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Abstract

Background:
The Platform Randomised trial of INterventions against COVID-19 In older peoPLE (PRINCIPLE) has provided in-pandemic evidence that azithromycin and doxycycline were not beneficial in the early primary care management of COVID-19.

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%CI1.19-1.26, 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 demonstrates scope for improved antimicrobial stewardship during a pandemic.

243/250 words

Keywords:
Primary health care
COVID-19
Clinical trial
Pandemics
Medical records systems, computerized
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 development of antimicrobials, there is a need to reduce unnecessary prescription to patients who may not benefit from them.

PRINCIPLE trial findings demonstrate scope for in-pandemic improvement in primary care antibiotic stewardship: retrospective sentinel network cohort study

Introduction:

The UK, primary care, prospective adaptive Platform Randomised trial of INterventions against COVID-19 In older peoPLE (PRINCIPLE)[1] has reported that two antibiotics, azithromycin and doxycycline, show no meaningful benefit in patient-reported recovery for coronavirus 2019 disease (COVID-19).[2,3] Azithromycin was included in PRINCIPLE between 23rd May and 30th November 2020; doxycycline between 24th July and 14th December 2020.

National Institute for Health and Care Excellence (NICE) states: *As COVID-19 pneumonia is caused by a virus, antibiotics are ineffective.* Though at the time of the study this statement was qualified by the suggestion that where antibiotics were used, doxycycline should be the first choice[4]. However, general practitioners may have had a lower threshold for prescribing antibiotics with more remote consultations, the excess COVID-19 associated mortality,[5] and its associated disparities. [6]

We carried out this study to assess whether there was scope for the PRINCIPLE findings to change practice.

Method:

Data source and population:
We used data from the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database; the primary care sentinel network.[7,8]

We included a convenience sample of 397 general practices, total registered list size of 4,453,626, where antibiotic drug codes were curated.

Reporting crude differences:
We reported monthly prescribing rates of azithromycin and doxycycline, comparing 2020 with 2019, also reporting consultations for incident respiratory tract infections (RTI) across a period where a range of non-pharmaceutical interventions (NPIs) were implemented.[9,10] RTIs were subdivided into lower respiratory infections (LRTI), upper respiratory infections (URTI), influenza-like-illness (ILI) and people with COVID-19. We only included incident cases with two or more weeks between events.

Modelling the difference:
We created negative binomial models; to report any difference between the use of azithromycin and doxycycline in 2020, compared with 2019. This model was preferred as there was over-dispersion in the data. Population at risk denominators were included in all regression models. We adjusted for age-band, gender, socioeconomic status using the index of multiple deprivation (IMD, derived from post code), NHS region (midlands and east regions combined to provide a more balanced distribution), and the incidence of LRTI, URTI and ILI. We examined antibiotic use across all age-bands and reported incident rate ratio (IRR) with 95% CI, and significance; we separately reported people aged 65 years and over.

Sensitivity analysis:
We conducted a sensitivity analysis and explored whether the RSC practices had higher rates of prescription of antibiotics than the rest of England as the PRINCIPLE trial participation may have encouraged increased prescribing. We used national data from OpenPrescribing,[11] using NHS Digital's national list-size as denominator.[12] We compared OpenPrescribing data for the first 10 months of the year, as only data to October 2020 were available.

Results:

Crude rates of azithromycin and doxycycline prescribing:
Azithromycin prescriptions increased by 6.98% between 2019 and 2020, while that of doxycycline fell by 7.02% (Supplementary file, Table S4.1).

In January/February 2020 prescriptions of azithromycin and doxycycline were similar to those in 2019. However, in March 2020 prescribing of both antibiotics peaked, coincident with the first wave of COVID-19. Azithromycin was prescribed in 2020 at or above the level prescribed in 2019, whereas the converse was true for doxycycline (Figure 1, Supplementary file S1.1 and S1.2).

