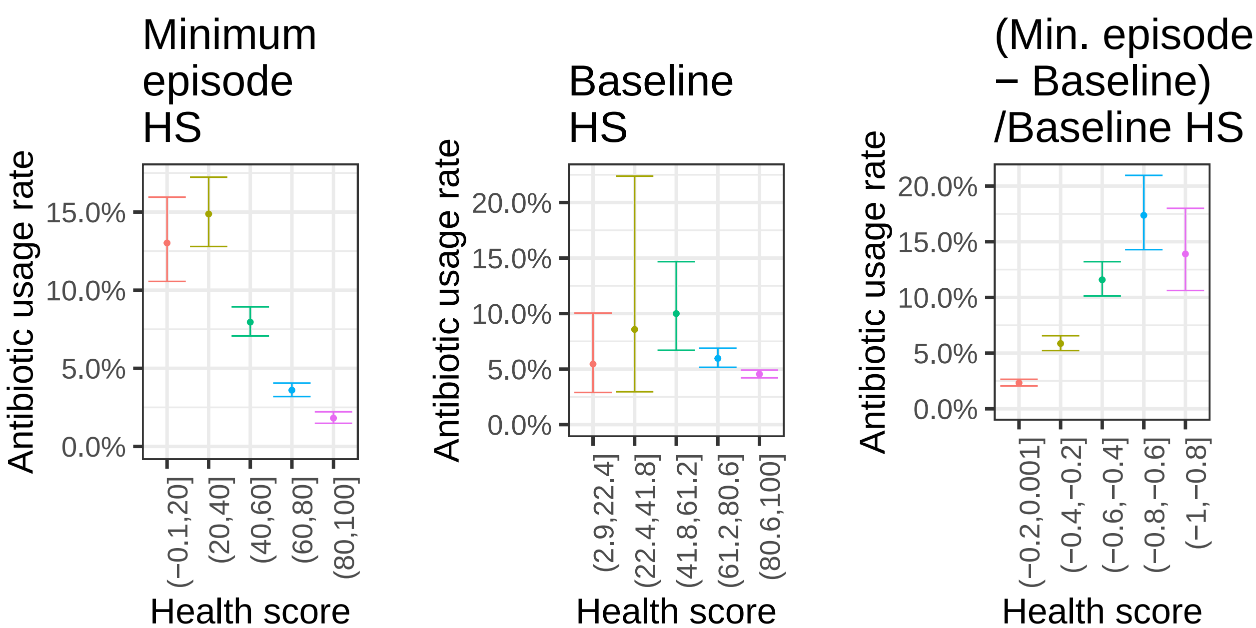

Figure 11: Data by episode health score (HS).

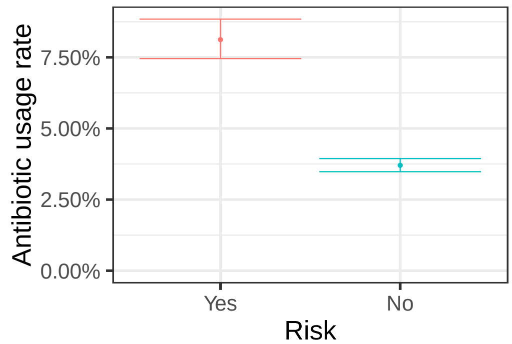

Figure 12: Data by underlying risk factor.

