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A Retrospective Survey of the Management of Acute Infections and the Indicators for Antibiotic Prescription in Primary Care in Northern Thailand

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A RETROSPECTIVE SURVEY OF THE MANAGEMENT OF ACUTE INFECTIONS AND THE INDICATORS FOR ANTIBIOTIC PRESCRIPTION IN PRIMARY CARE IN NORTHERN THAILAND

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ABSTRACT

Introduction Antibiotic use in low and middle income countries continues to rise despite the knowledge that antibiotic overuse can lead to antimicrobial resistance. There is a paucity of detailed data on the use of antibiotics in primary care in low resource settings.

Objective Describe the presentation of acute infections and the indicators for antibiotic prescription.

Design A two year retrospective survey.

Setting All 32 primary care units in one district in northern Thailand.

Participants Patients attending primary care with a history of fever, documented temperature, ICD 10 code for infection or prescribed a systemic antibiotic. Patients attending four centers where a study was initiated on C-reactive protein testing during this survey were excluded.

Outcome measures Antibiotic prescription rates, odds ratios for the indicators of antibiotic prescription and the clinical presentations.

Results 762,868 patients attended the health centers, of whom 103,196 met the inclusion criteria, 5,966 were excluded resulting in 97,230 attendances consisting of 83,661 illness episodes.

46.9% (39,242) of patients were prescribed an antibiotic during their illness. Indicators for antibiotic prescription in the multivariable logistic regression analysis included male sex (aOR 1.21 [Cl 1.16-1.28], p <0.001), adults (aOR 1.77 [Cl 1.57-2, p <0.001]) and a temperature >37.5°C (aOR 1.24 [Cl 1.03-1.48, p 0.02]). 77.9% of the presentations were for respiratory related problems, of which 98.6% were upper respiratory tract infections. The leading infection diagnoses were common cold (50%), acute pharyngitis (18.9%) and acute tonsillitis (5%), which were prescribed antibiotics in 10.5%, 88.7% and 87.1% of cases respectively. Amoxicillin was the most commonly prescribed antibiotic.

Conclusions Nearly half of the patients received an antibiotic, the majority had a respiratory infection. The results can be used to plan interventions to improve the rationale use of antibiotics. Further studies in private facilities, pharmacies and dental clinics are required.

Word count: 295

Keywords: antibiotic use, primary care, Thailand, fever, respiratory infections

ARTICLE SUMMARY

Strengths and limitations of this study

- Over 80,000 illness episodes reviewed from all primary care units in a district, over a 2 year time period
- Wide range of infections included rather than focusing on one specific infection
- Use of routine electronic data (no Hawthorne Effect), making this work reproducible
- Only included public healthcare facilities
- Reliant on the correct coding and clinical diagnoses of illnesses

BACKGROUND

The proportion of global deaths attributable to communicable diseases has greatly reduced in recent years. Despite these improvements, 10.6% of deaths worldwide in 2015 were thought to be caused by lower respiratory tract infections (LRTIs), diarrhoea, and tuberculosis (TB).¹ In under 5 year olds, 51.8% of deaths worldwide were due to infectious causes in 2013, with pneumonia causing 14.8% of the deaths overall.² In Thailand in 2010, respiratory infections were the leading cause of hospitalisations and deaths of children under the age of 5.³ Prompt access to appropriate antibiotics is vital to prevent many of these unnecessary deaths.⁴ But while inappropriate or no treatment remains a clear cause for concern, global antibiotic consumption increased by 35% between 2000 and 2010, fueled by low and middle income countries (LMIC),⁵ with the majority of antibiotics being consumed in the community.⁶

Overuse and misuse of antibiotics have been linked to the development of antimicrobial resistance (AMR).⁶⁻⁸ Antibiotics prescribed to individuals in primary care have been associated with bacterial resistance in that individual for up to 12 months, and longer and more frequent antibiotic courses are more likely to cause resistance.⁹ The World Health Organization have described AMR in Southeast Asia as being a 'burgeoning and often neglected' issue, stating that a 'post-antibiotic era' may become reality, resulting in common infections and minor injuries being untreatable.¹⁰ In Thailand in 2010, there were an estimated 19,122 deaths attributable to multidrug resistant hospital-acquired infections.¹¹ In August 2016 the Thai government endorsed a national strategic plan for AMR which aims to optimize antimicrobial drug use and reduce the mean consumption of antimicrobials in humans by 20% by 2021.¹²

To appreciate the scale of the problem and to target future interventions a greater understanding of the acute infections presenting to primary care and the conditions for which antibiotics are used in LMICs is required. Such data, however, are limited,¹³ with most studies deriving their estimates from a small sample of health providers and over a limited timeframe, therefore neglecting possible seasonal and spatial variation and other secular trends. In this paper we describe the indications for antibiotic prescription in 32 primary care units (PCUs) across a district in northern Thailand over a two year period.