Consultations for LRTI and URTI were over 50% lower in 2020 than 2019, incidence was lower in every month (Figure 2). ILI incidence in 2019 followed a typical higher winter incidence, whereas 2020 showed peaks that reflected the waves of COVID-19 (Figure 2, Supplementary file S2.3). However, ILI incidence in males under 16 years old fell while that of females age 16 to 64 years was higher (Table 1).

In 2020, compared with 2019, azithromycin and doxycycline prescribing in RTIs rose by 0.21% (95%CI 0.211-0.217), p<0.0001) and 4% (95%CI 3.73-4.14, *p*<0.0001) respectively.

Modelling the difference:
After adjusting for age, gender, socioeconomic status, NHS region and RTIs, the frequency of azithromycin prescriptions (for any reason) was 22% higher in 2020 compared to 2019 (IRR=1.22, 95%CI 1.19-1.26, p<0.0001, Table 2).

For every unit rise in COVID confirmed count there was an associated 3% rise in azithromycin prescription (IRR=1.023, 95%CI 1.02-1.03, 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, and 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.

The same negative binomial model found no change in the rate of prescribing of doxycycline, in 2020 compared 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 (supplementary table S3.6).

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 (supplementary table S3.7).

Sensitivity analysis:
OpenPrescribing showed a very similar pattern of prescribing (Figure 3, Supplementary Table S4.1).

Discussion:

Summary:
Crude rates of azithromycin prescribing, increased by 7% in 2020 compared to 2019, while doxycycline prescribing reduced by the same amount (7%).
Prescribing of both antibiotics peaked in the first wave of COVID-19 (March 2020), there was no equivalent peak of prescribing in the second wave; azithromycin prescribing overall mirrored 2019, while doxycycline prescribing decreased.

Through 2020 there was a much lower incidence of URTI and LRTI, though ILI incidence increased with the year, at the start of the year at the time of circulating influenza, and subsequently mirrored COVID-19 infection.

The adjusted rate of doxycycline did not change, whereas azithromycin prescribing increased by 22% in 2020 compared to 2019 and as the number of COVID-19 cases increased, azithromycin prescribing increased.

Strengths and limitations:
The PRINCIPLE trial has provided a robust in-pandemic trials platform[2,3,13] 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.[14,15]

Comparing the use of azithromycin and doxycycline between years, and their use in RTIs is complex and we are reporting relative change in antibiotic use, their absolute level of use in RTIs is very low. 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.[4]

Additionally, trial drugs may not have been recorded in the GP computer system, as supplied by the clinical trials unit.

Comparison with existing literature:
We do not know why azithromycin prescribing increased during 2020, as estimates of bacterial super-infection are low, around 3.5%.[16,17] There were widely reported studies about its use in COVID-19, though ultimately reporting negative outcomes;[18,19,20] and remote consultations increased substantially, possibly reducing the threshold for prescribing.[21]

Implications for practice:
The PRINCIPLE trial demonstrated no benefit from either antibiotic in the early treatment of COVID-19 and RSC involvement did not seem to be associated with higher rates of prescribing than those seen in OpenPrescribing.

Conclusions:
The PRINCIPLE trial demonstrated the lack of efficacy of azithromycin and doxycycline in primary care. Clinicians should apply good antibiotic stewardship and reduce their use, as these antibiotics are being prescribed in a higher proportion of people with respiratory infections than in the pre-pandemic year. There is scope, in-pandemic, to reduce the use of azithromycin and doxycycline in primary care.

Funding:
The PRINCIPLE trial is funded by UK Research and Innovation and the Department of Health and Social Care through the National Institute for Health Research.

Ethical approval:
This investigation used pseudonymised data held by the Oxford-RCGP RSC sentinel network. It 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.