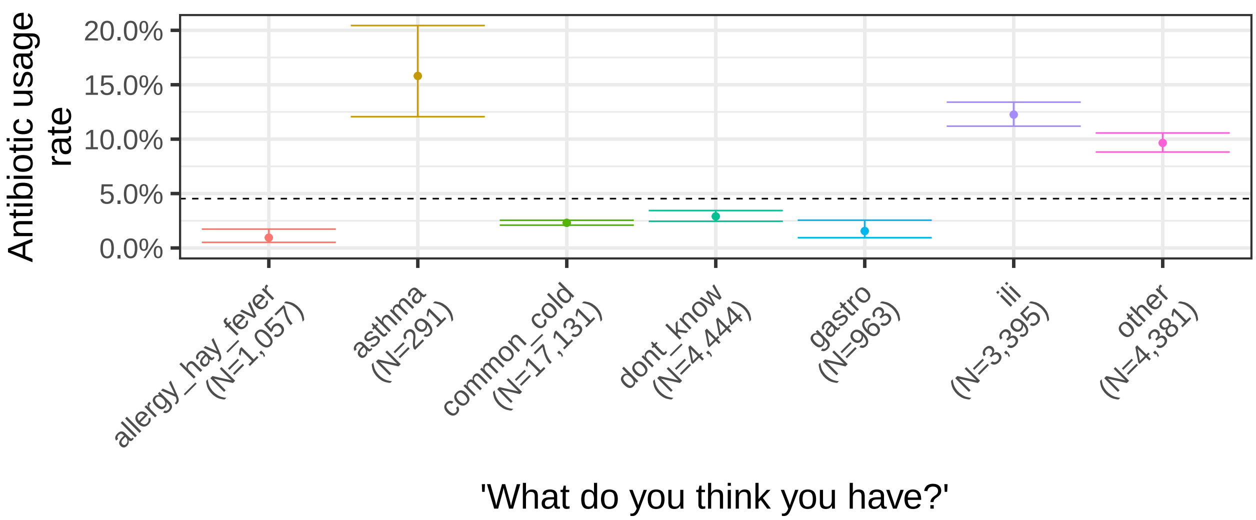

Figure 13: Data by what illness a participant believed the episode to be due to. The dashed horizontal line is the mean usage rate across all participants. N is the number of reported episodes.

It might be expected that those with an underlying health problem would also have a higher risk of receiving antibiotics. This is what we found in the Flusurvey data (Figure 12): 8.1% vs. 3.7%. This difference is significant (under a Pearson's chi-squared test statistic at the 0.05 significance level).

Underlying health issue was included in the multivariate analysis.

What do you think you have?

Flusurvey participants are asked if they have an idea of what illness they are suffering from when they register an episode. The options here included ILI, but also asthma, common cold, gastrointestinal issues or "don't know". The rates of antibiotic usage varied substantially by these conditions (Figure 13).

It might be expected that those who believe that they have a bacterial infection will have have a higher antibiotic usage rate. However, the highest rate of usage was in those who believe themselves to be suffering from an asthmatic episode (15.8%) or ILI (12.3%). For neither of these are antibiotics the recommended treatment guidelines. However, it has been found previously that people with asthma have high rates of antibiotic exposure (Baan et al. 2018; Pouwels et al. 2018).

What do you think you have? was ??? included in the multivariate analysis. Could include as categorical with three levels: "Think has asthma","Think has ili","Think has other illness"?

Multivariate analysis co-variates

Based on the above univariate analysis, the following were included in the multivariate analysis:

- Age (will be regularised)
- If have ILI and fever
- Influenza vaccine status from this season
- Whether they visited a medical service or not
- Gender
- Frequent contact with children
- Frequent contact with the elderly
- Underlying health risk

