BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020488
Article Type:	Research
Date Submitted by the Author:	07-Nov-2017
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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Infectious diseases
Keywords:	Antimicrobial resistance, COMPLEMENTARY MEDICINE, Integrative Medicine, Antibiotic prescription rate

NHS GP surgeries employing GPs additionally trained in Integrative or Complementary Medicine have lower antibiotic prescribing rates.

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Abstract

Objective

To determine differences in antibiotic prescription rates between conventional General Practice (GP) surgeries and GP surgeries employing General Practitioners (GPs) additionally trained in Integrative Medicine (IM) or Complementary and Alternative Medicine (CAM) (referred to as IM GPs) working within NHS England.

Design

Retrospective study on antibiotic prescription rates per STAR-PU (Specific Therapeutic group Age-sex weighting Related Prescribing Unit) using NHS digital data over 2016. Publicly available data were used on prevalence of relevant comorbidities, demographics of patient populations and deprivation scores.

Setting

Primary Care

Participants

7283 NHS GP surgeries in England

Primary outcome measure

The association between IM GPs and antibiotic prescribing rates per STARPU with the number of antibiotic prescriptions (total, and for respiratory- and urinary tract infection separately (RTI/UTI)) as outcome.

Results

IM GPs were comparable to conventional GPs in terms of list sizes, demographics, deprivation scores and comorbidity prevalences. Despite the very small proportion of NHS IM GPs in England (n=9), negative binomial regression models showed that statistically significantly fewer total antibiotics (RR: 0.79, 95% CI: 0.66 – 0.94) and RTI antibiotics (RR 0.73, 95% CI:0.60 – 0.89) were prescribed at IM GP surgeries compared with conventional NHS GP surgeries. In contrast, the number of antibiotics prescribed for UTI were similar between both practices (RR: 0.91, 95% CI: 0.91 – 1.17).

Conclusion

Evidence from the IM GP surgeries shows that a further decrease in prescribing in conventional GP surgeries might be possible. However, future research should include the differences in consultation behaviour of patients self-selecting to consult a IM GP or conventional surgery, and its effect on antibiotic prescription. Additional treatment strategies for common primary care infections used by this small number of IM GPs should be explored to see if they could be used to assist in the fight against AMR.

Strengths and limitations

- Use of NHS digital data on antibiotic prescription per STARPU provided a comprehensive insight into the prescribing practices of total antibiotics, and for respiratory- and urinary tract infection

separately in conventional GP surgeries and GP surgeries employing a GP additionally trained in Integrative Medicine (IM GPs).

- IM GP surgeries were comparable to conventional GP surgeries in terms of list sizes, demographics, deprivation scores and comorbidity prevalence.
- Accessibility of IM/CAM within the NHS in General Practice in England is very limited. IM/CAM provision is currently almost exclusively private in the UK.
- Results are limited by the lack of data on 1) number of consultations, 2) individual deprivation scores and 3) continuum of care.

Word count

N=3488

4 Tables

Introduction

Antimicrobial resistance (AMR) and the inappropriate use of antibiotics represent a serious threat to public health internationally.[1] Antibiotics are currently indispensable throughout the healthcare system, and the consequences of AMR, not only in primary care, but also in major surgery and cancer treatment for example, are dire. Fortunately, reductions in antibiotic use have been shown to be associated with a reduction in some resistance[2], and the reduction in the use of antibiotics, especially in primary care, to control the development of AMR is therefore a pressing national and international priority.[1 3]

In the UK, 74 percent of antibiotics are prescribed in primary care making this one of the most important contributors to the development of AMR.[4] Antibiotics are commonly prescribed for respiratory tract infections (RTIs) in adults and children in primary care, and are the reason for 60% of all antibiotic prescribing in general practice in the UK.[5] Several studies have shown that there is substantial overprescribing of antibiotics for, often viral and self-limiting, RTIs in primary care.[6-8] Consequently, there is a large potential to reduce antibiotic prescribing for RTIs, potentially by using other treatment strategies that do not increase the development or spread of AMR. Urinary tract infections (UTIs) are the most common confirmed bacterial infection, with about half of all women experiencing one of more UTIs in their life time. [9] Most women with UTIs are currently treated with antibiotics, with longer duration and multiple courses associated with higher AMR rates.[9 10] However, guidelines indicate that antibiotics should be prescribed for UTIs and overprescribing seems to be much less common than for RTIs[11]. Consequently, it may be easier to safely reduce antibiotic prescribing for RTIs than for UTIs in primary care.

There is great variability in the use of antimicrobial medications between countries, with the lowest prescription rates reported in northern European nations, and higher rates in southern Europe and the US. [12-14] Variations in the prescription of antibiotics both within and between countries may indicate poor practice with inappropriate use of antibiotics which increases the risk of adverse events for the patient[9] , wastes health care resources[15] and contributes to the rise in antibiotic resistance. [13] Previous studies have shown that a complex array of factors influence antibiotic prescribing, which may explain the wide variety of antibiotic usage both at the clinician level and worldwide. The attitudes of both doctor[16-18] and patient[19-21] are shown to be of major significance in prescribing decisions.

GPs as a professional group are expected to react homogenously to external demands, basing their prescription on objective measures and (local) guidelines. However, it is possible that different views on medicalisation, differences in guidelines between countries and between specialists and the use of complementary and alternative medicines (CAM)/integrative medicine (IM)[22-24] could result in variations in antibiotic prescribing. The association between the use of CAM/IM by GPs and antibiotic prescribing has so far not been widely scrutinised.

The aim of this study is to determine the differences in antibiotic prescription rates between 'conventional GPs' and GP surgeries employing a GP additionally trained in IM/CAM (hereafter referred to as Integrative medicine (IM) GPs), and the association between having an additional training in CAM/ IM and antibiotic prescription (measured as total antibiotics, respiratory tract infection (RTI) specific antibiotics and urinary tract infection (UTI) specific antibiotics) within the NHS in England.

Methods

IM GP surgeries

To identify NHS General Practices employing an IM GP in 2016, two sequential tasks were required. Firstly, IM GPs were identified and then a current working link was made to an NHS General Practice.

(i) Identification of NHS GPs registered with an additional CAM qualification

We included the 'Big 5' CAM therapies as defined in a report by the House of Lords in 2000[25] (chiropractic, osteopathy, acupuncture, herbal medicine and homoeopathy); as well as Anthroposophic Medicine (AM). AM is an extension of conventional medicine and incorporates a holistic approach to people and nature and to illness and healing and is established in 80 countries, mostly in Central Europe.[26] AM has been included so that future comparison with data in other European countries is possible.

In the UK each of these six therapies are either state regulated (osteopathy and chiropractic) or have voluntary regulation (including a voluntary regulatory body for mainstream healthcare practitioners in the case of acupuncture and homoeopathy). The regulatory bodies were therefore initially approached by email to check the best route of establishing which practitioners on their registers were trained as a conventional GP and trained in IM/CAM as well. Details of the organisations and methods by which IM GPs were identified are indicated in Table 1. Where organisations were not able to provide this information, searches were made of the online registers (between May and June 2017) for the following:

1. Location – the registers enabled us to search for practitioners either a country (England/ UK) limit or by county (in the latter case, all English counties were checked, including recent boundary changes).
2. Qualification – in some databases, only healthcare professionals (e.g. practitioners qualified in biomedicine) were included, and GP status was specified. Where this was not the case, titles were given and the absence of the title 'Dr' was used to exclude practitioners from our study. Where qualifications were also identified, practitioners with PhDs but not being a GP could be excluded. And if no additional information was given on the register, online searches were made of the practitioner to establish their professional qualifications. In all cases, putative IM GPs were checked against the General Medical Council (GMC) register, to confirm whether they were currently permitted to work in medical practice in the UK.

(ii) Identification of NHS General Practices employing IM GPs

Practice location(s) were indicated for each GP registrant identified in the CAM registers indicated in Table 1. These workplaces were then checked against both the practice websites and the NHS website (www.nhs.uk), which lists all NHS practices and gives information such as staff lists. This

acted to confirm the working location of the GP and whether this practice offered provision within NHS England.

Data

Monthly prescribing data was obtained from NHS Digital. NHS Digital collect data and information about a wide range of General Practice (GP) services, for many different organisations and purposes. It also collates all primary care prescribing data. This data is released for monthly download via the NHS Digital website (http://digital.nhs.uk/searchcatalogue). Data is released at the specific health care provider level and volumes are provided by full British National Formulation code (BNF code). To determine mean antibiotic prescription rates we used the total number of oral antibiotic prescriptions per general practice for the most recent calendar year for which antibiotic prescribing was publicly available via the NHS digital website (Jan 2016 – Dec 2016).

Specific Therapeutic group Age-sex weighting Related Prescribing Units (STAR-PU)

STAR-PU have been used as the denominator instead of the number of registered patients as STAR-PUs allow more accurate and meaningful comparisons within a specific therapeutic group by considering the types of people who will be receiving that treatment. The amount of STAR-PU per practice was estimated by multiplying the number of patients in each age-gender category[27].

Comorbidities

The prevalence of various comorbidities that may adversely influence the outcome of infections, based on the conditions that indicate high-risk patients who qualify for the free seasonal influenza vaccination programme [28], was also measured to identify potential case-mix differences that may explain different antibiotic prescribing rates. General practice-specific prevalence is available for the following high-risk comorbidities via the Quality Outcomes Framework (QOF) indicators at the NHS digital website: asthma, cancer, chronic kidney disease, chronic obstructive pulmonary disease (COPD), heart failure and diabetes. We extracted comorbidity prevalence for the financial year 2015-2016.

Indices of multiple deprivation

Previously it has been shown that indices of multiple deprivation are indicators of poor health in a population. Tosas Auguet et al.[29] for example, found that more deprived areas are at higher risk of Methicillin-Resistant Staphylococcus Aureus (MRSA) infection. The most recent index of multiple deprivation was calculated in 2015 and is available from the Department for Communities and Local Government. [30] Deprivation scores are available at a lower-layer super output area (LSOA), which consists of approximately 1,500 residents each. Linkage of the data from NHS Digital was performed using a lookup table from NHS digital. Where a practice served multiple LSOAs, the average deprivation score for that practice was calculated, weighted by the number of patients in each LSOA.

The final dataset included only practices that were present in both the comorbidity and deprivation, and antibiotic prescribing files. We removed outliers based on practice size, since there were some doubts about the validity of this data (e.g. a practice with 157 patients registered). We removed the outer 2% of data based on practice size.

Statistical analysis

All analyses are performed on GP surgery level (hereafter referred to as GPs). Potential differences in antibiotic prescribing rates per STAR-PU between the IM and conventional GPs were evaluated. NHS Digital defines a prescription item as: 'a prescription item is a single supply of a medicine, dressing or appliance written on a prescription form. If a prescription form includes three medicines, it is counted as three prescription items. We tested for between group differences using a random effects meta-analysis model for proportions (R package 'meta'). For continuous variables like the number of STAR-PU per practices Mann-Whitney U tests were used to test for statistically significant differences.

