PRINCIPLE trial demonstrates scope for in-pandemic improvement in primary care antibiotic stewardship

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Abstract

Background
The Platform Randomised trial of INterventions against COVID-19 In older peoPLE (PRINCIPLE) has provided in-pandemic evidence of potential therapeutics in early primary care management of COVID-19. PRINCIPLE’s first finding was that azithromycin and doxycycline were not effective.

Aim
To explore the extent of azithromycin and doxycycline use in-pandemic, and the scope for trial findings impacting on practice.

Design and Setting
We compared crude rates of prescribing and respiratory tract infections (RTI) in 2020 with 2019, using the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC).

Methods
We used a negative binomial model to compare azithromycin and doxycycline lower respiratory tract infections (LRTI), upper respiratory tract infections (URTI), and influenza-like-illness (ILI) in 2020 with 2019; reporting incident rate ratios (IRR) between years and 95% confidence intervals (95%CI).

Results
Azithromycin prescriptions increased 7% in 2020 compared to 2019, whereas doxycycline decreased by 7%. Concurrently, LRTI and URTI incidence fell by over half (58.3% and 54.4% respectively) while ILI rose slightly (6.4%). The overall percentage of RTI prescribed azithromycin rose from 0.51% in 2019 to 0.72% in 2020 (risk difference of 0.214% (0.211,0.217)); doxycycline rose from 11.86% in 2019 to 15.79% in 2020 (risk difference: 3.93% (3.73,4.14)).

Our adjusted IRR showed azithromycin prescribing was 22% higher in 2020 (IRR=1.22, 95%CI:1.19-1.26, p<0.0001), for every unit rise in confirmed COVID there was an associated 3% rise in prescription (IRR=1.03, 95%CI 1.02-1.03, p<0.0001); whereas these measures were static for doxycycline.

Conclusion
PRINCIPLE flags scope for improvement in antimicrobial stewardship during a pandemic.

250/250 words

Keywords:
Primary health care
COVID-19
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Antimicrobial Stewardship
How this fits in

Antimicrobial stewardship is key to appropriate clinical management of patients and preventing an increase in antimicrobial resistance. With the slowing down of development of antimicrobials, there is a need to reduce unnecessary prescription to patients to minimize antimicrobial resistance.
PRINCIPLE trial findings demonstrate scope for in-pandemic improvement in primary care antibiotic stewardship

Introduction:

The Platform Randomised trial of INterventions against COVID-19 In older peoPLE (PRINCIPLE)\(^1\) has reported that two antibiotics, azithromycin and doxycycline, commonly prescribed to people with possible coronavirus 2019 infections (COVID-19) in primary care show no meaningful benefit in terms of patient reported recovery outcomes.\(^2\) Azithromycin was included in PRINCIPLE between 23\(^{rd}\) May and 30\(^{th}\) November 2020; doxycycline between 24\(^{th}\) July and 14\(^{th}\) December 2020.

There is no published evidence to know whether these antibiotics are being prescribed differently in primary care during the pandemic and therefore the extent to which these findings have potential to impact or change practice. Whilst the National Institute for Health and Care Excellence (NICE) states: *As COVID-19 pneumonia is caused by a virus, antibiotics are ineffective;*\(^3\) it is entirely understandable given the disparities in who test positive,\(^4\) the excess mortality associated with COVID-19,\(^5\) and a move to routine remote consultations, that general practitioners might have a lower threshold for prescribing antibiotics. NICE suggest that where antibiotics might be used doxycycline should be the first choice.

We describe whether there was any change in the prescribing of these antibiotics in primary care during 2020, compared with the pre-pandemic year, taking into account any reduction in the incidence of consultations for respiratory tract infections (RTI) associated with the lockdowns, advice about where and when to seek help (e.g. NHS 111), and other non-pharmaceutical interventions (NPIs).\(^6\) We also report if azithromycin and doxycycline were more likely to be prescribed to people with a COVID-19 diagnosis.

Method:

*Data source and population:*

We used data from the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) sentinel network database. The RSC is one of Europe’s oldest sentinel systems and recruited to be nationally representative, with a history since 1967 of publishing a weekly report of monitored conditions – principally influenza-like-illness (ILI) and other respiratory infections and diseases.\(^7\) The RSC is actively involved, working closely with Public Health England (PHE) to deliver sentinel surveillance including of COVID-19.\(^8\)

We carried out this analysis using a sample of 397 general practices that met data quality standards in RSC with a total registered list size of 4,453,626. This subset was used because their antibiotic drug codes were carefully curated and met quality standards, and the patient group included also had near complete socioeconomic status recording (in most samples around 2.5% are missing).

