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RESEARCH ARTICLE

Thank Martin Luther that ciprofloxacin could cure your gonorrhoea? Ecological association between Protestantism and antimicrobial consumption in 30 European countries [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: Higher consumption of antimicrobials plays an important role in driving the higher prevalence of antimicrobial resistance in Southern compared to Northern Europe. Poor controls on corruption (CoC), high uncertainty avoidance (UA) and performance vs. cooperation orientation (POCO) of societies have been found to explain much of this higher consumption in Southern European countries. We hypothesized that these predictors were in turn influenced by the Protestant Reformation in the 16th century onwards.

Methods: We used structural equation modelling (SEM) to assess the relationships between country-level proportions being Protestant, CoC, UA, POCO and four markers of antimicrobial consumption in the community (all antibacterials, cephalosporin, macrolides and fluoroquinolones).

Results: The proportion of a country that was Protestant was negatively correlated with the consumption of all antibacterials. SEM revealed that UA predicted all antibacterial consumption (direct effect coef. 0.15, 95% Confidence Interval [CI] 0.04-0.26). The proportion Protestant exerted an indirect effect on consumption (coef. -0.13, 95% CI -0.21- -0.05). This effect was mediated predominantly via its effect on UA (direct effect coef. 0.15, 95% CI 0.04-0.26). The model explained 37% of the variation in consumption. Similar results were obtained for each of the other three classes of antimicrobials investigated.

Conclusions: Our results are compatible with the theory that

Open Peer Review

Approval Status ✓ ?

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version 2 (revision) 06 May 2022		
version 1 06 Oct 2020	✓ view	? view

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contemporary differences in antimicrobial consumption in Europe stem in part from cultural differences that emerged in the Reformation. These findings may explain the differential efficacy of similar antibiotic stewardship campaigns in Northern and Southern European populations.

Keywords

antibiotic consumption, antimicrobial resistance, culture, Hofstede model, Protestant, Catholic, spandrel

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Introduction

Countries in Southern Europe have been noted for some time to have a higher prevalence of antimicrobial resistance (AMR) than Northern European countries[1,2]. As an example, the prevalence of *Neisseria gonorrhoeae* resistance to ciprofloxacin varies over three fold between countries in Europe[3].

The major determinant of these variations in AMR is the higher consumption of antimicrobials (AMC) in Southern European countries[3,4]. Fluoroquinolone consumption for example varies 6-fold between European countries and is associated with the prevalence of ciprofloxacin resistance in *N. gonorrhoeae*[3]. What is less clear is what the underlying reason is for the variations in AMC[4,5].

Previous studies have found a range of cultural and structural factors underpin the large variations in the consumption of fluoroquinolone and other antibiotics between European countries and globally[5–10]. The act of prescribing an antimicrobial is highly social. Providing an antimicrobial represents the doctor's concern for the patient, legitimizes the patient's sick-role and reinforces the doctor's claim to expert knowledge[8,10–13]. These vary between countries as do patients perceptions of the need for antimicrobials to treat infections[8,11,13,14]. One study compared a Dutch and Belgian city, 60km apart, both Dutch speaking but the two cities being historically Protestant and Catholic, respectively[14]. Where the Dutch labelled their upper respiratory tract infections (URTI) as 'colds' or 'flu' the Belgians labelled most episodes as 'bronchitis' and used more antimicrobials. In general, the researchers found that those from a Protestant background were more sceptical about using antimicrobials than those from Catholic backgrounds. This type of observation has led to some authors to speculate that there may be a negative association between the proportion of a country that is Protestant and antimicrobial consumption[2,12,15]. Others have contested this claim[11], but no one has, to the best of our knowledge, formally tested this association. In this paper, we test the hypothesis that the proportion of a country's population that are reported to be Protestant is negatively associated with AMC in Europe. Furthermore, we assess if the pathway through which this operates is via cultural and structural factors associated with Protestantism and AMC.