The association between the IM GPs and antibiotic prescribing rates per STAR-PU was assessed using negative binomial regression models with the number of antibiotic prescriptions as the outcome and the natural logarithm of the number of STAR-PU per practice as an offset. A negative binomial regression model was used as this type of regression model can handle count data (number of antibiotic prescriptions), accounts for differences in the number of antibiotics purely caused by practice size (by including the offset), and can still provide valid results when the variance in antibiotic use does not equal the mean antibiotic use.[31] Both crude results and results adjusted for additional variables to correct for potential confounding are presented.

We also evaluated associations between IM GPs and antibiotics commonly used for respiratory tract infection (RTI) (amoxicillin, amoxicillin and enzyme inhibitor, ampicillin, clarithromycin, doxycycline, erythromycin, and phenoxymethylpenicillin) and for urinary tract infection (UTI) (cephalexin, cefixime, ciprofloxacin, nitrofurantoin, pivmecillinam, and trimethoprim).[32]

Results

Identification of NHS IM GPs in England

850 CAM practitioner records were checked against the various CAM registers (Table 1) to identify 21 GPs who are conventionally trained as a GP and also trained in CAM at 19 NHS GP surgeries in England (Table 2). It should be noted that the 850 registrants were not the total numbers of CAM practitioners on the registers, as (as previously described) some registers permitted limiting searches to medical practitioners, or more specifically to medically qualified doctors.

While some practices were publicly working in an IM structure, in others it was unknown whether the identified GP was using IM/CAM or indeed whether or the practice permitted this, as no mention was made of it on the websites (including no reference to privately available CAM clinics). General Practices were therefore classified into two subsets as indicated in Table 2. There were further IM GPs on the register who were either not practicing (or at least not in England), or working in private practice. As any level of IM/CAM activity in subset 2 practices could not be determined, it was decided to exclude these GP surgeries from further analysis. Table 2 also shows the CAM therapies for which each IM GP in our subsequent analysis was registered.

Antibiotic prescription rates

Table 3 presents the baseline characteristic of the NHS IM GP surgeries compared to those characteristic of NHS conventional GPs in England. It also shows the prevalence of various comorbidities that may adversely influence the outcome of infections and may consequently influence antibiotic prescribing. The patient populations of both kinds of practices were comparable for most of the listed comorbidities. Statistically significant differences (P<0.05) between the IM GP- and conventional GP surgery patient population were found in the percentage of patients with coronary heart disease, cancer and diabetes, although absolute differences were relatively small. No statistical differences (P<0.05) were found in deprivation score between IM GP surgeries and conventional GP surgeries.

IM GP surgeries and antibiotic prescription rates

Overall within the NHS in England, the median prescription rates of IM GP surgeries were lower for 'any antibiotic' and for 'RTI specific antibiotic' compared to the rates of the conventional GP surgeries over 2016, while the median prescription rates of 'UTI specific antibiotic' per STAR-PU was comparable for the two groups (Table 4).

The Relative Risks (RR) in table 4 were obtained using negative binomial regression models with the number of antibiotic prescriptions as the outcome and taking into account differences in practice sizes. Our analysis show that IM GP surgeries were associated with lower prescriptions of 'any antibiotic' (RR: 0.79, 95%C.I: 0.66 – 0.94) and with lower prescriptions of 'RTI specific antibiotic' (RR: 0.73, 95%C.I: 0.60 – 0.89). Patients consulting an IM GP surgery were 21% less likely to get 'any antibiotic' prescription compared to those who consulted a conventional GP surgery. Receiving a RTI specific antibiotic prescription was 27% less likely among those who consulted an IM GP surgery compared with those who consulted a conventional GP surgery. No statistically significant difference ($P<0.05$) was found in the number of prescriptions of UTI specific antibiotic prescriptions per STAR-PU between IM GP surgeries and conventional GP surgeries within the NHS in England.

Adjustment for deprivation score or diabetes resulted in virtually identical results. For 'any antibiotic' if adjusted for deprivation score the RR for IM GP surgeries remains virtually identical RR: 0.78 (95% CI: 0.64 – 0.97), and for diabetes RR: 0.80 (95% CI: 0.65 – 0.99). This was the case regardless of which confounder was added to the model, however adjusting for multiple potential confounders was not possible due to the small number of cases.

Discussion

There were 7274 conventional NHS General Practices included in our analyses. This puts into sharp focus the very small number of General Practitioners with an additional training in IM or CAM identified working in NHS General Practice in England. Despite the very small proportion of IM GP surgeries, our data shows that significantly fewer total and RTI antibiotics per STAR-PU were prescribed at IM GP surgeries compared to conventional GP surgeries within NHS England. No statistically significant differences were found in median prescription rate of 'UTI specific antibiotic' per STAR-PU between the two kind of NHS GP surgeries.

Our study shows that accessibility of IM/CAM within the NHS in General Practice is very limited, which limited the number of IM GPs included in our analysis. IM/CAM provision is currently almost exclusively private in the UK, which could be at least partly linked to the austerity measures currently imposed in the UK possibly resulting in NHS IM/CAM provision being withdrawn at a local level in recent years (and imminently nationally). It was seen on practice websites that there was a noticeable amount of 'private' CAM provision available at several NHS surgeries by non-GP CAM practitioners – in weekly clinics for example. However, these surgeries have not been included in our analysis as this study specifically aimed to determine the differences in antibiotic prescribing between conventional GP surgeries and GP surgeries staffing GPs who were additionally trained in IM/CAM.

The small proportion of NHS IM GPs in England asks for careful interpretation of the results. We found that IM GP surgeries prescribed significantly fewer total- and RTI antibiotics compared to conventional NHS GP surgeries. Accounting for one other variable (e.g. deprivation or diabetes) did not change our results, however, due to the low number of cases it was not possible to similarly account for more variables.

Our data is also limited by the lack of information on 1) number of consultations, 2) individual deprivation scores and 3) continuum of care. Firstly, consultation rates might explain most of the variation in antibiotic prescribing. Using the current data, it is not clear whether patients consulting at IM GP surgeries consulted less in general. If this were the case, they may be equally likely to receive antibiotics when they do consult their GP. Besides, previous studies show that the consultation rate is also dependent on the previous likelihood to receive antibiotics for a RTI [33-35]. Future studies should therefore include consultation behaviour/number of consultations as a confounding factor. Furthermore, no statistically significant differences were found in deprivation score on practice level. However, this may be partly because deprivation is area-based and not based on the individuals registered at the different practices. Finally, the data used for our analysis is based on the number of antibiotic 'prescriptions', which may differ from the numbers of antibiotics 'consumed' and does not include information on the continuum of care of patients (e.g. hospital admissions/re-consultation). Future studies using clinical practice data taking continuum of care into account are warranted.

The lower antibiotic prescription rates of IM GPs are in line with the current national guidance aimed at reducing antibiotic usage and AMR. [1]. IM GPs might possible comply more closely with this guidance. However, the difference found could also be partly explained by the fact that patients who consult IM GPs might demand less for antibiotics, and that GPs in IM surgeries have other avenues to offer to patients than antibiotics or that they are more confident to delay prescriptions and to assert themselves against the wishes of those patients who appear to want antibiotics. Our results are in line with a yet unpublished pilot study in The Netherlands in which the prescription of antimicrobials for systemic use in 23 unselected anthroposophic GP surgeries was compared to the national mean GP figures for the years 2012 – 2014. On average AM GPs in the Netherlands prescribed less antimicrobials: -13% (2012), -10% (2013) and -7% (2014).

Despite the differences we found in RTI antibiotics, no statistical significant differences were found in UTI antibiotics prescription rates between the two kind of NHS GP surgeries. This might reflect current UK GP clinical guidance. For the majority of RTIs it is recommended that antibiotics should be avoided or delayed, so that this is an area where the desired reduction in prescribing could take place. In the case of UTIs, antibiotics are advised more readily. [32] For several RTIs, including common colds, sore throat, sinusitis and acute bronchitis, randomized controlled trials (RCTs) have shown that antibiotics provide no, or negligible benefit compared to placebo[36-39]. As such, symptom management with paracetamol, ibuprofen or the use of CAM therapies for RTIs may safely reduce antibiotic prescribing among patients with a low risk for pneumonia. A recent RCT comparing ibuprofen with fosfomycin treatment for UTIs indicates that it may be more difficult to safely reduce antibiotic prescribing for UTIs using a similar approach.[40]

Attitudes of GPs to IM/CAM are extremely important for it to remain available within the NHS. A 2015 study of these attitudes in England, showed that, despite demand for CAM amongst the general public, GPs remain concerned about its limited evidence base as well as the lack of regulation of CAM practitioners. Nevertheless, those questioned continue to see a role for CAM in clinical practice. [41] The impact which any one IM GP could have in terms of antibiotic prescribing may vary hugely between practices partly depending on their status at the practice - as a partner or a salaried employee for example, or as a full-time or part-time worker. In the presented analysis we did not include NHS GP practices that are offering NHS IM/CAM provision by a 'non-GP NHS CAM practitioner' or private IM/CAM practitioner. However, having even one CAM contact within a surgery might give the possibility for others to experience CAM perspectives either formally or informally from them, and for long-held attitudes to be perhaps modified.

In line with Hawker et al [42], our results suggest that a further decrease in prescribing in conventional surgeries might be possible. It may be that advice should be sought from this small number of surgeries to establish whether their daily clinical practice may differ from other surgeries and whether this could be used to assist others in the fight against AMR.

Although this study found only a small number of NHS CAM practitioners working in England, the differences seen in prescribing rates at the IM GP surgeries warrant further study. In addition, analysis in comparison with other countries are indicated. As the clear majority of CAM practitioners (mainly non-GPs) work privately in England, there is also potential for research into non-antibiotic strategies in private practice, and to analysis of how these practitioners work with their patients' NHS GPs in this regard. However, as patients who self-select to consult IM GPs might be less likely to demand antibiotics, differences in lifestyle and the 'tranferabilty of lifestyle skills' need to be taken into account as well in future study design.

Contributor ship statement

- Substantial contributions to the conception and design of the work; EvdW/ LD/PvF/EB
- Acquisition, analysis, or interpretation of data for the work; EvdW/ LD
- Drafting the work and revising it critically for important intellectual content; EvdW/ LD/PvF/EB
- Final approval of the version to be published: EvdW/ LD/PvF/EB
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: EvdW/ LD/PvF/EB

Competing interests

None declared

Funding

This research was supported in part by an unrestricted grant of WALA Heilmittel GmbH, Germany.