METHOD

A retrospective computerised search of routinely collected data from primary care units in Mueang Chiangrai District between January 2015 and December 2016 was carried out.

Study sites

Thailand is an upper-middle income country. In 2016 its GDP (gross domestic product) was 406.8 billion (US\$). The average life expectancy at birth is 75 years.¹⁴ Chiangrai is the most northern province in Thailand and shares borders with Laos and Myanmar. It has a population of 1,157,302,¹⁵ of whom 106,987 reside in Mueang Chiangrai District.¹⁶

Thailand's healthcare system is made up of public and private providers. Universal health coverage was established in 2002 following significant investment in the healthcare system and infrastructure since the 1970s. In rural and poorer areas primary healthcare is predominantly provided by the public healthcare system whereas in urban areas hospitals and private clinics play a larger role.¹⁷ Antibiotics can be bought directly from pharmacies and local stores as well as being prescribed by healthcare workers.

In Mueang Chiangrai District family medicine doctors based at the provincial hospital oversee 32 public PCUs which are staffed primarily by two to five nurses and public health officers. On average PCUs look after 5000 patients each.¹⁷ They provide care for acute and chronic conditions as well as providing preventative services such as immunisations, cervical screening and health education. Dental and traditional medicine services are also available. The furthest PCU is 2 hours' drive through the mountains from the provincial hospital in Chiangrai city (see figure 1). Finger-prick blood glucose tests are the only investigations routinely available on site.

Inclusion criteria

Patients were identified with at least one of the following:

- Systemic antibiotic prescription
- International Statistical Classification of Diseases (ICD) 10 code for infection (see supplementary material, table S1)
- Fever as the chief complaint
- Documented temperature >37.5°C at the PCU

We excluded patients attending PCUs used as study sites during or after a recent trial on the use of C-reactive protein (CRP) point of care tests (https://www.clinicaltrials.gov/ct2/show/NCT02758821?term=NCT02758821&rank=1).

Study outcomes

The primary outcome was the overall antibiotic prescription rate. Secondary outcomes included odds ratios for the indicators of antibiotic use, percentages of patients receiving antibiotics according to their diagnosis, percentages of individual antibiotics used and the frequency and type of acute infection presentations.

Data collection and statistical analysis

With the approval of the Chiangrai Provincial and Public Health Office (PHO), a research data manager accessed the PHO's routine medical records database to search for relevant patients and extract the pre-specified variables. Data collected included the PCU attended, patients' number, age, sex, date of visit, chief complaint, temperature, ICD 10 code, and drug prescriptions.

The study database was cleaned with the aid of two native northern Thai speaking study nurses. Our list of ICD codes for infection were reviewed with the other variables to ensure their appropriateness. Repeat attendances within one month were classed as one illness episode allowing for the detection of subsequent antibiotics or treatment changes. If no prescription was recorded we made the assumption that this was because no medication was given rather than the data being missing. All other indicators such as the chief complaint and temperature were taken from the initial presentation. Children were defined as being less than 12 years of age.

The ICD 10 codes were grouped into gastrointestinal, respiratory, skin, urogenital, eye, ear and other categories. Each category was further broken down into conditions such as acute sinusitis and acute pharyngitis. The respiratory category was also grouped into upper and lower respiratory tract infections.

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The proportions of patients prescribed an antibiotic in different demographic groups were summarised and compared using the chi-square test. A logistic regression model was used to model the binary outcome of antibiotic prescription, both unadjusted and adjusted models were fitted. The odds ratios for the indicators of antibiotic prescription were first obtained from univariate logistic regression models and then considered in a multivariable model if they had a p value of <0.05. A temperature of >37.5°C was used rather than the more subjective history of fever. ICD codes were not included because of their strong association with antibiotic prescriptions (e.g. a health worker's diagnosis of acute pharyngitis and its affiliated ICD10 code was inherently associated with antibiotic prescription, as opposed to a diagnosis of 'common cold'). The PCUs were assumed to have a random effect in the model.