Competing interests:
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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Figures and Tables

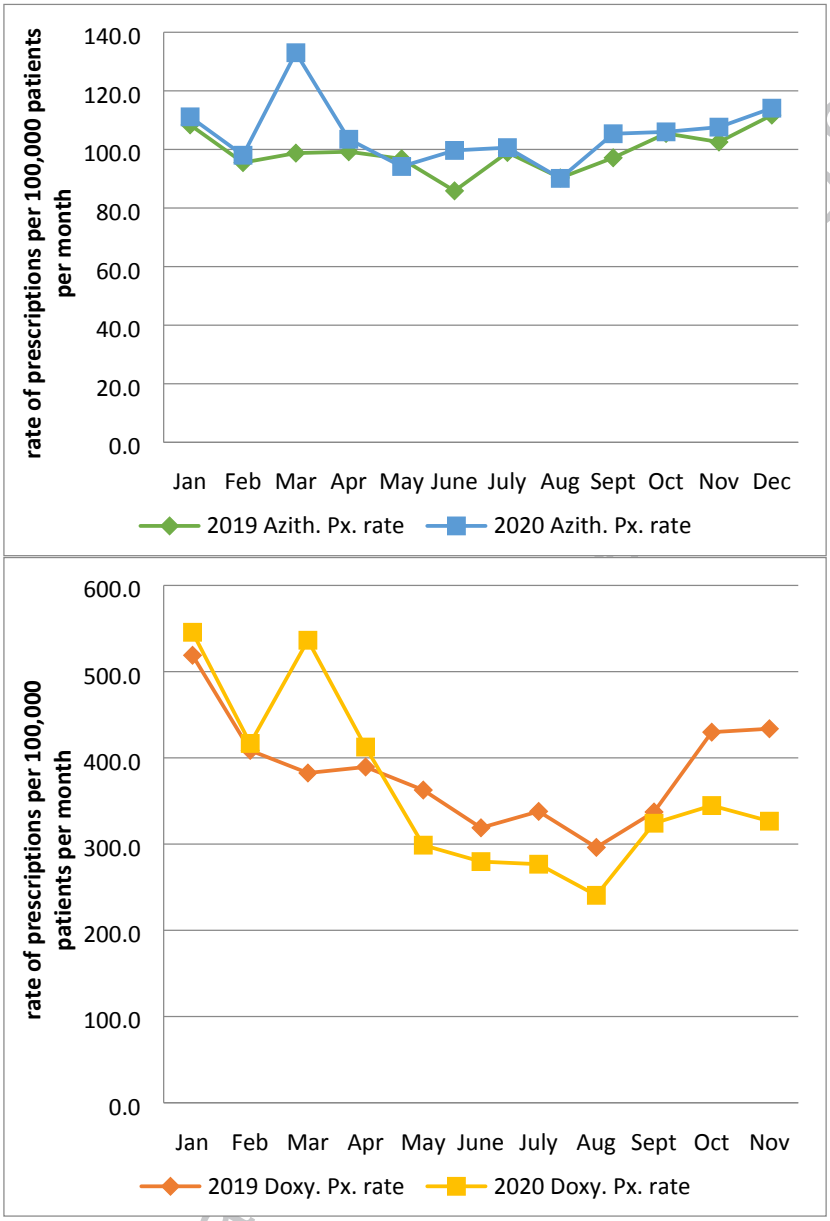
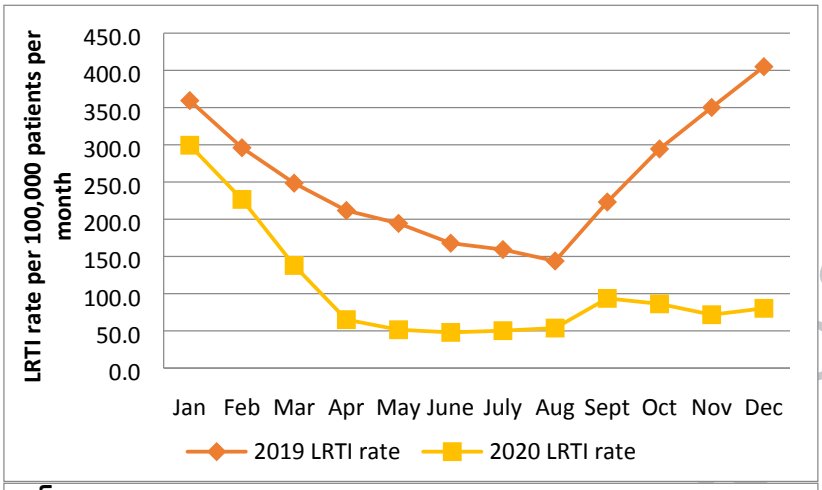
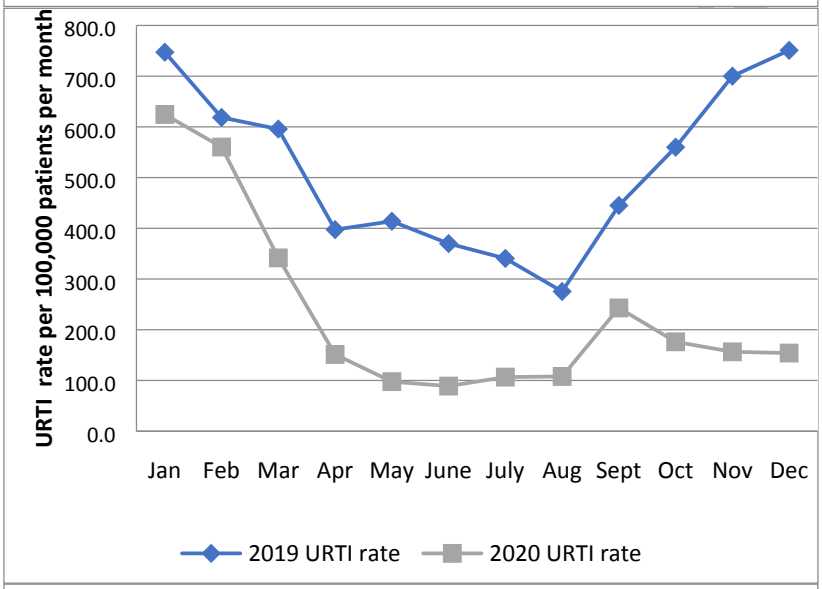