Data sharing statement

Data are available through NHS digital

Acknowledgement

The authors gratefully acknowledge the statistical support of Dr Koen Pouwels (Senior Mathematical/Economic Modeller)

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Table 1. Organisations from which details of training in IM/CAM of GPs were obtained

CAM specialism	Organisation	Website	Method for extracting GP information
Osteopathy	General Osteopathic Council	www.osteopathy.org.uk	Search of online database
Chiropractic	General Chiropractic Council (GCC)	www.gcc-uk.org	GCC staff identified GP registrants
Acupuncture	British Medical Acupuncture Council	www.medical-acupuncture.co.uk	Search of online database
Herbal Medicine	College of Practitioners of Phytotherapy	www.thecpp.uk	CPP staff identified GP registrants
	National Institute of Medical Herbalists	www.nimh.org.uk	NIMH staff identified GP registrants
	The Register of Chinese Herbal Medicine in the UK	www.rchm.co.uk	Search of online database
	The United Register of Herbal Practitioners	www.urhp.com	Search of online database
	The Association of Chinese Medicine and Acupuncture UK	www.atcm.co.uk	Search of online database
Homeopathy	British Homeopathic Association	www.britishhomeopathic.org	Search of online database
	Faculty of Homeopathy	www.facultyofhomeopathy.org	Search of online database
Anthroposophic Medicine	Anthroposophic Health, Education and Social Care Movement	www.ahasc.org.uk	Search of online database

Table 2. IM GP surgeries subdivision (based on website information)

	Apparent level of CAM practice	CAM (n)
Subset 1 (N=9)	General Practices where an integrative medicine (IM) approach is taken **with CAM-trained GP** (N=4)	Homeopathy (1) Anthroposophic Medicine (2) Acupuncture (3)
	General practices listing CAM therapy provision **with CAM-trained GP** (N=5)	Homeopathy (1) Acupuncture (4)
Subset 2 (N=10)	General practices mention a CAM therapy in the listing of the special interests of the GP, but no other information is given and it is **unclear whether the GP practises this CAM therapy at that site**	

Table 3. Baseline characteristics of included NHS GP surgeries

	Conventional GP surgery	IM/CAM GP surgery **(Subset 1)** $
	median (25th-75th percentile)	**median (25th-75th percentile)**
	n=7274	n=9
Number of registered patients	6698 (4162-9942)	7088 (4037-9534)
Male (%)	49.7 (48.8-50.9)	49.3 (46.9-49.4)
Aged 0-17y (%)	20.5 (18.5-23.0)	21.2 (18.7-22.0)
Aged 18-64y (%)	61.2 (58.7-64.2)	61.9 (60.3-62.4)
Aged 65+ y (%)	17.2 (12.3-21.4)	18.2 (14.0-18.4)
STAR-PU**	3705 (2276-5599)	3716 (2315-5382)
Coronary heart disease (%)	3.3 (2.5-4.0)	2.8 (2.1-3.1)*
Heart failure (%)	0.7 (0.5-0.9)	0.5 (0.4-0.8)
Asthma (%)	6.0 (4.9-6.7)	5.1 (4.8-6.2)
COPD (%)	1.8 (1.3-2.4)	1.0 (0.8-2.0)
Cancer (%)	2.4 (1.7-3.0)	2.5 (2.2-2.9)*
Chronic kidney disease (%)	3.0 (2.0-4.1)	1.9 (1.2-2.9)
Diabetes (%)	5.4 (4.5-6.2)	3.9 (2.9-4.6)*
Deprivation score	0.27 (0.11-0.63)	0.36 (0.15-0.48)

$ *Subset 1: General Practices where an integrative medicine approach is taken with CAM-trained GP (N=4)* ***and*** *General practices listing CAM therapy provision with CAM-trained GP (N=5);*

**p<0.05;*

*** STAR-PU stands for 'oral antibacterials item based Specific Therapeutic Group Age-sex weightings Related Prescribing Units. The amount of STAR-PU per practice was estimated by multiplying the number of patients in each age-gender category by the relevant STAR-PU weights (see methods section for detailed explanation on STAR-PUs).*

Table 4. Median antibiotic prescription rates and Relative Risk (RR) of prescribing antibiotics

	Any antibiotic/ STAR-PU[$] Median (25th-75th percentile)	RTI antibiotic/ STAR-PU[$] Median (25th-75th percentile)	UTI antibiotic/ STAR-PU[$] Median (25th-75th percentile)
Conventional GP surgeries (n=7,274)	1.01 (0.86 – 1.17)	0.56 (0.46 – 0.67)	0.22 (0.17 – 0.26)
IM GP surgeries with CAM trained GP (n=9)	0.79 (0.73 – 0.91)*	0.44 (0.37 – 0.48)*	0.21 (0.19 – 0.23)
	Relative Risk (RR)[$] (95% CI)	**Relative Risk (RR)[$] (95% CI)**	**Relative Risk (RR)[$] (95% CI)**
Conventional GP surgeries (n=7,274)	Ref.	Ref.	Ref.
IM GP surgeries with CAM trained GP (n=9)	0.78 (0.64 – 0.97)*	0.74 (0.59 – 0.94)*	0.91 (0.72 – 1.17)

[$] *This rate is obtained by dividing the total number of antibiotics prescribed by the number of STAR-PU registered.*
$p<0.05$

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page:2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page:2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page:4**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page:5**
Methods		
Study design	4	Present key elements of study design early in the paper **Page:6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page:6, 7**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **Page:6, 7**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page:7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page:7**
Bias	9	Describe any efforts to address potential sources of bias **Page:7**
Study size	10	Explain how the study size was arrived at **Page:6,7,8**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Page:8**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding

		Page:8
		(*b*) Describe any methods used to examine subgroups and interactions **Page:8**
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page:6**
		(b) Give reasons for non-participation at each stage **Page:6**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page: 9, 10 and Table 1, Table 2**
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures **Page: 9, 10 and Table 3, Table 4**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page:9, 10**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page: 11**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page: 11**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page: 11, 12**

Generalisability	21	Discuss the generalisability (external validity) of the study results **Page: 12, 13**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page: 13**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020488.R1
Article Type:	Research
Date Submitted by the Author:	12-Dec-2017
Complete List of Authors:	van der Werf, Esther; University of Bristol, Bristol Medical School Duncan, Lorna; University of Bristol, Bristol Medical School Von Flotow, Paschen; Sustainable Business Institute (SBI) Baars, Erik; Louis Bolk Instituut; University of Applied Sciences, Care
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Infectious diseases
Keywords:	Antimicrobial resistance, COMPLEMENTARY MEDICINE, Integrative Medicine, Antibiotic prescription rate

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Do NHS GP surgeries employing GPs additionally trained in Integrative or Complementary Medicine have lower antibiotic prescribing rates? Retrospective cross-sectional analysis of national primary care prescribing data in England in 2016.

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Abstract

Objective

To determine differences in antibiotic prescription rates between conventional General Practice (GP) surgeries and GP surgeries employing General Practitioners (GPs) additionally trained in Integrative Medicine (IM) or Complementary and Alternative Medicine (CAM) (referred to as IM GPs) working within NHS England.

Design

Retrospective study on antibiotic prescription rates per STAR-PU (Specific Therapeutic group Age-sex weighting Related Prescribing Unit) using NHS digital data over 2016. Publicly available data were used on prevalence of relevant comorbidities, demographics of patient populations and deprivation scores.

Setting

Primary Care

Participants

7283 NHS GP surgeries in England

Primary outcome measure

The association between IM GPs and antibiotic prescribing rates per STAR-PU with the number of antibiotic prescriptions (total, and for respiratory- and urinary tract infection separately (RTI/UTI)) as outcome.

Results

IM GPs were comparable to conventional GPs in terms of list sizes, demographics, deprivation scores and comorbidity prevalence. A negative binomial regression models showed that statistically significantly fewer total antibiotics (RR: 0.78, 95% CI:0.64 – 0.97) and RTI antibiotics (RR 0.74, 95% CI: 0.59 – 0.94) were prescribed at NHS IM GP surgeries compared with conventional NHS GP surgeries. In contrast, the number of antibiotics prescribed for UTI were similar between both practices (RR: 0.91, 95% CI: 0.72 – 1.17).

Conclusion

NHS England GP surgeries employing GPs additionally trained in Integrative or Complementary Medicine have lower antibiotic prescribing rates. Accessibility of IM/CAM within NHS England primary care is limited. Main study limitation is the lack of consultation data. Future research should include the differences in consultation behaviour of patients self-selecting to consult a IM GP or conventional surgery, and its effect on antibiotic prescription. Additional treatment strategies for common primary care infections used by IM GPs should be explored to see if they could be used to assist in the fight against AMR.

Strengths and limitations

- Use of NHS digital data on antibiotic prescription per STAR-PU provided a comprehensive insight into the prescribing practices of total antibiotics, and for respiratory- and urinary tract infection

separately in conventional GP surgeries and GP surgeries employing a GP additionally trained in Integrative Medicine (IM GPs).

- IM GP surgeries were comparable to conventional GP surgeries in terms of list sizes, demographics, deprivation scores and comorbidity prevalence.
- Accessibility of IM/CAM within the NHS in General Practice in England is very limited. IM/CAM provision is currently almost exclusively private in the UK.
- Results are limited by the lack of data on 1) number of consultations, 2) individual GP characteristics, 3) individual deprivation scores and 4) continuum of care.

Word count

N= 3796

4 Tables

Introduction

Antimicrobial resistance (AMR) and the inappropriate use of antibiotics represent a serious threat to public health internationally.[1] Antibiotics are currently indispensable throughout the healthcare system, and the consequences of AMR, not only in primary care, but also in major surgery and cancer treatment for example, are dire. Fortunately, reductions in antibiotic use have been shown to be associated with a reduction in some resistance[2], and the reduction in the use of antibiotics, especially in primary care, to control the development of AMR is therefore a pressing national and international priority.[1 3]

In the UK, 74 percent of antibiotics are prescribed in primary care making this one of the most important contributors to the development of AMR.[4] NICE guidelines on respiratory tract infection[5] (RTI) management advise that a no antibiotic prescribing strategy or a delayed antibiotic prescribing strategy should be considered for patients with the following conditions: acute otitis media, acute sore throat/acute pharyngitis/acute tonsillitis, common cold, acute rhinosinusitis and acute cough/acute bronchitis. Nevertheless, antibiotics are commonly prescribed for RTIs in adults and children in primary care, and are the reason for 60% of all antibiotic prescribing in general practice in the UK.[6] Several studies have shown that there is substantial overprescribing of antibiotics for, often viral and self-limiting, RTIs in primary care.[7-9] Consequently, there is a large potential to reduce antibiotic prescribing for RTIs, potentially by using other treatment strategies that do not increase the development or spread of AMR. Urinary tract infections (UTIs) are the most common confirmed bacterial infection, with about half of all women experiencing one of more UTIs in their life time.[10] Most women with UTIs are currently treated with antibiotics, with longer duration and multiple courses associated with higher AMR rates.[11 12] For example, the NICE guideline on uncomplicated UTIs in women advise offering symptom relief and an antibiotic to all women with a suspected urinary tract infection. It states that for a woman with mild symptoms who has normal immunity, normal renal function, and a normal renal tract, treatment can be delayed if the patient wishes to see if symptoms will resolve without treatment. For all other women treatment needs to start without delay.[13] Therefore, overprescribing seems to be much less common for UTIs than for RTIs.[14] Consequently, it may be easier to safely reduce antibiotic prescribing for RTIs than for UTIs in primary care.