Monthly antibiotic prescriptions were weighted by the number of contributing PCUs per month and modelled over the two year period. We used a time-series analysis to separate long-term trends from seasonal variations.^{18 19} Symmetric locally weighted moving averages were used. In this procedure, less weight was applied to time points (in months) furthest away from the present time point. A quarterly

window was used to identify seasonality as follows: $\hat{X}_t = \frac{1}{9}(X_{t-2} + 2X_{t-1} + 3X_t + 2X_{t+1} + X_{t+2})$

Similarly a 12-month time-series window was used to obtain a trend line that would be sensitive to monthly changes but with reduced noise from seasonal variation:

$$\hat{X}_{t} = \frac{1}{24} (X_{t-6} + X_{t+6}) + \frac{1}{12} (X_{t} + X_{t-1} + X_{t+1} + X_{t-2} + X_{t+2} + X_{t-3} + X_{t+3} + X_{t-4} + X_{t+4} + X_{t-5} + X_{t+5})$$

Where \hat{X}_t is the time-series modelled monthly prevalence of antibiotic prescription. Statistical significance was declared at alpha=0.05. Data analyses were performed with STATA version 14 (College Station, Texas, USA). Ethical approval was obtained from Chiangrai's Provincial and Public Health Office IRB (number 56/2560). Exemption was given by the Oxford Tropical Research Ethics Committee (OxTREC). Patients were not involved in the design of the study.

RESULTS

762,868 patients attended the PCUs between the 1st of January 2015 and the 31st of December 2016. The majority of patients' attendances included a chronic disease review or screening, the most common being screening for diseases such as diabetes, hypertension, mental health and dental disorders (145,410), essential hypertension reviews (98,822) and routine child health examinations (75,701).

The appropriateness of the ICD 10 codes for infection used in our inclusion criteria were reviewed alongside the other variables. For example, we found that patients with TB, HIV and Hepatitis B were only attending for regular medications rather than for acute illnesses so they were removed from the ICD 10 inclusion list. Mass head lice treatment at schools is carried out by the PCUs so these codes were also removed. The ICD 10 code 'K05' (dental) was also removed because it transpired that these patients are seen by dentists or dental nurses at the PCUs rather than by the regular PCU staff. All ICD 10 codes for myositis were removed from the inclusion criteria apart from M60.0 (infective myositis) because the other codes were being used for muscle pain or myalgia.

In total 103,196 attendances met our inclusion criteria; 5,966 were then excluded because the PCUs they attended were involved in the CRP study before or during their attendance, resulting in 97,230 attendances (12.8%) meeting our inclusion and exclusion criteria. 13,569 repeat attendances within one month were classed as a single illness episode, leaving 83,661 illness episodes.

Patient Characteristics

The median age was 24 years old with an interquartile range of 6 to 51 years old. Two patients had no age recorded. 54.7% of the patients were female (45,779) compared to 45.3% males (37,882) (p<0.001).

The proportion of patients meeting each inclusion criteria is shown in figure 2 and supplementary table S2. 29,246 (35.3%) patients presented with a history of fever, while 10,508 (13.7%) had a temperature of more than 37.5°C at presentation. 8,871 (11.6%) patients had both a history of fever and a temperature.

Antibiotics

Medications were prescribed for 81,691 (97.7%) illness episodes. 37,011 (44.2%) patients were prescribed an antibiotic during their first visit, and this increased to 39,242 (46.9%) throughout their illness episodes.

Antibiotics were prescribed to:

- 49.2% of men compared to 45% of women (p<0.001)
- 39% of children compared to 51.8% of adults (p < 0.001)
- 40.1% of those with a history of fever
- 47.6% with a temperature >37.5°C
- 38.8% with an ICD 10 code for infection

The proportion of patients within each age group prescribed an antibiotic varied, with the lowest rates in young children (0-4 year olds, 33.8%), peaking in adults (12-39 year olds, 55.9%) and then diminishing in the elderly (aged 65 years and older, 41%, see supplementary material, table S3).

Indicators for antibiotic prescription in the multivariable logistic regression analysis were male sex (aOR 1.21 [CI 1.16-1.28], p <0.001), patients aged 12 years of age or older (compared to those less than 12 years old) (aOR 1.77 [CI 1.57-2, p <0.001]) and having a temperature of more than 37.5°C (aOR 1.24 [CI 1.03-1.48, p 0.02]).