Two cultural dimensions have consistently been found to explain variations in AMC both within Europe and worldwide[5–8,13,14,16]. These are Hofstede's uncertainty avoidance index (UA) and performance-orientation versus cooperation-orientation index (POCO)[5–8,13,14,16]. Both indices are negatively associated with both the proportion of a country that is Protestant[17] and AMC[5–8,16]. The UA index is a measure of the extent to which a society feels threatened by ambiguous or unknown situations. In high UA cultures, individuals feel discomfort and stress in unstructured situations that are novel[15]. The POCO index (also termed the masculinity index) provides a measure of how performance-oriented cultures are. In high POCO cultures ego needs, assertiveness, targets and success are emphasized, whereas cooperation-oriented cultures place more focus on caring for all members of society, including the weak[14]. An important reason

not to take an antibiotic for an illness such as an URTI is that this will select for AMR – an adverse effect for the population at large. It has been argued that this low-POCO populations are more receptive to this population-benefit message than high POCO-populations[8,18].

The key structural factor found to be associated with AMC is control of corruption (CoC) at country and regional levels[19,20]. Countries with high levels of corruption (low CoC) have poorer institutional controls on prescribing practices and greater influence of pharmaceutical companies both of which can result in increased AMC[12,19,20]. Previous ecological studies have found associations between national level CoC, UA, POCO and the proportion of the country being Protestant[7,8,13,16,21]. Multivariate country-level studies from within Europe and elsewhere have also found that UA and POCO[7,8,18,22] are predictors of AMC and an additional study has found that UA, POCO and CoC are independently associated with AMC[16]. In this ecological study we use structural equation modelling to assess the association between countries' population proportions being protestant and AMC, modelling UA, POCO and CoC as potential mediating variables.

Methods
Data

Antibiotic consumption. Data from the European Surveillance of Antimicrobial Consumption (ESAC) were used as a measure of national general population-level antimicrobial drug consumption[23,24]. ESAC reports antimicrobial consumption as the number of defined daily doses per 1000 inhabitants (DID) following the World Health Organization guidelines[25]. In our study, we used four measures of country-specific antimicrobial drug use in ambulatory care: Total antibacterials for systemic use (ATC group J01), Cephalosporins/other Beta lactams (ATC group J01D), fluoroquinolones (ATC group J01MA), macrolides, lincosamides and streptogramins (ATC group J01F). Data was available from 1998 to 2018 and we used this data to calculate the peak consumption of each of these four classes of antimicrobial over this time period. All countries with available data were used in all the analyses. This data is available from ESAC without restrictions: https://www.ecdc.europa.eu/en/antimicrobial-consumption/database/quality-indicators

Percent protestant. The proportion of a national population that was protestant was sourced from the Pew Research Centre estimates for 2010: https://www.pewforum.org/2011/12/19/table-christian-population-as-percentages-of-total-population-by-country/

UA and POCO. Individual scores for UA and POCO were obtained for each country from Hofstede Insights, freely available from (https://www.hofstede-insights.com/product/compare-countries/) is denoted as masculinity on the website.

Control of corruption. The World Bank has provided indicators pertaining to six dimensions of governance since 1996. We used the dimension (control of corruption) that has been found to be most closely linked to AMC[12,16,17]: Control of corruption (CoC)

is defined as the country-level extent to which public power is exercised for private gain, including both petty and grand forms of corruption, as well as the capture of the state by elites. The index provides each country's score in units of standard normal distribution, ranging from approximately -2.5 (low CoC) to 2.5 (high CoC). The values used are average scores for the years 2013 to 2015, which we calculated from the original data, which was obtained from the following site: http://datatopics.worldbank.org/world-development-indicators/.

Data analysis

A correlation matrix was performed to investigate the relationship between the different variables hypothesized to be associated with AMC. This approach was complemented by scatterplots of the associations between percent Protestant and AMC. We used structural equation modelling (SEM) to analyse the factors predicting AMC. SEM provided a way to analyse and graphically represent the complex direct and indirect pathways between endogenous and exogenous variables. All variables were assessed for non-linearity. No transformation was necessary. The analyses were performed using the SEM-builder in STATA 16. A P-value of less than 0.05 was used as the threshold of statistical significance.

Results

Complete data was available for 29 of 30 countries with AMC data in the ESAC database (Table 1). Data for UA and POCO were missing for Cyprus. Peak total antibacterial consumption varied fourfold between 10.1 DID in the Netherlands and 40.4 DID in Greece (median 21.2 [IQR 16.7-23.9]; Table 2).