There is great variability in the use of antimicrobial medications between countries, with the lowest prescription rates reported in northern European nations, and higher rates in southern Europe and the US. [15-17] Variations in the prescription of antibiotics both within and between countries may indicate poor practice[18] with inappropriate use of antibiotics which increases the risk of adverse events for the patient[12], wastes health care resources[19] and contributes to the rise in antibiotic resistance.[16] Previous studies have shown that a complex array of factors influence antibiotic prescribing, which may explain the wide variety of antibiotic usage both at the clinician level and worldwide. The attitudes of both doctor[20-22] and patient[23-25] are shown to be of major significance in prescribing decisions.

GPs as a professional group are expected, following the principles of evidence based medicine, to apply best available evidence to patient's individual situation, within the framework of national and local funding and administrative guidance. Prescription style (measured as the prevalence of prescriptions per GP) is found to be an important factor in the variation in antibiotic prescribing behaviour.[18] Underlying factors for this finding might be differing views on medicalisation, differences in guidelines between countries and between specialists and knowledge and use of complementary and alternative medicines (CAM)/integrative medicine (IM).[26-28] The association between the knowledge/use of CAM/IM by GPs and antibiotic prescribing has so far not been widely scrutinised.

The aim of this study is to determine the differences in antibiotic prescription rates between 'conventional GPs' and GP surgeries employing a GP additionally trained in IM/CAM (hereafter referred to as Integrative medicine (IM) GPs), and the association between having (staff with) an additional training in CAM/ IM and antibiotic prescription (measured as total antibiotics, respiratory tract infection (RTI) specific antibiotics and urinary tract infection (UTI) specific antibiotics) within the NHS in England.

Methods

IM GP surgeries

To identify NHS General Practices employing an IM GP in 2016, two sequential tasks were required. Firstly, IM GPs were identified and then a current working link was made to an NHS General Practice.

(i) Identification of NHS GPs registered with an additional CAM qualification

We included the 'Big 5' CAM therapies as defined in a report by the House of Lords in 2000[29] (chiropractic, osteopathy, acupuncture, herbal medicine and homoeopathy); as well as Anthroposophic Medicine (AM). AM is an extension of conventional medicine and incorporates a holistic approach to people and nature and to illness and healing and is established in 80 countries, mostly in Central Europe.[30] AM has been included so that future comparison with data in other European countries is possible.

In the UK each of these six therapies are either state regulated (osteopathy and chiropractic) or have voluntary regulation (including a voluntary regulatory body for mainstream healthcare practitioners in the case of acupuncture and homoeopathy). The regulatory bodies were therefore initially approached by email to check the best route of establishing which practitioners on their registers were trained as a conventional GP and trained in IM/CAM as well. Details of the organisations and methods by which IM GPs were identified are indicated in Table 1. Where organisations were not able to provide this information, searches were made of the online registers (between May and June 2017) for the following:

1. Location – the registers enabled us to search for practitioners either on a nationwide (England/ UK) basis or by county (in the latter case, all English counties were checked, including recent boundary changes).
2. Qualification – in some databases, only healthcare professionals (e.g. practitioners qualified in biomedicine) were included, and GP status was specified. Where this was not the case, titles were given and the absence of the title 'Dr' was used to exclude practitioners from our study. Where qualifications were also identified, practitioners with PhDs but not being a GP could be excluded. And if no additional information was given on the register, online searches were made of the practitioner to establish their professional qualifications. In all cases, putative IM GPs were checked against the General Medical Council (GMC) register, to confirm whether they were currently permitted to work in medical practice in the UK.

(ii) Identification of NHS General Practices employing IM GPs

Practice location(s) were indicated for each GP registrant identified in the CAM registers indicated in Table 1. These workplaces were then checked against both the practice websites and the NHS website (www.nhs.uk), which lists all NHS practices and gives information such as staff lists. This

acted to confirm the working location of the GP and whether this practice offered provision within NHS England.

Data

Monthly prescribing data was obtained from NHS Digital. NHS Digital collect data and information about a wide range of General Practice (GP) services, for many different organisations and purposes. It also collates all primary care prescribing data. This data is released for monthly download via the NHS Digital website (http://digital.nhs.uk/searchcatalogue). Data is released at the specific health care provider level and volumes are provided by full British National Formulation code (BNF code). To determine mean antibiotic prescription rates, we used the total number of oral antibiotic prescriptions per general practice for the most recent calendar year for which antibiotic prescribing was publicly available via the NHS digital website (Jan 2016 – Dec 2016).

Specific Therapeutic group Age-sex weighting Related Prescribing Units (STAR-PU)

STAR-PU have been used as the denominator instead of the number of registered patients as STAR-PUs allow more accurate and meaningful comparisons within a specific therapeutic group by considering the types of people who will be receiving that treatment. The amount of STAR-PU per practice was estimated by multiplying the number of patients in each age-gender category.[31]

Comorbidities

The prevalence of various comorbidities that may adversely influence the outcome of infections, based on the conditions that indicate high-risk patients who qualify for the free seasonal influenza vaccination programme[32], was also measured to identify potential case-mix differences that may explain different antibiotic prescribing rates. General practice-specific prevalence is available for the following high-risk comorbidities via the Quality Outcomes Framework (QOF) indicators at the NHS digital website: asthma, cancer, chronic kidney disease, chronic obstructive pulmonary disease (COPD), heart failure and diabetes. We extracted comorbidity prevalence for the financial year 2015-2016.

Indices of multiple deprivation

Previously it has been shown that indices of multiple deprivation are indicators of poor health in a population. Tosas Auguet et al.[33] for example, found that more deprived areas are at higher risk of Methicillin-Resistant Staphylococcus Aureus (MRSA) infection. The most recent index of multiple deprivation was calculated in 2015 and is available from the Department for Communities and Local Government.[34] Deprivation scores are available at a lower-layer super output area (LSOA), which consists of approximately 1,500 residents each. Linkage of the data from NHS Digital was performed using a lookup table from NHS digital. Where a practice served multiple LSOAs, the average deprivation score for that practice was calculated, weighted by the number of patients in each LSOA.

The final dataset included only practices that were present in both the comorbidity and deprivation, and antibiotic prescribing files. We removed outliers based on practice size, since there were some doubts about the validity of this data (e.g. a practice with 157 patients registered). We removed the outer 2% of data based on practice size.

Statistical analysis

All analyses are performed on GP surgery level (hereafter referred to as GPs). Potential differences in antibiotic prescribing rates per STAR-PU between the IM and conventional GPs were evaluated. NHS Digital defines a prescription item as: 'a prescription item is a single supply of a medicine, dressing or appliance written on a prescription form. If a prescription form includes three medicines, it is counted as three prescription items. We tested for between group differences using a random effects meta-analysis model for proportions (R package 'meta'). For continuous variables like the number of STAR-PU per practices Mann-Whitney U tests were used to test for statistically significant differences.

The association between the IM GPs and antibiotic prescribing rates per STAR-PU was assessed using negative binomial regression models with the number of antibiotic prescriptions as the outcome and the natural logarithm of the number of STAR-PU per practice as an offset. A negative binomial regression model was used as this type of regression model can handle count data (number of antibiotic prescriptions), accounts for differences in the number of antibiotics purely caused by practice size (by including the offset), and can still provide valid results when the variance in antibiotic use does not equal the mean antibiotic use.[35] Both crude results and results adjusted for additional variables to correct for potential confounding are presented.

We additionally evaluated associations between IM GPs and antibiotics commonly used for respiratory tract infection (RTI) (amoxicillin, amoxicillin and enzyme inhibitor, ampicillin, clarithromycin, doxycycline, erythromycin, and phenoxymethylpenicillin) and for urinary tract infection (UTI) (cephalexin, cefixime, ciprofloxacin, nitrofurantoin, pivmecillinam, and trimethoprim).[36]

Results

Identification of NHS IM GPs in England

850 CAM practitioner records were checked against the various CAM registers (Table 1) to identify 21 GPs who are conventionally trained as a GP and also trained in CAM at 19 NHS GP surgeries in England (Table 2). It should be noted that the 850 registrants were not the total numbers of CAM practitioners on the registers, as (as previously described) some registers permitted limiting searches to medical practitioners, or more specifically to medically qualified doctors.

While some practices were publicly working in an IM structure, in others it was unknown whether the identified GP was using IM/CAM or indeed whether or the practice permitted this, as no mention was made of it on the websites (including no reference to privately available CAM clinics). General Practices were therefore classified into two subsets as indicated in Table 2. There were further IM GPs on the register who were either not practicing (or at least not in England), or working in private practice. As any level of IM/CAM activity in subset 2 practices could not be determined, it was decided to exclude these GP surgeries from further analysis. 9 NHS IM GP surgeries (urban (N=6), semi-urban (N=2) and semi-rural (N=1)) were included in the analysis. Table 2 also shows the CAM therapies for which each IM GP in our subsequent analysis was registered.

Antibiotic prescription rates

In total 7283 NHS England General Practices (N_conventional=7217/ N_IMGPs= 9) were included in the analyses. Table 3 presents the baseline characteristic of the NHS IM GP surgeries compared to those characteristic of NHS conventional GPs in England. It also shows the prevalence of various comorbidities that may adversely influence the outcome of infections and may consequently influence antibiotic prescribing. The patient populations of both kinds of practices were comparable for most of the listed comorbidities. Statistically significant differences ($P<0.05$) between the IM GP- and conventional GP surgery patient population were found in the percentage of patients with coronary heart disease, cancer and diabetes, although absolute differences were relatively small. No statistical differences ($P<0.05$) were found in deprivation score between IM GP surgeries and conventional GP surgeries.

IM GP surgeries and antibiotic prescription rates

Overall within the NHS in England, the median prescription rates of IM GP surgeries were lower for ‘any antibiotic’ and for ‘RTI specific antibiotic’ compared to the rates of the conventional GP surgeries over 2016, while the median prescription rates of ‘UTI specific antibiotic’ per STAR-PU was comparable for the two groups (Table 4).

The Relative Risks (RR) in table 4 were obtained using negative binomial regression models with the number of antibiotic prescriptions as the outcome and taking into account differences in practice sizes. Our analysis show that IM GP surgeries were associated with lower prescriptions of ‘any antibiotic’ (RR: 0.78, 95% CI:0.64 – 0.97) and with lower prescriptions of ‘RTI specific antibiotic’ (RR:

0.74, 95% C.I: 0.59 – 0.94*). Patients consulting an IM GP surgery were 22% less likely to get 'any antibiotic' prescription compared to those who consulted a conventional GP surgery. Receiving a RTI specific antibiotic prescription was 26% less likely among those who consulted an IM GP surgery compared with those who consulted a conventional GP surgery. No statistically significant difference ($P<0.05$) was found in the number of prescriptions of UTI specific antibiotic prescriptions per STAR-PU between IM GP surgeries and conventional GP surgeries within the NHS in England.

Adjustment for deprivation score or diabetes resulted in virtually identical results. For 'any antibiotic' if adjusted for deprivation score the RR for IM GP surgeries remains virtually identical RR: 0.78 (95% CI: 0.64 – 0.97), and for diabetes RR: 0.80 (95% CI: 0.65 – 0.99). This was the case regardless of which confounder was added to the model, however adjusting for multiple potential confounders was not possible due to the small number of cases.