Figure 3 is a time series plot for the monthly prevalence of antibiotic prescriptions. Overall there was no significant trend; incidence rate ratio (IRR) =0.99, 95% CI (0.990, 1.007), p=0.796, although there is a suggestion of a downward trend beginning in the final 6 months. The monthly prevalence of antibiotic prescriptions was at least 39% throughout the 2-year period. Overall prescription rates varied greatly between the PCUs from 8 to 71.6%, with prescribing consistently higher in adults than children.

The majority of patients prescribed an antibiotic received amoxicillin (56.7%) or dicloxacillin (25.1%). Other antibiotics prescribed include norfloxacin (8.9%), co-trimoxazole (4.2%), penicillin V (1.2%), roxithromycin (1.2%), metronidazole (1.2%), erythromycin 0.7%, cephalexin (0.4%) and tetracycline (0.2%).

Presentations and antibiotic prescriptions

The number of acute presentations with ICD 10 codes for infection related to a single system are shown in figure 4. 77.9% of these presentations were for respiratory related problems. 98.6% of these were diagnosed with an upper respiratory tract infection (URTI), 1.1% with an acute LRTI and 0.3% with a chronic LRTI, of these 36.1%, 81.8% and 53.5% were prescribed antibiotics respectively. The most common single infection diagnoses were common cold (34,549, 50%), acute pharyngitis (13,080, 18.9%) and acute tonsillitis (3,459, 5%), antibiotics were prescribed to 10.5%, 88.7% and 87.1% of the cases respectively (see table 1).

Number of presentations n/N (%)	Episode antibiotics prescribed n/N (%)	Commonest antibiotic prescribed (%)
34,549/69,115 (50)	3,643/34,549 (10.5)	Amoxicillin (71.7)
13,080/69,115 (18.9)	11,607/13,080 (88.7)	Amoxicillin (91.5)
3,459/69,115 (5)	3,014/3,459 (87.1)	Amoxicillin (93.4)
2,412/69,115 (3.5)	1,614/2,412 (66.9)	Norfloxacin (68.8)
2,097/69,115 (3.0)	330/2,097 (15.7)	Amoxicillin (56.4)
1,231/69,115 (1.8)	65/1,231 (5.3)	Amoxicillin (41.5)
1,230/69,115 (1.8)	1,165/1,230 (94.7)	Norfloxacin (75.9)
	presentations n/N (%) 34,549/69,115 (50) 13,080/69,115 (18.9) 3,459/69,115 (5) 2,412/69,115 (3.5) 2,097/69,115 (3.0) 1,231/69,115 (1.8)	presentations n/N (%) prescribed n/N (%) 34,549/69,115 (50) 3,643/34,549 (10.5) 13,080/69,115 (18.9) 11,607/13,080 (88.7) 3,459/69,115 (5) 3,014/3,459 (87.1) 2,412/69,115 (3.5) 1,614/2,412 (66.9) 2,097/69,115 (3.0) 330/2,097 (15.7) 1,231/69,115 (1.8) 65/1,231 (5.3)

Table 1: Common diagnoses in patients with one single ICD 10 code for infection, whether antibiotics were prescribed and which antibiotic was mostly commonly used

Supplementary table S4 shows the number of individual infection diagnoses by systems and the rates of antibiotic prescriptions. Antibiotics were prescribed to 59.4% of skin infections, 81.1% of otitis media, 79.5% of otitis externa, 94.7% of cystitis, 80.3% of hordeolum (styes) and chalazions as well as 15.7% of conjunctivitis cases. Of the total antibiotics prescribed almost a third (29.6%) were given to those with acute pharyngitis, followed by common cold (9.3%), acute tonsillitis (7.7%), gastroenteritis & colitis (4.1%) and cystitis (3%) as the single infection diagnoses.

13.8% of patients (11,547) were prescribed antibiotics without a temperature, history of fever or ICD 10 code for infection. Of those who had a single ICD 10 code recorded 1,815 (24.6%) of these antibiotics were for dental reasons, 1,002 (13.6%) for surgical follow up care, 526 (7.1%) for contact dermatitis and 473 (6.4%) for open wounds, see supplementary material, figure S1. These patients were more likely to be male (54.3%, p value <0.001) and older (median age of 41 compared to 24 years old) than the main patient group. The distribution of ages and temperatures between the main patient group and those meeting only the antibiotic inclusion criteria were both significantly different (p value <0.001).