The proportion of a country that was Protestant was negatively correlated with the consumption of all antibacterials (r= -0.38; P=0.041), cephalosporins (r= -0.59; P=0.001), macrolides (r= -0.50; P=0.005) and fluoroquinolones (r= -0.53; P=0.003) as well as UA (r= -0.69; P<0.001) and POCO (r= -0.46; P=0.012). It was also positively associated with CoC (r= 0.67; P<0.001; Table 2; Figure 1). UA was positively correlated with all four categories of AMC (all r≥ 0.55; P<0.005) and negatively associated with CoC (r= -0.62; P<0.001). POCO was correlated with three of four categories of AMC and also negatively associated with CoC (r= -0.37; P=0.049). CoC was negatively associated with all four categories of AMC (all r < -0.43; P<0.05).

Predictors of total antibacterial consumption

Structural equation modelling revealed that UA predicted community antimicrobial consumption (direct effect coef. 0.15, 95% Confidence Interval [CI] 0.04-0.26; Figure 2; Extended Data). The percent Protestant exerted only an indirect effect on consumption (coef. -0.13, 95% CI -0.21- -0.05; Extended Data). This effect was mediated predominantly via its effect on UA (direct effect coef. 0.15, 95% CI 0.04-0.26). The model explained 37% of the variation in consumption ().

Analysis by antibiotic class

The SEM analysis found that the consumption of each class of antimicrobial was positively associated with UA and POCO (Figure 2; Extended Data). Only in the case of POCO predicting

fluoroquinolone consumption was this association not statistically significant (Figure 2; Extended Data). Once again, the percent Protestant only exerted an indirect effect on AMC. This effect was mediated by UA and POCO both of which were negatively associated with percent Protestant. For each class of antimicrobial, the effect of UA explained the greatest proportion of variation in consumption (Extended Data). Overall the models explained 52% to 61% of the variation in consumption (Extended Data).

Discussion

Our results recapitulate those from other studies that UA and, to a lesser extent, POCO mediate a considerable proportion of the variation of AMC in Europe[6,8,10,16]. Whilst percent Protestant has little to no direct effect on AMC, our analysis found it has an indirect effect via its negative association with UA and POCO. The fact that this effect was similar for all 4 categories of antimicrobials investigated makes this finding more robust.

These results are compatible with the theory that the profound rupture in European society in the 16th century induced by the Reformation may have had enduring effects that explain a portion of the contemporary variations in antimicrobial consumption between European countries. Our study provides evidence supportive of the thesis that this effect is mediated via Protestantism's effect on two cultural variables – UA and POCO.

The reason that predominantly Catholic countries have higher UA and POCO scores is not clear, but may be related to factors such as the rituals and certainty-of-Faith that have characterized Catholicism[11,14,17,26]. It has been argued that Protestant teaching provided less certainty-of-Faith, encouraged more discussion, discouraged rituals, promoted austerity/simplicity and placed the locus of control less in the priest or church but in each individual[12,17,26]. Protestant populations may therefore be more tolerant of uncertainty, have less faith in quick fix solutions and be more amenable to discussions about therapeutic strategies not involving antibiotics[12,17]. Protestants have also been found to have more trust in the 'self-healing power of the body', which has in turn been found to be correlated with scepticism towards the use of antibiotics[14]. Both patients and doctors in historically Protestant, low-UA populations may therefore be more receptive to antibiotic stewardship messages that strongly discourage antibiotics for infections such as URTIs[2]. High-UA societies on the other hand, may be less receptive to stewardship messages due to the uncertainty of 'what if the URTI is caused by a bacterial infection?'[4,8,10].

There are a number of important limitations to this analysis. We should be extremely guarded about drawing causal inferences concerning processes hundreds of years ago based on contemporary data from a small selection of countries. We did not control for possible confounders in the association between proportion of the population Protestant and AMC. We did not control for socio-economic markers such as GDP/capita as previous analyses have found that these did not explain differences in AMC within Europe[16,18]. Our sample size was also too small to justify controlling for a large range of confounders. There are a number

Table 1. National antimicrobial consumption (defined daily doses/1000 individuals/day), Uncertainty Avoidance (UA) Index, Power oriented vs. cooperation oriented (POCO) Index, Percent Protestant in 30 European countries.