Discussion

There were 7283 NHS England General Practices included in our analyses. Despite the very small proportion of IM GP surgeries, our data show that significantly fewer 'total antibiotics' and 'RTI specific antibiotics' per STAR-PU were prescribed at IM GP surgeries compared to conventional GP surgeries within NHS England over 2016. No statistically significant differences were found in median prescription rates of 'UTI specific antibiotics' per STAR-PU in the two kinds of NHS GP surgeries.

This is the first study of retrospectively prescribed antibiotic prescribing in primary care in England with a specific focus on the possible association between the knowledge/use of CAM/IM by GPs within the NHS and antibiotic prescribing. However, the small proportion of NHS IM GPs in England asks for careful interpretation of the results. Accounting for one other variable (e.g. deprivation or diabetes) did not change our results, but, due to the low number of cases it was not possible to similarly account for more variables.

Lack of information on the number of consultations is the main limitation of this study. Consultation rates may explain most of the variation in antibiotic prescribing, and with the data used in this study, it is not clear whether patients consulting at IM GP surgeries consulted less in general. If this were the case, they may be equally likely to receive antibiotics when they do consult their GP. Besides, previous studies show that the consultation rate is also dependent on the previous likelihood to receive antibiotics for a RTI.[37-39] Future studies should therefore include consultation behaviour/number of consultations as a confounding factor.

Other study limitations that need to be taken into account when interpreting the results are the lack of information on 1) individual deprivation scores, 2) individual GP characteristics and 3) continuum of care. Firstly, no statistically significant differences were found in deprivation score on practice level. However, this may be partly because deprivation scores are area-based and not based on the individuals registered at the different practices. Secondly, our analyses are at GP practice level and include information on GP practice characteristics, such as list size and population. Data on GP characteristics on individual level are not part of NHS digital data and are therefore not included in our analysis. However, these GP characteristics may partly explain the variation in antibiotic prescribing.[40-42] Finally, the data used for our analysis is based on the number of antibiotic 'prescriptions', which may differ from the numbers of antibiotics 'consumed' and does not include information on the continuum of care of patients (e.g. hospital admissions/re-consultation). Future studies using clinical practice data taking continuum of care into account are warranted.

The lower antibiotic prescription rates of IM GPs are in line with the current national guidance aimed at reducing antibiotic usage and AMR.[1] IM GPs might possible comply more closely with this guidance. However, the difference found could also be partly explained by the fact that patients who consult IM GPs might demand less for antibiotics, and that GPs in IM surgeries have other avenues to offer to patients than antibiotics or that they are more confident to delay prescriptions and to assert themselves against the wishes of those patients who appear to want antibiotics. Our results are in line with a yet unpublished pilot study in The Netherlands in which the prescription of antimicrobials for systemic use in 23 unselected anthroposophic GP surgeries was compared to the national mean GP figures for the years 2012 – 2014. On average AM GPs in the Netherlands prescribed less antimicrobials: -13% (2012), -10% (2013) and -7% (2014) (unpublished data).

Despite the differences we found in RTI antibiotics, no statistically significant differences were found in UTI antibiotics prescription rates between the two kinds of NHS GP surgeries. Although it should be borne in mind that the use of prescribing data to infer the type of infection may be prone to errors, our finding reflects current UK GP clinical guidance.

For the majority of RTIs it is recommended that antibiotics should be avoided or delayed, so that this is an area where the desired reduction in prescribing could take place. In the case of UTIs, antibiotics are advised more readily.[36] For several RTIs, including common colds, sore throat, sinusitis and acute bronchitis, randomized controlled trials (RCTs) have shown that antibiotics provide no, or negligible benefit compared to placebo[43-46]. As such, symptom management with paracetamol, ibuprofen or the use of CAM therapies proven to be effective and safe for RTIs may safely reduce antibiotic prescribing among patients with a low risk for pneumonia. A recent RCT comparing ibuprofen with fosfomycin treatment for UTIs indicates that it may be more difficult to safely reduce antibiotic prescribing for UTIs using a similar approach.[47]

Our study shows that accessibility of IM/CAM within the NHS in General Practice is very limited, and this limited the number of IM GPs included in our analysis. IM/CAM provision is currently almost exclusively privately provided in the UK, which could be at least partly linked to the austerity measures currently imposed in the UK possibly resulting in NHS IM/CAM provision being withdrawn at a local level in recent years (and imminently nationally). It was seen on practice websites that there was a noticeable amount of ‘private’ CAM provision available at several NHS surgeries by non-GP CAM practitioners – in weekly clinics for example. However, these surgeries have not been included in our analysis as this study specifically aimed to determine the differences in antibiotic prescribing between conventional GP surgeries and GP surgeries staffing GPs who were additionally trained in IM/CAM.

Attitudes of GPs to IM/CAM are extremely important for it to remain available within the NHS. A 2015 study of these attitudes in England, showed that, despite demand for CAM amongst the general public, GPs remain concerned about its limited evidence base as well as the lack of regulation of CAM practitioners. Nevertheless, those questioned continue to see a role for CAM in clinical practice.[48] The impact which any one IM GP could have in terms of antibiotic prescribing may vary hugely between practices partly depending on their status at the practice - as a partner or a salaried employee for example, or as a full-time or part-time worker. In the presented analysis we did not include NHS GP practices that are offering NHS IM/CAM provision by a ‘non-GP NHS CAM practitioner' or private IM/CAM practitioner. However, having even one CAM contact within a surgery might give the possibility for others to experience CAM perspectives either formally or informally from them, and for long-held attitudes to be perhaps modified. Additionally, it would be of interest to explore if patients may be independently accessing IM GPs in the private sector and then seeking antibiotics from non-IM GPs in the NHS.

In line with Hawker et al[49], our results suggest that a further decrease in prescribing in conventional surgeries might be possible. It may be that advice should be sought from this small number of surgeries to establish whether their daily clinical practice may differ from other surgeries and whether this could be used to assist others in the fight against AMR.

Although this study found only a small number of NHS CAM practitioners working in England, the differences seen in prescribing rates at the IM GP surgeries warrant further study. In addition, analysis in comparison with other countries are indicated. As the clear majority of CAM practitioners (mainly non-GPs) work privately in England, there is also potential for research into non-antibiotic strategies in private practice, and to analysis of how these practitioners work with their patients' NHS GPs in this regard. However, as patients who self-select to consult IM GPs might be less likely to demand antibiotics, differences in lifestyle and the 'transferabilty of lifestyle skills' need to be taken into account as well in future study design.

Contributor ship statement

- Substantial contributions to the conception and design of the work; EvdW/ LD/PvF/EB
- Acquisition, analysis, or interpretation of data for the work; EvdW/ LD
- Drafting the work and revising it critically for important intellectual content; EvdW/ LD/PvF/EB
- Final approval of the version to be published: EvdW/ LD/PvF/EB
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: EvdW/ LD/PvF/EB

Competing interests

None declared

Funding

This research was supported in part by an unrestricted grant of WALA Heilmittel GmbH, Germany.

Data sharing statement

Data are available through NHS digital

Acknowledgement

The authors gratefully acknowledge the statistical support of Dr Koen Pouwels (Senior Mathematical/Economic Modeller)

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1 **Table 1. Organisations from which details of training in IM/CAM of GPs were obtained**

CAM specialism	Organisation	Website	Method for extracting GP information
Osteopathy	General Osteopathic Council	www.osteopathy.org.uk	Search of online database
Chiropractic	General Chiropractic Council (GCC)	www.gcc-uk.org	GCC staff identified GP registrants
Acupuncture	British Medical Acupuncture Council	www.medical-acupuncture.co.uk	Search of online database
Herbal Medicine	College of Practitioners of Phytotherapy	www.thecpp.uk	CPP staff identified GP registrants
	National Institute of Medical Herbalists	www.nimh.org.uk	NIMH staff identified GP registrants
	The Register of Chinese Herbal Medicine in the UK	www.rchm.co.uk	Search of online database
	The United Register of Herbal Practitioners	www.urhp.com	Search of online database
	The Association of Chinese Medicine and Acupuncture UK	www.atcm.co.uk	Search of online database
Homeopathy	British Homeopathic Association	www.britishhomeopathic.org	Search of online database
	Faculty of Homeopathy	www.facultyofhomeopathy.org	Search of online database
Anthroposophic Medicine	Anthroposophic Health, Education and Social Care Movement	www.ahasc.org.uk	Search of online database

2

3

1 **Table 2. IM GP surgeries subdivision (based on website information)**

	Apparent level of CAM practice	CAM (n)
Subset 1 (N=9)	General Practices where an integrative medicine (IM) approach is taken **with CAM-trained GP** (N=4)	Homeopathy (1) Anthroposophic Medicine (2) Acupuncture (3)
	General practices listing CAM therapy provision **with CAM-trained GP** (N=5)	Homeopathy (1) Acupuncture (4)
Subset 2 (N=10)	General practices mention a CAM therapy in the listing of the special interests of the GP, but no other information is given and it is **unclear whether the GP practises this CAM therapy at that site**	

2

Table 3. Baseline characteristics of included NHS GP surgeries

	Conventional GP surgery	IM/CAM GP surgery **(Subset 1)** [$]
	median (25th-75th percentile)	**median (25th-75th percentile)**
	n=7274	n=9
Number of registered patients	6698 (4162-9942)	7088 (4037-9534)
Male (%)	49.7 (48.8-50.9)	49.3 (46.9-49.4)
Aged 0-17y (%)	20.5 (18.5-23.0)	21.2 (18.7-22.0)
Aged 18-64y (%)	61.2 (58.7-64.2)	61.9 (60.3-62.4)
Aged 65+ y (%)	17.2 (12.3-21.4)	18.2 (14.0-18.4)
STAR-PU**	3705 (2276-5599)	3716 (2315-5382)
Coronary heart disease (%)	3.3 (2.5-4.0)	2.8 (2.1-3.1)*
Heart failure (%)	0.7 (0.5-0.9)	0.5 (0.4-0.8)
Asthma (%)	6.0 (4.9-6.7)	5.1 (4.8-6.2)
COPD (%)	1.8 (1.3-2.4)	1.0 (0.8-2.0)
Cancer (%)	2.4 (1.7-3.0)	2.5 (2.2-2.9)*
Chronic kidney disease (%)	3.0 (2.0-4.1)	1.9 (1.2-2.9)
Diabetes (%)	5.4 (4.5-6.2)	3.9 (2.9-4.6)*
Deprivation score	0.27 (0.11-0.63)	0.36 (0.15-0.48)

[$] *Subset 1: General Practices where an integrative medicine approach is taken with CAM-trained GP (N=4)* ***and*** *General practices listing CAM therapy provision with CAM-trained GP (N=5);*

**p<0.05;*

*** STAR-PU stands for ‘oral antibacterials item based Specific Therapeutic Group Age-sex weightings Related Prescribing Units. The amount of STAR-PU per practice was estimated by multiplying the number of patients in each age-gender category by the relevant STAR-PU weights (see methods section for detailed explanation on STAR-PUs).*