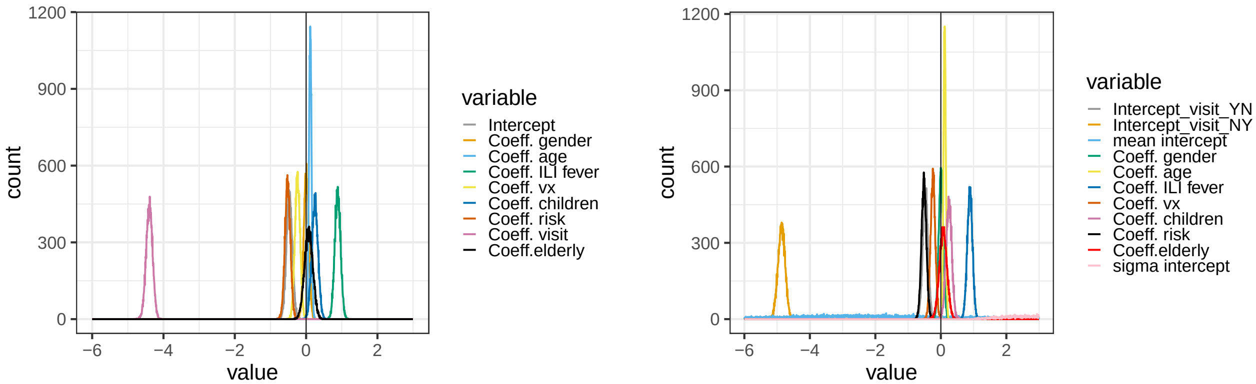

Figure 14: Posterior samples for each model including the intercept parameters)

Additional results

Posterior samples for each Model including intercepts

The parameter estimates for the coefficients are shown in Figures 14. Most are highly similar between the two models except for the intercept (which varies in model formulation).

Change in Odds for Model 1

The calculation in the change of odds for Model 1 shows that there is little evidence to support a correlation between gender and contact with the elderly and chance of taking an antibiotic. Other aOR are similar to those for Model 4 in the main analysis.

Table 1: Coefficient effect for Model 1. The estimate of the coefficient is taken from a 20,000 posterior sample. The adjusted Odds Ratio (aOR) is calculated by taking the exponential of the coefficient. 'Absolute' is the mean absolute effect of the coefficient taking into account the mean intercept estimate. The ranges are all 89 percent credible intervals.

Variable	Estimate	Estimate range	aOR	Absolute
Intercept	-0.47	[-0.57,-0.37]	0.63 [0.57,0.69]	0.38
Coeff. gender	0.00	[-0.08,0.09]	1 [0.92,1.1]	0.39
Coeff. age	0.12	[0.07,0.16]	1.12 [1.07,1.17]	0.41
Coeff. ILI fever	0.88	[0.79,0.98]	2.42 [2.2,2.67]	0.60
Coeff. vx	-0.24	[-0.33,-0.15]	0.79 [0.72,0.86]	0.33
Coeff. children	0.25	[0.14,0.35]	1.28 [1.15,1.42]	0.44
Coeff. risk	-0.52	[-0.61,-0.42]	0.6 [0.54,0.65]	0.27
Coeff. visit	-4.40	[-4.51,-4.29]	0.01 [0.01,0.01]	0.01
Coeff. elderly	0.07	[-0.07,0.21]	1.07 [0.93,1.24]	0.40

References

Baan, Esmé J, Hettie M Janssens, Tine Kerckaert, Patrick JE Bindels, Johan C de Jongste, Miriam CJM Sturkenboom, and Katia MC Verhamme. 2018. "Antibiotic Use in Children with Asthma: Cohort Study in Uk and Dutch Primary Care Databases." *BMJ Open* 8 (11): e022979.

Disease Prevention, European Centre for, and (ECDC)Control. 2015. *Influenza Case Definitions. Check Date.* http://ecdc.europa.eu/en/healthtopics/influenza/surveillance/Pages/influenza_case_definitions.aspx.

Pouwels, Koen B, F Christiaan K Dolk, David RM Smith, Timo Smieszek, and Julie V Robotham. 2018. "Explaining Variation in Antibiotic Prescribing Between General Practices in the Uk." *Journal of Antimicrobial Chemotherapy* 73 (suppl_2): ii27–ii35.

Shallcross, Laura, Nick Beckley, Greta Rait, Andrew Hayward, and Irene Petersen. 2017. "Antibiotic Prescribing Frequency Amongst Patients in Primary Care: A Cohort Study Using Electronic Health Records." *The Journal of Antimicrobial Chemotherapy* 72 (6): 1818–24. https://doi.org/10.1093/jac/dkx048.