Country	Protestant (%)	UA	POCO	CoC	All AB	Fluoroquinolone	Macrolide	Cephalosporin
Austria	5.1	70	79	1.51	14.2	1.5	3.9	1.95
Belgium	1.4	94	54	1.61	23.9	2.77	3.78	4.41
Bulgaria	0.6	85	40	-0.26	22.7	2.87	3.97	4.45
Croatia	0.3	80	40	0.2	21.1	1.61	3.5	4.11
Cyprus	0.1	NA	NA	1.11	29.2	7.02	4.0	7.01
Czech Republic	3.5	74	57	0.34	17.4	1.37	3.98	2.21
Denmark	81.9	23	16	2.29	16.7	0.57	2.66	0.05
Estonia	21.2	60	30	1.26	14.4	0.92	2.49	1.22
Finland	80.2	59	26	2.21	18.6	0.95	2.38	2.38
France	1.8	86	43	1.32	28.8	2.18	6.06	4.82
Germany	34.8	65	66	1.83	14.5	1.51	2.8	3.22
Greece	0.3	112	57	-0.08	40.4	2.97	12	9.5
Hungary	21.6	82	88	0.21	21.1	2.69	4.14	3.35
Iceland	91.3	50	10	1.89	23.1	1.12	1.89	0.76
Ireland	5.1	35	68	1.59	21.3	1.04	4.38	2.01
Italy	1.3	75	70	0.01	23.7	3.46	5.3	3.87
Latvia	20.1	63	9	0.4	12.1	1.07	2.04	0.66
Lithuania	1.4	65	19	0.53	22.1	1.41	2.38	3.2
Luxembourg	3.2	70	50	2.1	25.4	2.85	5.5	5.78
Malta	1.1	96	47	0.91	20.7	3.06	4.53	5.68
Netherlands	21.8	53	14	1.97	10.1	0.91	1.5	0.13
Norway	83.3	50	8	2.25	16.5	0.56	2.1	0.29
Poland	0.4	93	64	0.63	23.8	1.48	6.01	3.99
Portugal	1.6	99	31	0.95	22.4	3.7	4.4	3.77
Romania	6.3	90	42	-0.11	28	3.71	3.18	5.33
Slovakia	9.8	51	100	0.14	25.8	2.41	6.3	6.21
Slovenia	1.2	88	19	0.74	16.8	1.53	3.91	0.91
Spain	1	86	42	0.71	25.6	2.88	3.4	2.62
Sweden	64.4	29	5	2.23	15.5	1.09	1.02	0.62
United Kingdom	54.5	35	66	1.77	18.5	0.62	3.24	1.08

of fundamental problems with classifying countries by religion. To an important extent, countries have a fluid mix of particular religions and both the relative sizes of the religions and the nature of these religions vary over time[26]. There are also considerable differences within a religion such as differences between Catholicism in different countries and regions[17]. This problem is compounded by our percent-Protestant-variable which combines a heterologous group of Catholic, Orthodox and other groups into one non-Protestant category. This classification could, however, be defended since our hypothesis is that low AMC was a byproduct (spandrel) of the Protestant Reformation. This line of thought is strengthened by a European study that found that the

Table 2. Pearson's correlation coefficients between study variables. Significance levels are highlighted by * for P<0.05, ** for P<0.005. Abbreviations: All AB – All antibacterials, CoC – Control of Corruption; UA- Uncertainty Avoidance Index; POCO – Performance Oriented vs. Cooperation Oriented society.