General practices in the RSC are expected to code as a ‘problem’ the diagnosis that the patient presents with in their computerised medical record. This is particularly for our monitored conditions and key data required for determining vaccine effectiveness. We feedback to practices about their data quality via a dashboard, and do not include in our published reports those practices with monitored events where the data quality level is below threshold.\(^9\)
Reporting crude differences:
We described the monthly rate of prescribing of azithromycin and doxycycline, comparing 2020 with 2019 (1/1/2020-31/12/2020 with 1/1/2019-31/12/2019). We next reported the monthly incidence of RTIs, again comparing 2020 with 2019. We only included coded cases that were labelled as an incident event or which were at least two weeks after any earlier recording. We compared lower respiratory infections (LRTI), upper respiratory infections (URTI), and influenza-like-illness (ILI) between the two years. We then summarised the rates of antibiotic use and of RTIs, providing 95% confidence intervals (95%CI) to discern differences in rates.

Modelling the difference:
We created negative binomial models; the first pair to report any difference between the use of azithromycin and doxycycline in 2020, compared with 2019. We adjusted for age-band, gender, socioeconomic status using the index of multiple deprivation (derived from post code), NHS region (though we combined midlands and east regions to provide a more balanced distribution), and the incidence of LRTI, URTI and ILI. Concerning age, the population included in the PRINCIPLE trial was people over 50 years old with one or more comorbidities and people aged 65 years or older. We therefore included a 65 years and older age-band in our analysis as this most closely compared with PRINCIPLE, but decided to include antibiotic use across all age-bands. We report an incident rate ratio (IRR) with 95% CI, and significance. We ran the same model using 2020 data to explore whether COVID-19 cases were more likely prescribed azithromycin or doxycycline.

Sensitivity analysis
We conducted a sensitivity analysis to explore whether the RSC practices had higher rates of prescription of antibiotics than the rest of England. We did this because the PRINCIPLE trial has been widely promoted to RSC practices and this may have encouraged increased prescribing. We therefore compared the pattern of prescribing in the RSC using national data from OpenPrescribing.\(^\text{10}\) We also compared the lowest prescribing rates in 2020, and average monthly rates of prescribing to see if there were any difference in prescribing rates. As OpenPrescribing does not publish a denominator we used the list size of all English practices published by NHS Digital as denominator.\(^\text{11}\) Finally, we reported from OpenPrescribing the mean difference in prescribing of these antibiotics between 2020 and 2019, comparing the first 10 months of the year, as there were only data to October 2020 available.

Ethical considerations:
This investigation used pseudonymised data held by the Oxford-RCGP RSC sentinel network. The investigation is classified by the Health Research Authority Decision tool (http://www.hra-decisiontools.org.uk/research/) as not being considered research, and not requiring formal research ethics approval. This investigation was approved by the Oxford-RCGP RSC Joint Research and Surveillance Centre Committee.

Results:

Crude rates of azithromycin and doxycycline prescribing:
Overall, the number of azithromycin prescriptions increased by 6.98% between 2019 and 2020, while that of doxycycline fell by 7.02% (Supplementary file, Table S4.1). However, the patterns of prescription of both antibiotics through 2020 were very different from 2019; prescriptions in 2019 followed a more typical pattern.
In January and February 2020 prescriptions of azithromycin and doxycycline were similar to those in 2019. However, in March 2020 both antibiotics reached their peak prescribing rate. This was coincident with the first wave of COVID-19. From then on, the use of these antibiotics in 2020 diverged in their use. Azithromycin was prescribed in 2020 at or above the level prescribed in 2019, the converse was true for doxycycline (Figure 1, tables of rates S1.1 and S1.2 in Supplementary file).