Table 4. Median antibiotic prescription rates and Relative Risk (RR) of prescribing antibiotics in primary care England over 2016

	Any antibiotic/ STAR-PU[$] **Median ($25^{th}$-$75^{th}$ percentile)**	**RTI antibiotic/** STAR-PU[$] **Median ($25^{th}$-$75^{th}$ percentile)**	**UTI antibiotic/** STAR-PU[$] **Median ($25^{th}$-$75^{th}$ percentile)**
Conventional GP surgeries (n=7,274)	1.01 (0.86 – 1.17)	0.56 (0.46 – 0.67)	0.22 (0.17 – 0.26)
IM GP surgeries with CAM trained GP (n=9)	0.79 (0.73 – 0.91)*	0.44 (0.37 – 0.48)*	0.21 (0.19 – 0.23)
	Relative Risk (RR)[$] (95% CI)	**Relative Risk (RR)[$] (95% CI)**	**Relative Risk (RR)[$] (95% CI)**
Conventional GP surgeries (n=7,274)	Ref.	Ref.	Ref.
IM GP surgeries with CAM trained GP (n=9)	0.78 (0.64 – 0.97)*	0.74 (0.59 – 0.94)*	0.91 (0.72 – 1.17)

[$]*This rate is obtained by dividing the total number of antibiotics prescribed by the number of STAR-PU registered.*
**p<0.05*

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page:2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page:2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page:4**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page:5**
Methods		
Study design	4	Present key elements of study design early in the paper **Page:6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page:6, 7**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **Page:6, 7**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page:7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page:7**
Bias	9	Describe any efforts to address potential sources of bias **Page:7**
Study size	10	Explain how the study size was arrived at **Page:6,7,8**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Page:8**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding

		Page:8
		(*b*) Describe any methods used to examine subgroups and interactions **Page:8**
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page:6**
		(b) Give reasons for non-participation at each stage **Page:6**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page: 9, 10 and Table 1, Table 2**
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures **Page: 9, 10 and Table 3, Table 4**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page:9, 10**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page: 11**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page: 11**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page: 11, 12**

Generalisability	21	Discuss the generalisability (external validity) of the study results **Page: 12, 13**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page: 13**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Do NHS GP surgeries employing GPs additionally trained in Integrative or Complementary Medicine have lower antibiotic prescribing rates? Retrospective cross-sectional analysis of national primary care prescribing data in England in 2016.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020488.R2
Article Type:	Research
Date Submitted by the Author:	19-Dec-2017
Complete List of Authors:	van der Werf, Esther; University of Bristol, Bristol Medical School Duncan, Lorna; University of Bristol, Bristol Medical School Von Flotow, Paschen; Sustainable Business Institute (SBI) Baars, Erik; Louis Bolk Instituut; University of Applied Sciences, Care
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Infectious diseases
Keywords:	Antimicrobial resistance, COMPLEMENTARY MEDICINE, Integrative Medicine, Antibiotic prescription rate

Do NHS GP surgeries employing GPs additionally trained in Integrative or Complementary Medicine have lower antibiotic prescribing rates? Retrospective cross-sectional analysis of national primary care prescribing data in England in 2016.

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Abstract

Objective

To determine differences in antibiotic prescription rates between conventional General Practice (GP) surgeries and GP surgeries employing General Practitioners (GPs) additionally trained in Integrative Medicine (IM) or Complementary and Alternative Medicine (CAM) (referred to as IM GPs) working within NHS England.

Design

Retrospective study on antibiotic prescription rates per STAR-PU (Specific Therapeutic group Age-sex weighting Related Prescribing Unit) using NHS digital data over 2016. Publicly available data were used on prevalence of relevant comorbidities, demographics of patient populations and deprivation scores.

Setting

Primary Care

Participants

7283 NHS GP surgeries in England

Primary outcome measure

The association between IM GPs and antibiotic prescribing rates per STAR-PU with the number of antibiotic prescriptions (total, and for respiratory- and urinary tract infection separately (RTI/UTI)) as outcome.

Results

IM GPs (N=9) were comparable to conventional GPs in terms of list sizes, demographics, deprivation scores and comorbidity prevalence. A negative binomial regression models showed that statistically significantly fewer total antibiotics (RR: 0.78, 95% CI:0.64 – 0.97) and RTI antibiotics (RR 0.74, 95% CI: 0.59 – 0.94) were prescribed at NHS IM GP surgeries compared with conventional NHS GP surgeries. In contrast, the number of antibiotics prescribed for UTI were similar between both practices (RR: 0.91, 95% CI: 0.72 – 1.17).

Conclusion

NHS England GP surgeries employing GPs additionally trained in Integrative or Complementary Medicine have lower antibiotic prescribing rates. Accessibility of IM/CAM within NHS England primary care is limited. Main study limitation is the lack of consultation data. Future research should include the differences in consultation behaviour of patients self-selecting to consult a IM GP or conventional surgery, and its effect on antibiotic prescription. Additional treatment strategies for common primary care infections used by IM GPs should be explored to see if they could be used to assist in the fight against AMR.

Strengths and limitations

- Use of NHS digital data on antibiotic prescription per STAR-PU provided a comprehensive insight into the prescribing practices of total antibiotics, and for respiratory- and urinary tract infection

separately in conventional GP surgeries and GP surgeries employing a GP additionally trained in Integrative Medicine (IM GPs).

- IM GP surgeries were comparable to conventional GP surgeries in terms of list sizes, demographics, deprivation scores and comorbidity prevalence.
- Accessibility of IM/CAM within the NHS in General Practice in England is very limited. IM/CAM provision is currently almost exclusively private in the UK.
- Results are limited by the lack of data on 1) number of consultations, 2) individual GP characteristics, 3) individual deprivation scores and 4) continuum of care.

Word count

N= 4008

4 Tables

Introduction

Antimicrobial resistance (AMR) and the inappropriate use of antibiotics represent a serious threat to public health internationally.[1] Antibiotics are currently indispensable throughout the healthcare system, and the consequences of AMR, not only in primary care, but also in major surgery and cancer treatment for example, are dire. Fortunately, reductions in antibiotic use have been shown to be associated with a reduction in some resistance[2], and the reduction in the use of antibiotics, especially in primary care, to control the development of AMR is therefore a pressing national and international priority.[1 3]

In the UK, 74 percent of antibiotics are prescribed in primary care making this one of the most important contributors to the development of AMR.[4] NICE guidelines on respiratory tract infection[5] (RTI) management advise that a no antibiotic prescribing strategy or a delayed antibiotic prescribing strategy should be considered for patients with the following conditions: acute otitis media, acute sore throat/acute pharyngitis/acute tonsillitis, common cold, acute rhinosinusitis and acute cough/acute bronchitis. Nevertheless, antibiotics are commonly prescribed for RTIs in adults and children in primary care, and are the reason for 60% of all antibiotic prescribing in general practice in the UK.[6] Several studies have shown that there is substantial overprescribing of antibiotics for, often viral and self-limiting, RTIs in primary care.[7-9] Consequently, there is a large potential to reduce antibiotic prescribing for RTIs, potentially by using other treatment strategies that do not increase the development or spread of AMR. Urinary tract infections (UTIs) are the most common confirmed bacterial infection, with about half of all women experiencing one of more UTIs in their life time.[10] Most women with UTIs are currently treated with antibiotics, with longer duration and multiple courses associated with higher AMR rates.[11 12] For example, the NICE guideline on uncomplicated UTIs in women advise offering symptom relief and an antibiotic to all women with a suspected urinary tract infection. It states that for a woman with mild symptoms who has normal immunity, normal renal function, and a normal renal tract, treatment can be delayed if the patient wishes to see if symptoms will resolve without treatment. For all other women treatment needs to start without delay.[13] Therefore, overprescribing seems to be much less common for UTIs than for RTIs.[14] Consequently, it may be easier to safely reduce antibiotic prescribing for RTIs than for UTIs in primary care.

There is great variability in the use of antimicrobial medications between countries, with the lowest prescription rates reported in northern European nations, and higher rates in southern Europe and the US. [15-17] Variations in the prescription of antibiotics both within and between countries may indicate poor practice[18] with inappropriate use of antibiotics which increases the risk of adverse events for the patient[12], wastes health care resources[19] and contributes to the rise in antibiotic resistance.[16] Previous studies have shown that a complex array of factors influence antibiotic prescribing, which may explain the wide variety of antibiotic usage both at the clinician level and worldwide. The attitudes of both doctor[20-22] and patient[23-25] are shown to be of major significance in prescribing decisions.

GPs as a professional group are expected, following the principles of evidence based medicine, to apply best available evidence to patient's individual situation, within the framework of national and local funding and administrative guidance. Prescription style (measured as the prevalence of prescriptions per GP) is found to be an important factor in the variation in antibiotic prescribing behaviour.[18] Underlying factors for this finding might be differing views on medicalisation, differences in guidelines between countries and between specialists and knowledge and use of complementary and alternative medicines (CAM)/integrative medicine (IM).[26-28] The association between the knowledge/use of CAM/IM by GPs and antibiotic prescribing has so far not been widely scrutinised.

The aim of this study is to determine the differences in antibiotic prescription rates between 'conventional GPs' and GP surgeries employing a GP additionally trained in IM/CAM (hereafter referred to as Integrative medicine (IM) GPs), and the association between having (staff with) an additional training in CAM/ IM and antibiotic prescription (measured as total antibiotics, respiratory tract infection (RTI) specific antibiotics and urinary tract infection (UTI) specific antibiotics) within the NHS in England.

Methods

IM GP surgeries

To identify NHS General Practices employing an IM GP in 2016, two sequential tasks were required. Firstly, IM GPs were identified and then a current working link was made to an NHS General Practice.

(i) Identification of NHS GPs registered with an additional CAM qualification

We included the 'Big 5' CAM therapies as defined in a report by the House of Lords in 2000[29] (chiropractic, osteopathy, acupuncture, herbal medicine and homoeopathy); as well as Anthroposophic Medicine (AM). AM is an extension of conventional medicine and incorporates a holistic approach to people and nature and to illness and healing and is established in 80 countries, mostly in Central Europe.[30] AM has been included so that future comparison with data in other European countries is possible.

In the UK each of these six therapies are either state regulated (osteopathy and chiropractic) or have voluntary regulation (including a voluntary regulatory body for mainstream healthcare practitioners in the case of acupuncture and homoeopathy). The regulatory bodies were therefore initially approached by email to check the best route of establishing which practitioners on their registers were trained as a conventional GP and trained in IM/CAM as well. Details of the organisations and methods by which IM GPs were identified are indicated in Table 1. Where organisations were not able to provide this information, searches were made of the online registers (between May and June 2017) for the following:

1. Location – the registers enabled us to search for practitioners either on a nationwide (England/ UK) basis or by county (in the latter case, all English counties were checked, including recent boundary changes).
2. Qualification – in some databases, only healthcare professionals (e.g. practitioners qualified in biomedicine) were included, and GP status was specified. Where this was not the case, titles were given and the absence of the title 'Dr' was used to exclude practitioners from our study. Where qualifications were also identified, practitioners with PhDs but not being a GP could be excluded. And if no additional information was given on the register, online searches were made of the practitioner to establish their professional qualifications. In all cases, putative IM GPs were checked against the General Medical Council (GMC) register, to confirm whether they were currently permitted to work in medical practice in the UK.