	Protestant (%)	UA	POCO	CoC	All AB	Cephalosporin	Macrolide	Fluoroquinolone
Protestant (%)	1.0000							
UA	-0.69*	1.00						
POCO	-0.46*	0.23	1.00					
CoC	0.67**	-0.62**	-0.37*	1.00				
All AB	-0.38*	0.55**	0.34	-0.44*	1.00			
Cephalosporins	-0.59**	0.68**	0.52**	-0.52**	0.85**	1.00		
Macrolides	-0.50**	0.57**	0.54**	-0.47*	0.78**	0.79**	1.00	
Fluoroquinoloes	-0.53**	0.74**	0.38*	-0.42*	0.62**	0.73**	0.38*	1.000
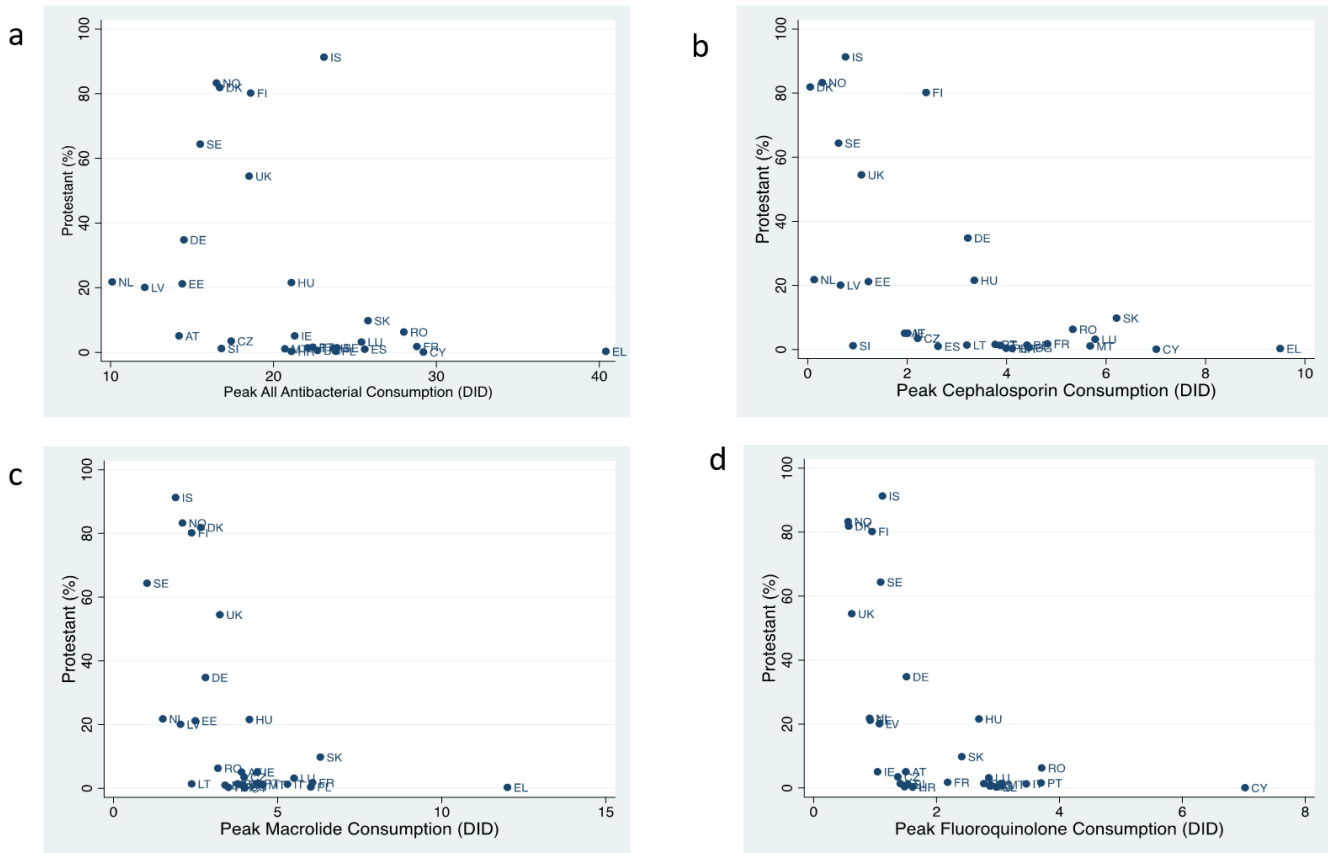
Abbreviations: AT, Austria; BE, Belgium; CZ, Czech Republic; DE, Germany; DK, Denmark; EE, Estonia; EL, Greece; ES, Spain; FI, Finland; FR, France; HR, Croatia; HU, Hungary; IE, Ireland; IT, Italy; LU, Luxembourg; LV, Latvia; NL, the Netherlands; NO, Norway; PL, Poland; PT, Portugal; SE, Sweden; SI, Slovenia; SK, Slovakia; UK, United Kingdom.