DISCUSSION

To the best of our knowledge this is the largest review of acute illness presentations and community antibiotic prescribing in a LMIC. Over a 2 year period there were more than 97,000 attendances to 32 PCUs for acute infections and nearly half these patients received an antibiotic, with no significant change in prescribing levels over the 2 year study period. Studies of this magnitude are required to

increase our knowledge of the scale of antibiotic prescribing as well as the common conditions they are used for.²⁰²¹ Thailand's 2016 national strategic plan on AMR also highlighted the importance of monitoring and reporting antimicrobial consumption.²²

Comparing overall antibiotic prescribing rates with other studies is challenging because of varying definitions of acute illnesses and the different patient populations. However the antibiotic prescribing rate in our study is more than double the prescribing in a Malaysian study but similar to studies in India and Laos.²³⁻²⁵ A third of our patients had a history of fever, which is similar to a point prevalence study in India where fever was the most common symptom.²⁶ Almost 80% of the ICD 10 codes for infection were related to respiratory infections, which is consistent with respiratory infections being the leading cause of hospitalisations and deaths in Thai under 5 year olds³ but is higher than the proportion of respiratory presentations in other South and Southeast Asian countries.^{26 27} Antibiotic prescribing in Thailand for tonsillitis and pharyngitis remains high despite Group A beta-haemolytic Streptococci being isolated in only 3.8-7.9% of those with URTI.^{28 29}

Thailand's Antibiotic Smart Use 2007 project targets three conditions which are unlikely to require antibiotic treatment but for which they are commonly prescribed; URTIs, acute diarrhoea and simple wounds.³⁰ In the first phase of this project overall antibiotic use in PCUs was reduced by between 39% and 46%. Prescriptions for the three target conditions reduced from 54.5% to 25.4%.³¹ Despite the lower prescribing levels for common colds in our survey there were still 3,643 antibiotic prescriptions for this condition and 66.9% of those with gastroenteritis and colitis received antibiotics. Open wounds and superficial injuries were common diagnoses in those prescribed an antibiotic without a history of fever, temperature or ICD 10 code for infection. The results reveal the ongoing high levels of prescribing for these conditions and present an opportunity to further improve antibiotic use. Since October 2016 an antibiotic prescribing target of less than 20% for these three conditions has been incorporated into Thailand's rationale drug use service plan as well as the pay for performance health criteria, financial incentives are given to the PCUs achieving this target. A review of the long term effectiveness of this policy including any impact on patient safety is required.

Our study also identifies high levels of prescribing for skin infections, otitis media, otitis externa, cystitis, hordeolum (styes) and chalazions. A lack of available topical antibiotics may account for the high prescribing for skin infections as well as for otitis externa. However, despite antibacterial eye drops being available, 15.7% of conjunctivitis cases were still prescribed a systemic antibiotic. Urine dipstick tests are not available on site to assess patients with cystitis or suspected urinary tract infections. Introduction of these simple tests may help to rationalize prescribing for these conditions in a setting where urine cultures are not readily available or achievable.

While we did not set out to review dental prescribing, this area accounted for 25% of the antibiotics prescribed to those without a history of fever, temperature or ICD 10 code for infection, which warrants further investigation.

Some of the variation in antibiotic prescribing rates between PCUs may be accounted for by the degree of staff training. Two out of the three highest prescribing PCUs are staffed only by public health officers. The study findings are being used to guide educational updates and training for the PCU staff, with priority being given to those PCUs without nurses and with high prescription rates for conditions unlikely to require antibiotics.

Strengths and limitations

The main strength of this study is the large number of illness episodes included. The two year time period should allow for seasonal variations and disease epidemics. We reviewed prescribing in all of the PCUs in Mueang Chiangrai District which covers a large geographical area and has a range of rural and urban facilities, making the results generalizable to the region more broadly. Many studies have focused on prescribing for specific conditions such as URTIs but our study covers a wide range of infections that present in the community. Having research staff on site has been shown to influence healthcare workers' prescribing habits (the Hawthorne Effect), but due to the retrospective nature of the study this was not a source of bias. The use of routinely collected data means that this methodology could be repeated in other districts and provinces in Thailand, although a lot of the data are entered as free text which presents challenges for analysis. Searching for patients with a history of fever, for instance, was problematic because the Thai word 'lit' or fever is also part of the Thai words for patient, influenza, antipyrexials, etc.