Figure 1: **Prescribing of azithromycin (top) and doxycycline (bottom) by month within the RSC. 2020 prescription of both antibiotics (red line) was very similar in January and February to 2019 rates (blue line), then in March there was a peak of prescribing in 2020 coincident with the first wave of the COVID-19 pandemic. Thereafter azithromycin was prescribed in 2020 at or above the level in 2019, whereas doxycycline was prescribed less.**


LRTI rate per 100,000 patients per month
450.0
400.0
350.0
300.0
250.0
200.0
150.0
100.0
50.0
0.0
Jan Feb Mar Apr May June July Aug Sept Oct Nov Dec
2019 LRTI rate
2020 LRTI rate


URTI rate per 100,000 patients per month
800.0
700.0
600.0
500.0
400.0
300.0
200.0
100.0
0.0
Jan Feb Mar Apr May June July Aug Sept Oct Nov Dec
2019 URTI rate
2020 URTI rate

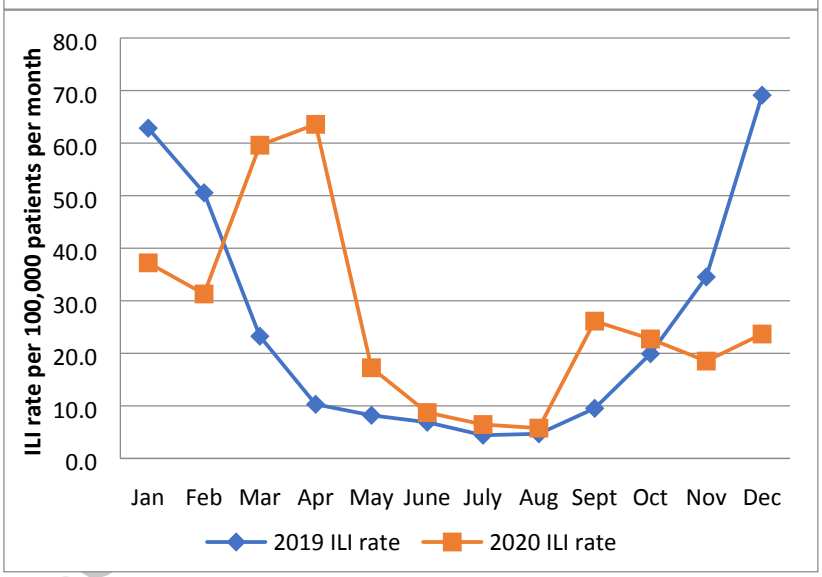

ILI rate per 100,000 patients per month
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
Jan Feb Mar Apr May June July Aug Sept Oct Nov Dec
2019 ILI rate
2020 ILI rate

Figure 2: **Comparison of monthly incidence of consultations for LRTI (top), URTI (middle) and ILI (bottom) comparing 2020 with 2019 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.**

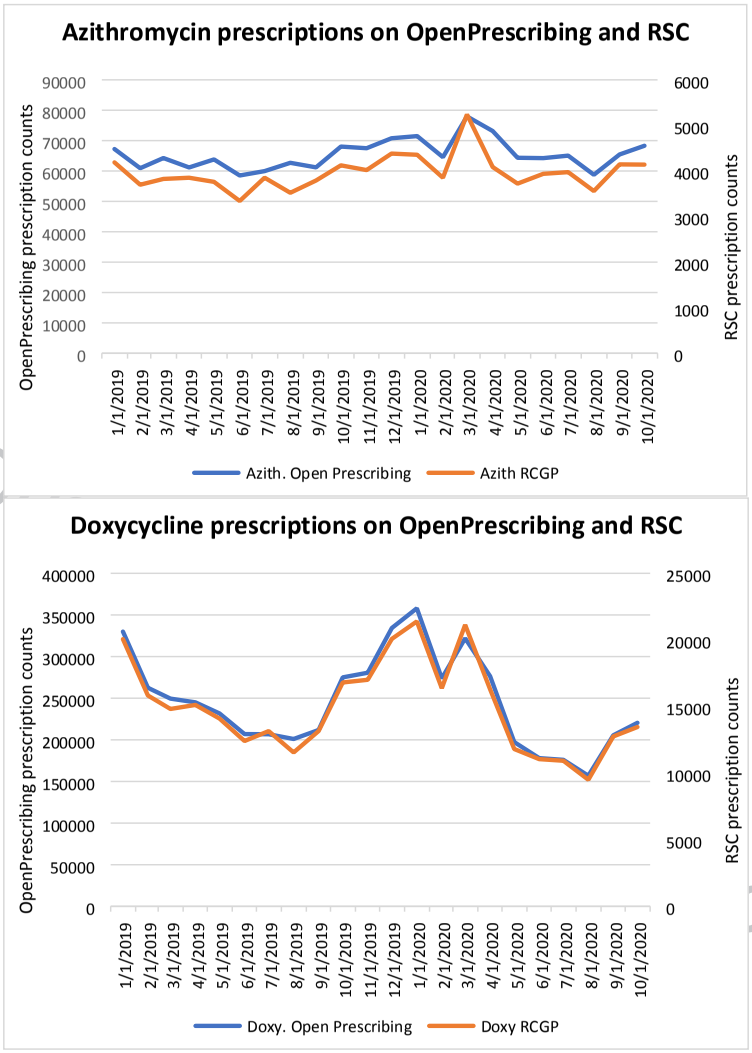


Figure 3: **Monthly pattern of doxycycline and azithromycin, prescription counts, for 2019 and 2020 (OpenPrescribing data are only available up to October 2020).**

			2019		2020	
		Age	*Female*	*Male*	*Female*	*Male*
Antibiotic Rates (per 100,000 patients)	**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 (per 100,000 patients)	**LRTI**	*under 16*	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	*under 16*	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	*under 16*	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.**

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

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**