Figure 1. Scatter diagrams of percent of a country that is Protestant and consumption (defined daily doses/ 1000 individuals/ day – DID) of all antibacterials (**a**), cephalosporins (**b**), macrolides (**c**) and fluoroquinolones (**d**) in 30 European countries.

percent of the population describing themselves as atheist as opposed to religious was strongly associated with lower AMC[9]. The study did not include a religious denomination variable but the authors noted evidence that secularization has been more pronounced in historically Protestant countries[26] and concluded that the lower AMC in these countries may be indirectly related to
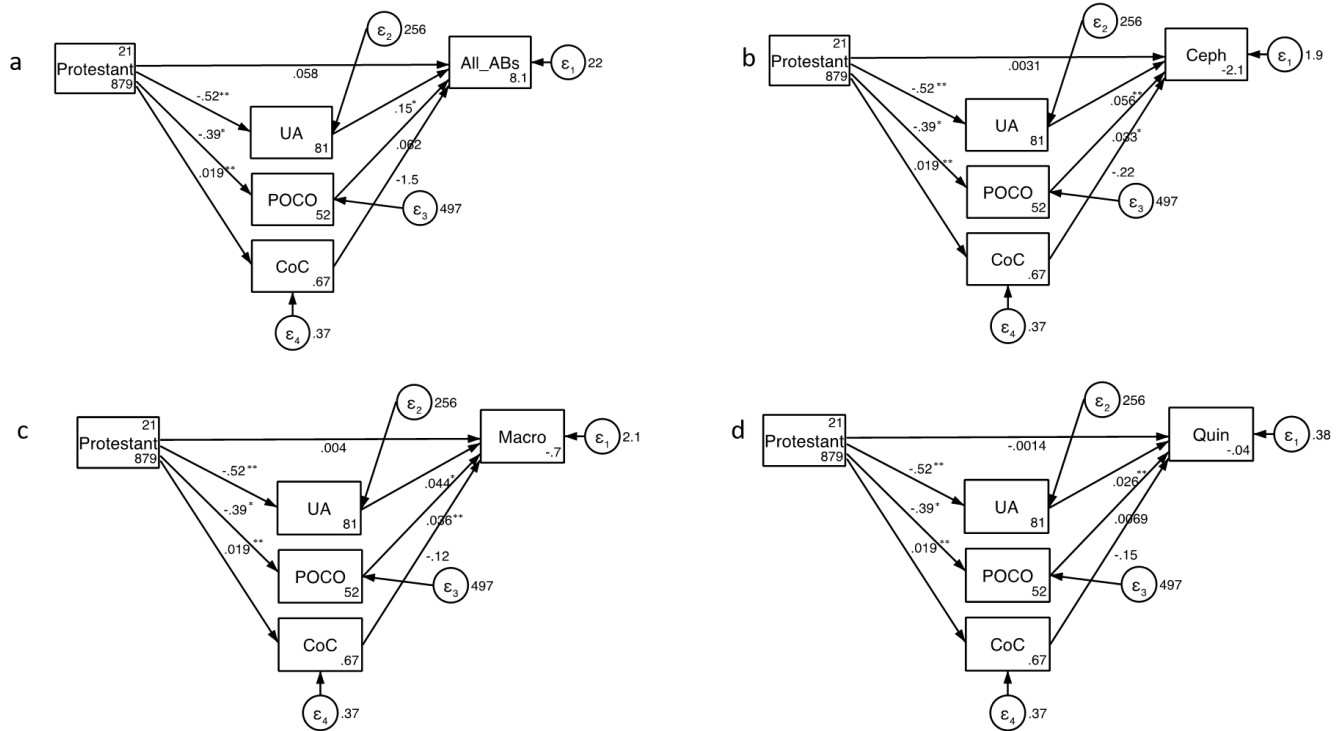
Figure 2. Structural equation modelling of predictors of consumption of total antibacterials (**a**), cephalosporins (**b**), macrolides (**c**) and fluoroquinolones. The numbers next to the arrows are coefficients and their significance is indicated as follows: * P<0.05, ** P<0.005 (Abbreviations: All AB – All Antibacterial consumption; Ceph – Cephalosporins, CoC – Control of Corruption, Macro – Macrolides; POCO – Performance Oriented vs. Cooperation Oriented Index; Quin – Fluoroquinolones; UA - Uncertainty Avoidance Index).