Limitations of this study are that we only included public PCUs and have no data on antibiotic use by private clinics, pharmacies or family medicine doctors based at the provincial hospital, which requires further study. The PCU data is taken from routine electronic records and in some instances there were tranches of missing data (5 PCUs had missing data for several months). Verifying the quality of the data is also challenging; coding of clinical diagnoses for instance using ICD 10 could be inaccurate or inconsistent between healthcare workers. Our decision to class all attendances within a one month period as a single illness episode means that we may have incorrectly classed some new illnesses as a repeat attendance but did allow us to review antibiotic prescribing over the course of the illness.

CONCLUSIONS

This study provides much needed insight into the use of antibiotics in primary care in northern Thailand, allowing targeting of interventions to improve the rationale use of antibiotics. Nearly half of all patients attending with an acute illness received an antibiotic. The majority of presentations were for respiratory infections. Further education and resources are required to support clinicians in the targeting of antibiotics. This could include the introduction of clinical algorithms and point of care tests such as CRP and urine dipsticks. Antibiotic guidelines are required for common conditions seen in primary care outside of the current Antibiotic Smart Use policy. Further studies including qualitative work are required to appreciate the use of antibiotics in other settings such as private facilities, pharmacies and dental clinics.

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Competing interests

None declared

Author contribution statement

All authors (RCG, DI, MM, PW, NPJD, SN and YL) were involved in the design of the study. PW collected the data. RCG carried out the analysis with support from YL. MM provided statistical support. RCG, YL, DI SN and MM interpreted the data. RCG wrote the first draft of the paper. YL, NPJD and MM reviewed subsequent drafts. All authors (RCG, DI, MM, PW, NPJD, SN and YL) contributed to and approved the final draft for publication.

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Data sharing statement

We are unable to share additional unpublished data which falls under the jurisdiction of the Chiang Rai PHO.

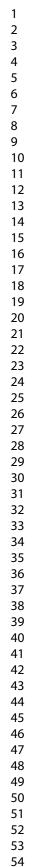
Ethical approval

Ethical approval was obtained from Chiangrai's Provincial and Public Health Office IRB (number 56/2560). Exemption was given by the Oxford Tropical Research Ethics Committee (OxTREC). Individual informed consent was not required.

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4 5 6	Figure 1: Chiangrai and the 32 PCUs
7 8	Figure 2: A Venn diagram to show the inclusion criteria
9 10 11	Figure 3: Trend and seasonality of antibiotic prescriptions overlaid by mean antibiotic prescription rates per PCU
12 13	Figure 4: Number of acute presentations by single systems and whether antibiotics were prescribed
13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32	Figure 4: Number of acute presentations by single systems and whether antibiotics were prescribed
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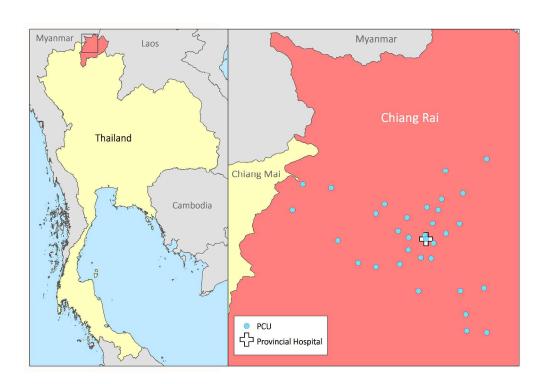
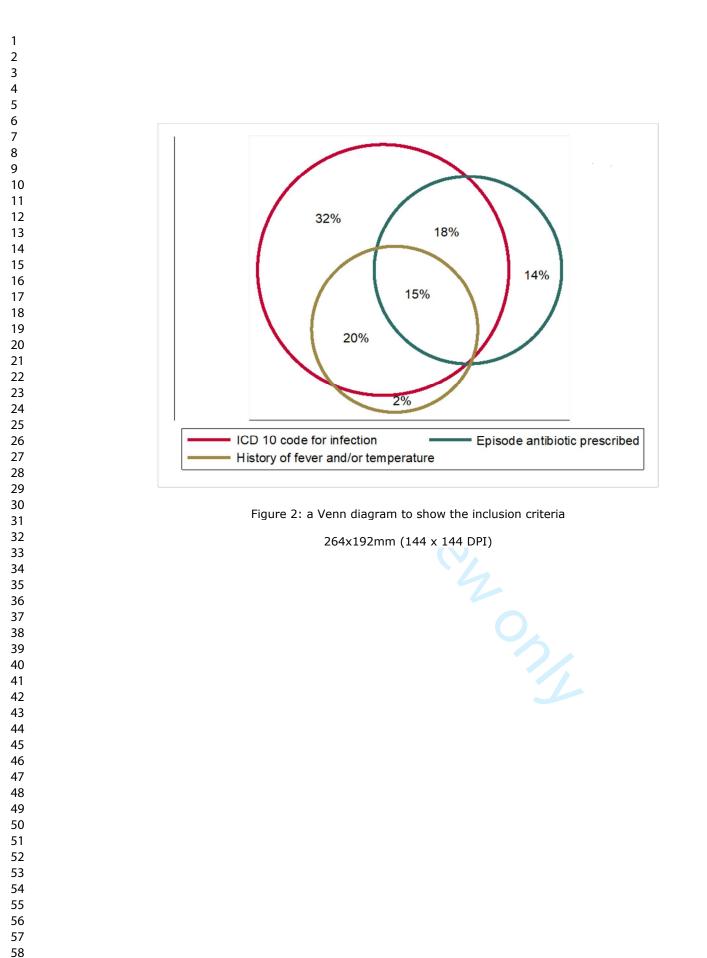