The monthly incidence of patient consultations with a RTI, diagnosed by GPs and recorded in their computerised medical records, was over 50% lower in 2020 than in 2019. For LRTI and URTI the incidence was lower every month. The year 2019 shows a typical pattern for LRTI and URTI; the incidence is lowest at the end of the school summer holidays, peaks at the end of the year, and then falls slowly back to its low point at the end of August (Figure 1). In contrast, the pattern of ILI is different each year. Its peak generally follows the peak in influenza A. For example, 2019 was a typical year with a peak incidence around or just after the year end. In comparison, 2020 showed changes in ILI incidence largely reflecting the waves of the COVID-19 pandemic with peaks in March, April coinciding with the first wave, and a second rise as schools go back, with this modestly increased level continuing to year end (Figure 2, Supplementary file Table S2.3). With social distancing measures and lockdown, there was a lower rate of LRTI and URTI consultations across all age bands. ILI consultation rates overall were slightly increased between the years. However, there was a fall in ILI in males under 16 years old and a rise in presentation of females age 16 to 64 years in 2020 compared with 2019 (Table 1).

In 2020, the use of azithromycin increased in both genders in the 65 years and over age-band, and in males under 16 years old, compared with 2019; the overall increase was 6.98%. Notwithstanding the observed fall in RTI rates, there has been a concomitant rise of 0.21% (95%CI: 0.16-0.26), p<0.0001) in the proportion of RTIs where azithromycin was prescribed - a 42.1% rise on the previous year.

The converse occurred with doxycycline with a reduction in the rate of prescribing in the 65 years and older age-band. Overall, there was a decline in prescribing of 7.02% between 2019 and 2020. However, in relation to the fall in acute respiratory infections in 2020, there was nearly a 4% rise (3.93%, 95%CI:[3.73-4.14], p<0.0001) in doxycycline prescribing, a 33.1% rise compared with the previous year.

After having adjusted for age, gender, socioeconomic status, NHS region and RTIs (LRTI, URTI and ILI), the negative binomial model indicated that the frequency of azithromycin prescriptions (for any reason) in the RSC registered population was 22% higher in 2020 compared to 2019 (IRR=1.22, 95%CI 1.19-1.26, p<0.0001, Table 2).

In addition, for every unit rise in COVID confirmed status there was an associated 3% rise in azithromycin prescription (IRR=1.026, 95%CI 1.024-1.0285, p<0.0001, Table 3). With azithromycin, there was a much higher rate of prescribing to those age 65 years and over, and less to those age 16 to 64 years. There was less azithromycin prescribing for males compared with females, higher rates of prescribing to the most deprived regions and in the north compared to the south. Comparing 2020 with 2019 overall there was more azithromycin prescribing for people with LRTI and URTI. During 2020 there was a higher rate of prescribing to people with LRTI and ILI and reduced prescribing to people with URTI.
For doxycycline, there was no change in the rate of prescribing comparing 2020 with 2019 (IRR=1.012, 95%CI 0.994-1.030, p=0.199). Female gender, the most deprived quintile, midlands and southwest region LRTI and ILI were associated with higher rates of prescription in 2020 compared with 2019 (see supplementary material table S3.1).

Adjusting for age, gender, socioeconomic status, region and RTI, there was a very small rise of 0.3% in the rate of prescribing in doxycycline (IRR=1.0003, 95%CI 1.0002-1.0005, p<0.0001). Female gender, the most deprived quintile, midlands and southwest region LRTI and ILI were associated with higher rates of prescription of doxycycline (see supplementary material table S3.7).

Our sensitivity analysis showed a very similar pattern of month-by-month azithromycin and doxycycline prescribing as OpenPrescribing (Figure 3), a national database. We used the NHS Digital registered patient population denominator (N=60,570,367); compared with the RSC sample denominator (N=4,453,626). We compared the rates of the lowest monthly overall prescription count in 2020. We found a prescribing rate (per registered patient) of 0.248% for OpenPrescribing and 0.225% for the RSC for doxycycline; and 0.099% and 0.075% for azithromycin. We also compared the year-on-year change. In OpenPrescribing, azithromycin prescribing increased by 7.25% and doxycycline reduced by 2.31%, between 2019 and 2020, compared with 6.98% and 7.02% in the RSC for azithromycin and doxycycline, respectively (Supplementary file Table S4.1).

Discussion:

Summary
Azithromycin prescribing, for all indications, increased by 7% in 2020 compared to 2019; doxycycline prescribing reduced by the same amount (7%). The RSC mirrors the pattern and rate of azithromycin prescribing reported by OpenPrescribing. There was also a similar pattern of doxycycline prescription, but OpenPrescribing reports a smaller year-on-year decline.

Prescribing of both antibiotics peaked in the first wave of COVID-19 (March 2020), with the use of azithromycin prescribing overall remaining like 2019, while there is a lower rate of doxycycline prescribing overall. There was no equivalent peak of prescribing of these antibiotics in the second wave of COVID-19 (autumn 2020).