Protestantism. We considered reverse causation unlikely, but this cannot be excluded. Finally, the various dimensions of Hofstede's model have been criticized as being over-simplifications of cultural differences[27].

A spandrel is an architectural term referring to the tapering triangular space formed by the intersection of two rounded arches at right angles[28]. Gould argued that "evolutionary biology needs such an explicit term (spandrels) for features arising as by-products, rather than adaptations, whatever their subsequent exaptive utility…Causes of historical origin must always be separated from current utilities; their conflation has seriously hampered the evolutionary analysis of form in the history of life"[28]. Previous analyses have found evidence of a range of spandrels exerting their effects hundreds of years later[29,30]. One example comes from Southern Africa, where differential HIV prevalence by ethnic group has been linked to distant historical processes. A number of colonial policies that were imposed on indigenous ethnic groups practicing polygamous partnering resulted in dense sexual networks that facilitated the spread of HIV in these groups hundreds of years later[29,31]. In contrast, Southern African ethnic groups from European origin have low sexual network connectivity and HIV prevalence. This low connectivity stems primarily from historical processes in Europe many centuries

prior that resulted in forms of monogamous partnering being normative[29]. Appreciating this historical connection has been shown to have three major benefits. Firstly, it provides an explanation as to how dramatic differences in behaviour and disease outcome can emerge. Secondly, it provides clues to the high HIV-prevalence populations as to how to tackle the underlying determinants of high prevalence. Thirdly, it does this in a non-judgemental way. Contemporary populations cannot be held responsible for events and processes occurring centuries prior[29].

Similar arguments could be made as to the relevance of the current analysis. It provides a possible deep historical explanation for how differences in AMC have emerged in Europe. It suggests that the lower AMC in predominantly Protestant countries could be explained by cultural differences that emerged in a process starting centuries ago. If this is correct, then this insight should generate greater understanding for how much harder antibiotic stewardship work is in non-Protestant countries. This is not an argument that stewardship is impossible or should not be attempted, but rather that campaigns might need to be more intense to achieve the same outcomes. It also provides further evidence that stewardship efforts need to be adapted to the local cultural context[6,7]. A concrete example of this would be to incorporate rapid diagnostic tests (that can remove uncertainty

about bacterial infections) as a part of stewardship campaigns in high UA populations[7]. If evidence were to come to light of ways to decrease uncertainty avoidance and favour cooperation- vs. performance-orientation these may also be considered as upstream interventions to reduce AMC.

Data availability
Underlying data
All data underlying the results are available as part of the article and no additional source data are required.

Extended data
Figshare: Thank Martin Luther that ciprofloxacin could cure your gonorrhoea? Ecological association between Protestantism and antimicrobial consumption in 30 European countries, https://doi.org/10.6084/m9.figshare.12994439.v1[32].

This project contains the following extended data:
- SEM models and estimates of Goodness of Fit

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

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    http://www.doi.org/10.6084/m9.figshare.12994439.v1

Open Peer Review

Current Peer Review Status: ✔ ❓

❓ **Peter J Collignon**

Infectious Diseases and Microbiology, Canberra Hospital, Australian National University, Acton, Australia

This is an interesting paper with the thesis being that a Catholic tradition will result in higher use of antimicrobials than having a protestant background. While there appears to be an association using the limited parameters looked at in this study, that is very different from being able to infer any cause-and-effect relationship, however.

The countries looked at that are "protestant" are generally colder as well. So maybe temperature has as big an effect. Or do those with a catholic tradition have more sexual encounters than those of a protestant background – especially as the focus is on *gonococcus*? But these and many other parameters were not measured to see what influence, if any, they might have in their correlation analysis.