(ii) Identification of NHS General Practices employing IM GPs

Practice location(s) were indicated for each GP registrant identified in the CAM registers indicated in Table 1. These workplaces were then checked against both the practice websites and the NHS website (www.nhs.uk), which lists all NHS practices and gives information such as staff lists. This

acted to confirm the working location of the GP and whether this practice offered provision within NHS England.

Data

Monthly prescribing data was obtained from NHS Digital. NHS Digital collect data and information about a wide range of General Practice (GP) services, for many different organisations and purposes. It also collates all primary care prescribing data. This data is released for monthly download via the NHS Digital website (http://digital.nhs.uk/searchcatalogue). Data is released at the specific health care provider level and volumes are provided by full British National Formulation code (BNF code). To determine mean antibiotic prescription rates, we used the total number of oral antibiotic prescriptions per general practice for the most recent calendar year for which antibiotic prescribing was publicly available via the NHS digital website (Jan 2016 – Dec 2016).

Specific Therapeutic group Age-sex weighting Related Prescribing Units (STAR-PU)

STAR-PU have been used as the denominator instead of the number of registered patients as STAR-PUs allow more accurate and meaningful comparisons within a specific therapeutic group by considering the types of people who will be receiving that treatment. The amount of STAR-PU per practice was estimated by multiplying the number of patients in each age-gender category.[31]

Comorbidities

The prevalence of various comorbidities that may adversely influence the outcome of infections, based on the conditions that indicate high-risk patients who qualify for the free seasonal influenza vaccination programme[32], was also measured to identify potential case-mix differences that may explain different antibiotic prescribing rates. General practice-specific prevalence is available for the following high-risk comorbidities via the Quality Outcomes Framework (QOF) indicators at the NHS digital website: asthma, cancer, chronic kidney disease, chronic obstructive pulmonary disease (COPD), heart failure and diabetes. We extracted comorbidity prevalence for the financial year 2015-2016.

Indices of multiple deprivation

Previously it has been shown that indices of multiple deprivation are indicators of poor health in a population. Tosas Auguet et al.[33] for example, found that more deprived areas are at higher risk of Methicillin-Resistant Staphylococcus Aureus (MRSA) infection. The most recent index of multiple deprivation was calculated in 2015 and is available from the Department for Communities and Local Government.[34] Deprivation scores are available at a lower-layer super output area (LSOA), which consists of approximately 1,500 residents each. Linkage of the data from NHS Digital was performed using a lookup table from NHS digital. Where a practice served multiple LSOAs, the average deprivation score for that practice was calculated, weighted by the number of patients in each LSOA.

The final dataset included only practices that were present in both the comorbidity and deprivation, and antibiotic prescribing files. We removed outliers based on practice size, since there were some doubts about the validity of this data (e.g. a practice with 157 patients registered). We removed the outer 2% of data based on practice size.

Statistical analysis

All analyses are performed on GP surgery level (hereafter referred to as GPs). Potential differences in antibiotic prescribing rates per STAR-PU between the IM and conventional GPs were evaluated. NHS Digital defines a prescription item as: 'a prescription item is a single supply of a medicine, dressing or appliance written on a prescription form. If a prescription form includes three medicines, it is counted as three prescription items. We tested for between group differences using a random effects meta-analysis model for proportions (R package 'meta'). For continuous variables like the number of STAR-PU per practices Mann-Whitney U tests were used to test for statistically significant differences.

The association between the IM GPs and antibiotic prescribing rates per STAR-PU was assessed using negative binomial regression models with the number of antibiotic prescriptions as the outcome and the natural logarithm of the number of STAR-PU per practice as an offset. A negative binomial regression model was used as this type of regression model can handle count data (number of antibiotic prescriptions), accounts for differences in the number of antibiotics purely caused by practice size (by including the offset), and can still provide valid results when the variance in antibiotic use does not equal the mean antibiotic use.[35] Both crude results and results adjusted for additional variables to correct for potential confounding are presented.

We additionally evaluated associations between IM GPs and antibiotics commonly used for respiratory tract infection (RTI) (amoxicillin, amoxicillin and enzyme inhibitor, ampicillin, clarithromycin, doxycycline, erythromycin, and phenoxymethylpenicillin) and for urinary tract infection (UTI) (cephalexin, cefixime, ciprofloxacin, nitrofurantoin, pivmecillinam, and trimethoprim).[36]

Results

Identification of NHS IM GPs in England

850 CAM practitioner records were checked against the various CAM registers (Table 1) to identify 21 GPs who are conventionally trained as a GP and also trained in CAM at 19 NHS GP surgeries in England (Table 2). It should be noted that the 850 registrants were not the total numbers of CAM practitioners on the registers, as (as previously described) some registers permitted limiting searches to medical practitioners, or more specifically to medically qualified doctors.

While some practices were publicly working in an IM structure, in others it was unknown whether the identified GP was using IM/CAM or indeed whether or the practice permitted this, as no mention was made of it on the websites (including no reference to privately available CAM clinics). General Practices were therefore classified into two subsets as indicated in Table 2. There were further IM GPs on the register who were either not practicing (or at least not in England), or working in private practice. As any level of IM/CAM activity in subset 2 practices could not be determined, it was decided to exclude these GP surgeries from further analysis. 9 NHS IM GP surgeries (urban (N=6), semi-urban (N=2) and semi-rural (N=1)) were included in the analysis. Table 2 also shows the CAM therapies for which each IM GP in our subsequent analysis was registered. Each practice included has at least one IM GP, as GP partner or salaried. The number of IM GPs per practice varies from a minimum of 1 IM GP in a practice with 12 GPs of whom 6 part-time, to a maximum of 3 IM GPs (of whom 2 full time GP practice partners) in a practice with 7 GPs (2 fulltime GPs and 5 part time GPs).

Antibiotic prescription rates

In total 7283 NHS England General Practices (N_conventional=7217/ N_IMGPs= 9) were included in the analyses. Table 3 presents the baseline characteristic of the NHS IM GP surgeries compared to those characteristic of NHS conventional GPs in England. It also shows the prevalence of various comorbidities that may adversely influence the outcome of infections and may consequently influence antibiotic prescribing. The patient populations of both kinds of practices were comparable for most of the listed comorbidities. Statistically significant differences ($P<0.05$) between the IM GP- and conventional GP surgery patient population were found in the percentage of patients with coronary heart disease, cancer and diabetes, although absolute differences were relatively small. No statistical differences ($P<0.05$) were found in deprivation score between IM GP surgeries and conventional GP surgeries.

IM GP surgeries and antibiotic prescription rates

Overall within the NHS in England, the median prescription rates of IM GP surgeries were lower for 'any antibiotic' and for 'RTI specific antibiotic' compared to the rates of the conventional GP surgeries over 2016, while the median prescription rates of 'UTI specific antibiotic' per STAR-PU was comparable for the two groups (Table 4).

The Relative Risks (RR) in table 4 were obtained using negative binomial regression models with the number of antibiotic prescriptions as the outcome and taking into account differences in practice sizes. Our analysis show that IM GP surgeries were associated with lower prescriptions of 'any antibiotic' (RR: 0.78, 95% CI:0.64 – 0.97) and with lower prescriptions of 'RTI specific antibiotic' (RR: 0.74, 95% C.I: 0.59 – 0.94*). Patients consulting an IM GP surgery were 22% less likely to get 'any antibiotic' prescription compared to those who consulted a conventional GP surgery. Receiving a RTI specific antibiotic prescription was 26% less likely among those who consulted an IM GP surgery compared with those who consulted a conventional GP surgery. No statistically significant difference (P<0.05) was found in the number of prescriptions of UTI specific antibiotic prescriptions per STAR-PU between IM GP surgeries and conventional GP surgeries within the NHS in England.

Adjustment for deprivation score or diabetes resulted in virtually identical results. For 'any antibiotic' if adjusted for deprivation score the RR for IM GP surgeries remains virtually identical RR: 0.78 (95% CI: 0.64 – 0.97), and for diabetes RR: 0.80 (95% CI: 0.65 – 0.99). This was the case regardless of which confounder was added to the model, however adjusting for multiple potential confounders was not possible due to the small number of cases.

Discussion

There were 7283 NHS England General Practices included in our analyses. Despite the very small proportion of IM GP surgeries, our data show that significantly fewer ‘total antibiotics’ and ‘RTI specific antibiotics’ per STAR-PU were prescribed at IM GP surgeries compared to conventional GP surgeries within NHS England over 2016. No statistically significant differences were found in median prescription rates of ‘UTI specific antibiotics’ per STAR-PU in the two kinds of NHS GP surgeries.

This is the first (retrospective) study comparing antibiotic prescribing rates between IM GP surgeries and conventional GP surgeries in England. However, the small proportion of NHS IM GPs in England asks for careful interpretation of the results. Accounting for one other variable (e.g. deprivation or diabetes) did not change our results, but, due to the low number of cases it was not possible to similarly account for more variables.

Lack of information on the number of consultations is the main limitation of this study. Consultation rates may explain most of the variation in antibiotic prescribing, and with the data used in this study, it is not clear whether patients consulting at IM GP surgeries consulted less in general. If this were the case, they may be equally likely to receive antibiotics when they do consult their GP. Besides, previous studies show that the consultation rate is also dependent on the previous likelihood to receive antibiotics for a RTI.[37-39] Future studies should therefore include consultation behaviour/number of consultations as a confounding factor.

Other study limitations that need to be taken into account when interpreting the results are the lack of information on 1) individual deprivation scores, 2) individual GP characteristics and 3) continuum of care. Firstly, no statistically significant differences were found in deprivation score on practice level. However, this may be partly because deprivation scores are area-based and not based on the individuals registered at the different practices. Secondly, our analyses are at GP practice level and include information on GP practice characteristics, such as list size and population. Data on GP characteristics on individual level are not part of NHS digital data and are therefore not included in our analysis. However, these GP characteristics may partly explain the variation in antibiotic prescribing.[40-42] Finally, the data used for our analysis is based on the number of antibiotic ‘prescriptions’, which may differ from the numbers of antibiotics ‘consumed’ and does not include information on the continuum of care of patients (e.g. hospital admissions/re-consultation). Future studies using clinical practice data taking continuum of care into account are warranted.

The lower antibiotic prescription rates of IM GPs are in line with the current national guidance aimed at reducing antibiotic usage and AMR.[1] IM GPs might possible comply more closely with this guidance. However, the difference found could also be partly explained by the fact that patients who consult IM GPs might demand less for antibiotics, and that GPs in IM surgeries have other avenues to offer to patients than antibiotics or that they are more confident to delay prescriptions and to assert themselves against the wishes of those patients who appear to want antibiotics. Our results are in line with a yet unpublished pilot study in The Netherlands in which the prescription of antimicrobials for systemic use in 23 unselected anthroposophic GP surgeries was compared to the national mean GP figures for the years 2012 – 2014. On average AM GPs in the Netherlands prescribed less antimicrobials: -13% (2012), -10% (2013) and -7% (2014) (unpublished data).