Through 2020 there was a much lower incidence of consultations with a diagnosis of upper and lower RTIs, though ILI incidence increased with the year. ILI incidence was initially raised at the start of the year at the time of circulating influenza, and subsequently mirrored COVID-19 infection.

The rate of azithromycin prescribing, taking into account the other variables in our model, has increased by 22% in 2020 compared to 2019. Further, as the number of COVID-19 cases increased, so the prescribing of azithromycin increased. Doxycycline, shows a different pattern. Its rate of prescription has not changed between 2019 and 2020, although there has been an increase in prescriptions of around 4% for RTIs and its use marginally changes with increasing COVID-19 cases.

Strengths and limitations
The strength of this analysis is that the RSC has good data quality and is able to capture routine data about RTIs and their incidence. The network encourages our key monitored conditions to be coded as problems with an episode type, to distinguish new from follow-up consultations. Where episode type
is not recorded, we use a time interval to distinguish incidence from follow-up cases.\textsuperscript{12} RTI data are extracted from practices either daily or twice weekly, with data fed back to practices via a dashboard to try to raise awareness of data quality.\textsuperscript{13}

Comparing the use of azithromycin and doxycycline between years, and their use in respiratory infections is complex. Whist the overall azithromycin prescribing has risen by the same proportion by which doxycycline has decreased (7%) the incidence in the respiratory conditions they treat has decreased by a greater proportion (>50%). Both antibiotics have had a significantly increased use in RTIs in 2020 (16.5%) compared to 2019 (12.4%). The decrease in doxycycline is discordant with NICE guidance, which suggest using doxycycline first line.\textsuperscript{3}

We do not think that the increased use of antibiotics was related to involvement of the RSC in the PRINCIPLE trial. RSC data are very similar to those from OpenPrescribing, and only people aged 50 years and above were eligible for the PRINCIPLE trial; whereas we saw changes in prescribing across people of all ages.

\textit{Comparison with existing literature}
We don’t know why azithromycin prescribing increased during 2021. It is possible that colleagues were wanting to trial interventions that might improve COVID-19 and are in the public eye, notwithstanding that most of these studies were of hospitalised patients and ultimately reported negative outcomes.\textsuperscript{14,15,16} Furthermore, remote consultations have increased substantially,\textsuperscript{17} and may make it harder for clinicians to accurately diagnose pneumonia that has complicated COVID-19, leading to a reduced threshold to prescribe antibiotics. However, observational studies suggest that even amongst patients hospitalised with COVID-19, the prevalence of bacterial super-infection is low with estimates of around 3.5%.\textsuperscript{18,19} Routine antimicrobial prescription for COVID-19 patients in the community should now change in light of the new evidence.

\textit{Implications for practice}
The PRINCIPLE trial has demonstrated that there is no benefit from either antibiotic in early treatment of COVID-19 in the absence of bacterial pneumonia. There is therefore considerable scope to reduce the prescribing of these antibiotics in primary care.

Additionally, it appears that awareness of, or involvement in the PRINCIPLE trial by RSC practices, does not seem to be associated with higher rates of prescribing than those seen in national data reported by OpenPrescribing.

\textit{Conclusions:}
An in-pandemic trial has studied the value of prescribing two antibiotics for people with COVID-19. Given the lack of efficacy of azithromycin and doxycycline demonstrated in the PRINCIPLE trial, primary care clinicians should apply good antibiotic stewardship and use them less. The national sentinel network, the Oxford-RCGP RSC has demonstrated that these antibiotics are being extensively used and that they are being prescribed to a higher proportion of people with respiratory infections than in the pre-pandemic year. There is scope, in-pandemic, to reduce the use of doxycycline and azithromycin in primary care.
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Declaration of interest:
CB and FDRH are co-Principal and SdeL an investigator of the PRINCIPLE trial. SdeL is Director of the Oxford-RCGP RSC. SdeL has received funding through his University for studies from Wellcome Trust (Grant reference number: 212763), AstraZeneca, Daiichi Sankyo, Eli Lilly, Sanofi, GSK, MSD, Seqirus and Takeda; and has been a member of advisory boards for Seqirus and Sanofi.
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Prescribing of azithromycin (top) and doxycycline (bottom) by month within the RSC. 2020 prescription of both antibiotics (red line) was very similar in January and February to 2019 rates (blue line), then in March there was a peak of prescribing in 2020 coincident with the first wave of the COVID-19 pandemic.
Thereafter azithromycin was prescribed in 2020 at or above the level in 2019, whereas doxycycline was prescribed less.