They only looked at a few parameters to assess the relationship with Antimicrobial consumption; poor controls on corruption (CoC), high uncertainty avoidance (UA) and performance vs. cooperation orientation (POCO) and proportion of a population that was protestant. These are not enough parameters given the complexities involved with antimicrobial resistance and consumption (e.g. many more parameters were looked at by Collignon P, Beggs JJ, Walsh TR, Gandra S, Laxminarayan R, in Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. Lancet Planet Health. 2018 https://www.sciencedirect.com/science/article/pii/S2542519618301864?via%3Dihub)[1]

It is important to note that even of the limited parameters they looked at, the percent Protestantism, was the least associated parameter with antimicrobial use. As they note "Once again, the percent Protestant only exerted an indirect effect on AMC. This effect was mediated by UA and POCO both of which were negatively associated with percent Protestant. For each class of antimicrobial, the effect of UA explained the greatest proportion of variation in consumption."

In a paper entitled "Corruption and use of antibiotics in regions of Europe" (their reference 19), Rönnerstrand, and Lapuente show that within countries in Europe, there are marked variations by regions and presumably not likely influenced by the percent of that country's population that were protestant, as it also occurs within countries where there is little Protestantism e.g., Italy. What did correlate, however, were the local levels of corruption. This again is what these authors have shown in their data.

So, in summary, the authors (Kenyon and Fatti) did show an association with Protestantism and antimicrobial consumption, but even though they only looked at limited parameters, their own data suggest religion itself plays little part in any cause and effect. It appears that lower consumption of antimicrobials is likely very much more associated with regions that have better governance and lower corruption rates, rate than their conclusion of cultural differences that emerged in the Reformation.

References
1. Collignon P, Beggs J, Walsh T, Gandra S, et al.: Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. *The Lancet Planetary Health*. 2018; **2** (9): e398-e405 Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Microbiology, Infectious diseases, Antimicrobial resistance

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 04 May 2022

Chris Kenyon, Institute of Tropical Medicine, Antwerp, Antwerp, Belgium

We thank the reviewer for their useful comments. We agree that we need to be very careful with the conclusions we draw from this study for all the reasons outlined by the reviewer. We acknowledge that the Collignon *et al*., paper referred to by the reviewer is one of the most definitive ecological analyses of the drivers of AMR globally. This is however different to our research questions which were: what are the determinants of antimicrobial

consumption (AMC), is the percent of a countries population that is Protestant associated with AMC and if so is this association a direct or an indirect one (via UA, POCO or CoC)?

As the reviewer notes, we find that there is a weak positive association and the effect is indirect- acting via UA and POCO. One parsimonious explanation for these findings is that an upstream determinant of UA and POCO is the percent of the population that is Protestant. As we note in the discussion, while we cannot prove that this is the causal pathway, this is at least a plausible way to interpret the data. To the best of our knowledge, this is the first time that statistical evidence has been produced to back up the percent Protestant-POCO/UA-AMC pathway.

Once again we have endeavoured in our discussion to make it very clear that whilst we find some statistical support for this pathway, this does not constitute strong evidence that this pathway played any role in the genesis of differential levels of AMC in European countries.

To address the reviewer's valid concerns, we have added the Collignon *et al.* reference and the following text in the discussion (4th paragraph):

We also did not control for differences in environmental temperatures. Southern European countries tend to be both hotter and more Catholic than Northern European countries. A previous ecological study has found that environmental temperature is associated with the prevalence of certain types of antimicrobial resistance [33]

Competing Interests: No competing interests

Reviewer Report 03 March 2021

✔ **Christoph M. Tang**
Sir William Dunn School of Pathology, University of Oxford, Oxford, UK

This is an interesting and somewhat provocative paper that shows a relationship between events several hundred years ago and current use of antimicrobials.

The authors show a link between the consumption of antimicrobials in a given country and the prevalence of Protestantism.

As the authors correctly acknowledge in their discussion, studies of this nature cannot derive causal relationships (and only highlight associations) and they acknowledge that many potential confounding factors are likely to be at play. They did not control for socio-economic markers (eg

GDP), reasoning that '*these did not explain differences in AMC within Europe*'. Whilst this might be true when considering socioeconomic factors on their own, it does not mean that these factors would not impact findings when incorporated into a multivariate analysis. The authors also discuss the multiplicity of faiths within many individual countries (which report overall antibiotic consumption levels and not levels according to religion) and how the practice and teaching of the same religion can differ between countries (*There are also considerable differences within a religion such as differences between Catholicism in different countries and regions*).

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Microbial pathogenesis and virulence

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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