Despite the differences we found in RTI antibiotics, no statistically significant differences were found in UTI antibiotics prescription rates between the two kinds of NHS GP surgeries. Although it should be borne in mind that the use of prescribing data to infer the type of infection may be prone to errors, our finding reflects current UK GP clinical guidance.

For the majority of RTIs it is recommended that antibiotics should be avoided or delayed, so that this is an area where the desired reduction in prescribing could take place. In the case of UTIs, antibiotics are advised more readily.[36] For several RTIs, including common colds, sore throat, sinusitis and acute bronchitis, randomized controlled trials (RCTs) have shown that antibiotics provide no, or negligible benefit compared to placebo[43-46]. As such, symptom management with paracetamol, ibuprofen or the use of CAM therapies proven to be effective and safe for RTIs may safely reduce antibiotic prescribing among patients with a low risk for pneumonia. A recent RCT comparing ibuprofen with fosfomycin treatment for UTIs indicates that it may be more difficult to safely reduce antibiotic prescribing for UTIs using a similar approach.[47]

Our study shows that accessibility of IM/CAM within the NHS in General Practice is very limited, and this limited the number of IM GPs included in our analysis. IM/CAM provision is currently almost exclusively privately provided in the UK, which could be at least partly linked to the austerity measures currently imposed in the UK possibly resulting in NHS IM/CAM provision being withdrawn at a local level in recent years (and imminently nationally). It was seen on practice websites that there was a noticeable amount of 'private' CAM provision available at several NHS surgeries by non-GP CAM practitioners – in weekly clinics for example. However, these surgeries have not been included in our analysis as this study specifically aimed to determine the differences in antibiotic prescribing between conventional GP surgeries and GP surgeries staffing GPs who were additionally trained in IM/CAM.

Attitudes of GPs to IM/CAM are extremely important for it to remain available within the NHS. A 2015 study of these attitudes in England, showed that, despite demand for CAM amongst the general public, GPs remain concerned about its limited evidence base as well as the lack of regulation of CAM practitioners. Nevertheless, those questioned continue to see a role for CAM in clinical practice.[48]

In our study each of the NHS IM GP practices included at least 1 IM GP. However, as the number of (IM) GP partners and salaried (IM) GPs (full time and part time) in these practices varies, proportions of the number of IM GPs per included NHS IM GP surgery are difficult to determine and in addition, will not provide meaningful information as they do not take into account the power balance of the different GPs within these practices.

The impact which any one IM GP could have in terms of antibiotic prescribing may vary hugely between practices partly depending on their status at the practice - as a partner or a salaried employee for example, or as a full-time or part-time worker. In the presented analysis we did not include NHS GP practices that are offering NHS IM/CAM provision by a 'non-GP NHS CAM practitioner' or private IM/CAM practitioner. However, having even one CAM contact within a surgery might give the possibility for others to experience CAM perspectives either formally or informally from them, and for long-held attitudes to be perhaps modified. Additionally, it would be of interest to explore if patients may be independently accessing IM GPs in the private sector and then seeking antibiotics from non-IM GPs in the NHS.

In line with Hawker et al[49], our results suggest that a further decrease in prescribing in conventional surgeries might be possible. It may be that advice should be sought from this small number of surgeries to establish whether their daily clinical practice may differ from other surgeries and whether this could be used to assist others in the fight against AMR.

Although this study found only a small number of CAM practitioners working at NHS General Practices in England, the difference seen in antibiotic prescribing rates at IM GP surgeries warrants further study. It is very likely that, due to similarity in healthcare system (NHS) and the number of NHS IM GPs and - surgeries, our findings are generalisable to Scotland, Wales and Northern-Ireland. However, differences in healthcare systems and the general level of Integrative Medicine practice may lead to other results in other (European) countries. Therefore, analysis in comparison with other (European) countries are indicated to prove whether in general IM GP (surgeries) tend to prescribe less antibiotics or whether other (socio-economic) factors dominate the prescription rate for specific infections.

As the clear majority of CAM practitioners (mainly non-GPs) work privately in England, there is also potential for research into non-antibiotic strategies in private practice, and to analysis of how these practitioners work with their patients' NHS GPs in this regard. However, as patients who self-select to consult IM GPs might be less likely to demand antibiotics, differences in lifestyle and the 'transferabilty of lifestyle skills' need to be taken into account as well in future study design.

Contributor ship statement

- Substantial contributions to the conception and design of the work; EvdW/ LD/PvF/EB
- Acquisition, analysis, or interpretation of data for the work; EvdW/ LD
- Drafting the work and revising it critically for important intellectual content; EvdW/ LD/PvF/EB
- Final approval of the version to be published: EvdW/ LD/PvF/EB

- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: EvdW/ LD/PvF/EB

Competing interests

None declared

Funding

This research was supported in part by an unrestricted grant of WALA Heilmittel GmbH, Germany.

Data sharing statement

Data are available through NHS digital

Acknowledgement

The authors gratefully acknowledge the statistical support of Dr Koen Pouwels (Senior Mathematical/Economic Modeller)

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Table 1. Organisations from which details of training in IM/CAM of GPs were obtained

CAM specialism	Organisation	Website	Method for extracting GP information
Osteopathy	General Osteopathic Council	www.osteopathy.org.uk	Search of online database
Chiropractic	General Chiropractic Council (GCC)	www.gcc-uk.org	GCC staff identified GP registrants
Acupuncture	British Medical Acupuncture Council	www.medical-acupuncture.co.uk	Search of online database
Herbal Medicine	College of Practitioners of Phytotherapy	www.thecpp.uk	CPP staff identified GP registrants
	National Institute of Medical Herbalists	www.nimh.org.uk	NIMH staff identified GP registrants
	The Register of Chinese Herbal Medicine in the UK	www.rchm.co.uk	Search of online database
	The United Register of Herbal Practitioners	www.urhp.com	Search of online database
	The Association of Chinese Medicine and Acupuncture UK	www.atcm.co.uk	Search of online database
Homeopathy	British Homeopathic Association	www.britishhomeopathic.org	Search of online database
	Faculty of Homeopathy	www.facultyofhomeopathy.org	Search of online database
Anthroposophic Medicine	Anthroposophic Health, Education and Social Care Movement	www.ahasc.org.uk	Search of online database

Table 2. IM GP surgeries subdivision (based on website information)

	Apparent level of CAM practice	CAM (n)
Subset 1 (N=9)	General Practices where an integrative medicine (IM) approach is taken **with CAM-trained GP** (N=4)	Homeopathy (1) Anthroposophic Medicine (4) Acupuncture (1)
	General practices listing CAM therapy provision **with CAM-trained GP** (N=5)	Homeopathy (1) Acupuncture (4)
Subset 2 (N=10)	General practices mention a CAM therapy in the listing of the special interests of the GP, but no other information is given and it is **unclear whether the GP practises this CAM therapy at that site**	

Table 3. Baseline characteristics of included NHS GP surgeries

	Conventional GP surgery	IM/CAM GP surgery **(Subset 1)** $
	median (25th-75th percentile)	**median (25th-75th percentile)**
	n=7274	n=9
Number of registered patients	6698 (4162-9942)	7088 (4037-9534)
Male (%)	49.7 (48.8-50.9)	49.3 (46.9-49.4)
Aged 0-17y (%)	20.5 (18.5-23.0)	21.2 (18.7-22.0)
Aged 18-64y (%)	61.2 (58.7-64.2)	61.9 (60.3-62.4)
Aged 65+ y (%)	17.2 (12.3-21.4)	18.2 (14.0-18.4)
STAR-PU**	3705 (2276-5599)	3716 (2315-5382)
Coronary heart disease (%)	3.3 (2.5-4.0)	2.8 (2.1-3.1)*
Heart failure (%)	0.7 (0.5-0.9)	0.5 (0.4-0.8)
Asthma (%)	6.0 (4.9-6.7)	5.1 (4.8-6.2)
COPD (%)	1.8 (1.3-2.4)	1.0 (0.8-2.0)
Cancer (%)	2.4 (1.7-3.0)	2.5 (2.2-2.9)*
Chronic kidney disease (%)	3.0 (2.0-4.1)	1.9 (1.2-2.9)
Diabetes (%)	5.4 (4.5-6.2)	3.9 (2.9-4.6)*
Deprivation score	0.27 (0.11-0.63)	0.36 (0.15-0.48)

$ *Subset 1: General Practices where an integrative medicine approach is taken with CAM-trained GP (N=4)* ***and*** *General practices listing CAM therapy provision with CAM-trained GP (N=5);*

$p<0.05$;

*** STAR-PU stands for 'oral antibacterials item based Specific Therapeutic Group Age-sex weightings Related Prescribing Units. The amount of STAR-PU per practice was estimated by multiplying the number of patients in each age-gender category by the relevant STAR-PU weights (see methods section for detailed explanation on STAR-PUs).*

Table 4. Median antibiotic prescription rates and Relative Risk (RR) of prescribing antibiotics in primary care England over 2016

	Any antibiotic/ STAR-PU[$] Median ($25^{th}$-$75^{th}$ percentile)	RTI antibiotic/ STAR-PU[$] Median ($25^{th}$-$75^{th}$ percentile)	UTI antibiotic/ STAR-PU[$] Median ($25^{th}$-$75^{th}$ percentile)
Conventional GP surgeries (n=7,274)	1.01 (0.86 – 1.17)	0.56 (0.46 – 0.67)	0.22 (0.17 – 0.26)
IM GP surgeries with CAM trained GP (n=9)	0.79 (0.73 – 0.91)*	0.44 (0.37 – 0.48)*	0.21 (0.19 – 0.23)
	Relative Risk (RR)[$] (95% CI)	**Relative Risk (RR)[$] (95% CI)**	**Relative Risk (RR)[$] (95% CI)**
Conventional GP surgeries (n=7,274)	Ref.	Ref.	Ref.
IM GP surgeries with CAM trained GP (n=9)	0.78 (0.64 – 0.97)*	0.74 (0.59 – 0.94)*	0.91 (0.72 – 1.17)

[$]This rate is obtained by dividing the total number of antibiotics prescribed by the number of STAR-PU registered.
**p<0.05*

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page:2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page:2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page:4**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page:5**
Methods		
Study design	4	Present key elements of study design early in the paper **Page:6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page:6, 7**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **Page:6, 7**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page:7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page:7**
Bias	9	Describe any efforts to address potential sources of bias **Page:7**
Study size	10	Explain how the study size was arrived at **Page:6,7,8**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Page:8**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding

		Page:8
		(*b*) Describe any methods used to examine subgroups and interactions **Page:8**
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page:6**
		(b) Give reasons for non-participation at each stage **Page:6**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page: 9, 10 and Table 1, Table 2**
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures **Page: 9, 10 and Table 3, Table 4**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page:9, 10**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page: 11**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page: 11**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page: 11, 12**

Generalisability	21	Discuss the generalisability (external validity) of the study results **Page: 12, 13**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page: 13**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.