Figure 2: Comparison of monthly incidence of consultations for LRTI (top), URTI (middle) and ILI (bottom) comparing 2020 (red) with 2019 (blue) in the RSC dataset. There was a lower incidence of LRTI and URI in 2020 compared with 2019, with a small
peak when schools returned in September 2020. ILI peaked with the first wave of the COVID-19 pandemic also with the return to school.

Figure 3: Monthly pattern of doxycycline and azithromycin, prescription counts, for 2019 and 2020 (OpenPrescribing data are only available up to October 2020).
|               | 2019               | 2020               |
|---------------|--------------------|--------------------|
|               | Age                | Female             | Male               | Female             | Male               |
|               | Doxy.              |                    |                    |                    |                    |
| under 16      | 21.74 (20.4,23.2)* | 17.75 (16.5,19.0)  | 19.12 (17.8,20.5)  | 15.96 (14.8,17.2)  |
| 16-64         | 385.28 (382.1,388.5)| 231.99 (229.6,234.4)| 380.15 (377.8,383.3)| 222.57 (220.2,224.9)|
| 65+           | 1136.15 (1126.4,1145.9)| 1038.78 (1028.6,1048.9)| 968.28 (959.3,977.3)| 913.57 (904.1,923.1)|
|               | Azith.             |                    |                    |                    |                    |
| under 16      | 56.89 (54.6,59.2)  | 67.50 (65.1,69.9)  | 53.29 (51.1,55.5)  | 75.91 (73.4,78.5)  |
| 16-64         | 70.02 (68.7,71.4)  | 39.39 (38.4,40.4)  | 70.69 (69.4,72.1)  | 40.77 (39.8,41.8)  |
| 65+           | 305.17 (300.1,310.3)| 288.43 (283.1,293.9)| 339.13 (333.8,344.5)| 307.59 (302.1,313.2)|
|               | Resp. Disease      |                    |                    |                    |                    |
|               | Rates             | LRTI               | URTI               | ILI                |
|               | (per 100,000)     | under 16           | 16-64              | 65+                |
| LRTI          | 229.25 (224.67,233.82)| 292.18 (287.1,297.2)| 68.43 (65.9,70.9)  | 90.9 (88.1,93.8)  |
|               | 16-64              | 191.30 (189.1,193.54)| 126.84 (125.0,128.6)| 81.45 (79.9,82.9)  | 53.2 (52.0,54.4)  |
|               | 65+                | 609.27 (602.05,616.5)| 568.32 (560.8,575.8)| 267.9 (263.2,272.8)| 268.0 (262.9,273.2)|
| URTI          | 1320.33 (1309.5,1331.3)| 1349.86 (1339.1,1360.7)| 485.15 (455.0,467.7)| 493.1 (486.6,499.7)|
|               | 16-64              | 485.65 (482.1,489.2)| 229.3 (226.9,231.8) | 265.73 (254.9,260.1)| 117.38 (115.7,119.1)|
|               | 65+                | 285.17 (280.3,290.1)| 208.6 (204.1,213.2) | 148.01 (144.5,151.6)| 104.61 (101.4,107.9)|
| ILI           | 19.30 (17.1,19.7)  | 20.78 (19.5,22.2)  | 16.38 (15.2,17.7)  | 16.23 (15.1,17.5)  |
|               | 16-64              | 32.57 (30.8,32.6)  | 22.15 (21.4,22.9)  | 37.68 (36.7,38.7)  | 21.86 (21.1,22.6)  |
|               | 65+                | 25.40 (28.2,31.7)  | 22.18 (20.7,23.7)  | 29.41 (27.9,31.0)  | 24.38 (22.9,25.9)  |

*95% conf. Int.

Table 1: Comparison of rates of prescription of doxycycline and azithromycin in 2020 with 2019. In people 65 years old and older there was a decrease in doxycycline use but an increase in azithromycin prescription. LRTI and URTI incidence fell across all age bands and both genders. ILI was much more similar between years.
Model reporting the incident rate ratio (IRR) comparing prescribing of azithromycin in 2020 with 2019. Taking the variables in the model into account there was a 22% increase, with people 65 years and older, female gender, the most deprived, northern regions and people with LRTI and URTI.

| Azithromycin prescribing rates       | IRR   | Lower  | Upper  | p       |
|--------------------------------------|-------|--------|--------|---------|
| comparing 2020 with 2019             |       | 95% CI | 95% CI |         |
| **Yr 2020 (ref level 2019)**         | 1.22  | 1.19   | 1.26   | <0.0001 |
| **Age Band (ref. level 0-15)**       |       |        |        |         |
| 16-64                                | 0.71  | 0.68   | 0.73   | <0.0001 |
| 65+                                  | 4.77  | 4.58   | 4.98   | <0.0001 |
| **Gender (ref. level F)**            | 0.91  | 0.88   | 0.93   | <0.0001 |
| IMD Quintile (ref. level Most Deprived) |       |        |        |         |
| Q2                                   | 0.90  | 0.86   | 0.94   | <0.0001 |
| Q3                                   | 0.87  | 0.83   | 0.90   | <0.0001 |
| Q4                                   | 0.75  | 0.72   | 0.78   | <0.0001 |
| Q5 (least deprived)                  | 0.67  | 0.64   | 0.70   | <0.0001 |
| **NHS Region (Ref London)**          |       |        |        |         |
| Midlands and East                    | 1.08  | 1.03   | 1.12   | <0.0001 |
| North East and Yorkshire             | 1.47  | 1.40   | 1.54   | <0.0001 |
| North West                           | 1.13  | 1.08   | 1.18   | <0.0001 |
| South East                           | 0.94  | 0.89   | 0.98   | <0.0001 |
| South West                           | 0.72  | 0.69   | 0.76   | <0.0001 |
| **Resp. Disease**                    |       |        |        |         |
| LRTI Count                           | 1.0051| 1.0043 | 1.0058 | <0.0001 |
| URTI Count                           | 1.0030| 1.0026 | 1.0035 | <0.0001 |
| ILI Count                            | 1.0017| 0.9982 | 1.0053 | 0.3400  |

Table 2:
Azithromycin prescribing rate & IRR & Lower & Upper & p & 95% CI & 95% CI \\
--- & --- & --- & --- & --- & --- & --- \\
Covid19 Confirmed Count & 1.03 & 1.02 & 1.03 & <0.0001 & 1.02 & 1.03 \\
Age Band (ref. level 0-15) & & & & & & \\
16-64 & 0.25 & 0.20 & 0.31 & <0.0001 & 0.20 & 0.31 \\
65+ & 10.95 & 8.67 & 13.83 & <0.0001 & 8.67 & 13.83 \\
Gender (ref. level F) & 0.54 & 0.45 & 0.65 & <0.0001 & 0.45 & 0.65 \\
IMD Quintile (ref. level Most Deprived) & & & & & & \\
Q2 & 0.54 & 0.41 & 0.72 & <0.0001 & 0.41 & 0.72 \\
Q3 & 0.41 & 0.31 & 0.55 & <0.0001 & 0.31 & 0.55 \\
Q4 & 0.54 & 0.41 & 0.72 & <0.0001 & 0.41 & 0.72 \\
Q5 (least deprived) & 0.66 & 0.50 & 0.88 & 0.0048 & 0.50 & 0.88 \\
NHS Region (Ref London) & & & & & & \\
Midlands and East & 5.73 & 4.28 & 7.69 & <0.0001 & 4.28 & 7.69 \\
North East and Yorkshire & 12.88 & 9.18 & 18.07 & <0.0001 & 9.18 & 18.07 \\
North West & 10.31 & 7.34 & 14.49 & <0.0001 & 7.34 & 14.49 \\
South East & 2.82 & 2.01 & 3.96 & <0.0001 & 2.01 & 3.96 \\
South West & 1.41 & 1.01 & 1.98 & 0.0453 & 1.01 & 1.98 \\
Resp. Disease & & & & & & \\
LRTI Count & 1.94 & 1.92 & 1.97 & <0.0001 & 1.92 & 1.97 \\
URTI Count & 0.89 & 0.88 & 0.90 & <0.0001 & 0.88 & 0.90 \\
ILI Count & 1.60 & 1.54 & 1.68 & <0.0001 & 1.54 & 1.68 \\

Table 3: Azithromycin prescribing in cases of COVID-19, for each unit rise in COVID-19 cases there has been a 3% rise in azithromycin prescriptions. Age 65 years and older, female gender, being more deprived, northern regions LRTI or ILI infections are all associated with a higher rate of prescribing.