Figure 1: Chiangrai and the 32 PCUs

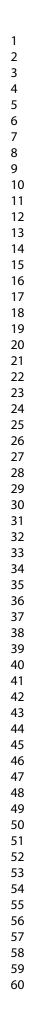
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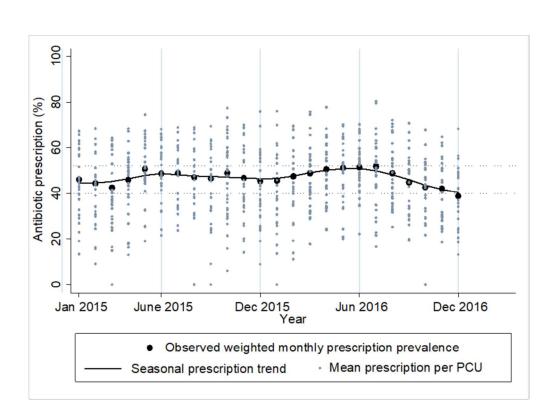
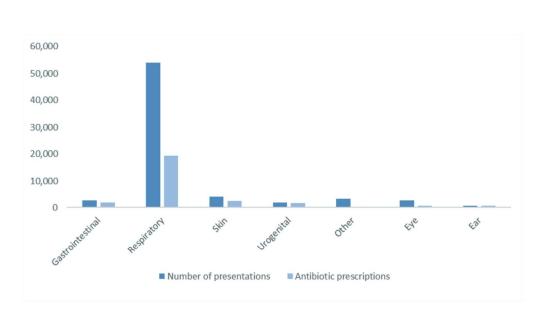


Figure 3: Trend and seasonality of antibiotic prescriptions overlaid by mean antibiotic prescription rates per PCU

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SUPPLEMENTARY MATERIAL

Code	Description	Excluded
А00-В99	Certain infectious and parasitic	A15, A16, A18, A319, B18, B24,
	diseases	B85
G00-G07	Inflammatory diseases of the central	
	nervous system	
H00-01	Hordeolum, chalazion and other	H01.1
	inflammation of the eyelid	
H05.0	Acute inflammation of orbit	
H10	Conjunctivitis	
H60-H70	Otitis externa, otitis media and	H61
	mastoiditis	
H72-73	Perforation and other disorders of the	H73.9
	tympanic membrane	
J00-43	Respiratory tract infections	J30, J31, J33, J35.1
J47	Bronchiectasis	
К05	Gingivitis and periodontal diseases	Exclude all
K11-12	Diseases of salivary glands, stomatitis	K11.1, K11.88, K11.9, K12.0,
	and related lesions	K12.1
K35-37	Appendicitis	
K57	Diverticulitis	K57
K61	Abscess of anal and rectal regions	
K81	Cholecystitis	
K83-85	Cholangitis and pancreatitis	
L00-08 Infections of the skin and		
	subcutaneous tissue	
L20-22	Dermatitis	Exclude all
L30.3	Infective dermatitis	<u> </u>
L70-73.2	Acne, rosacea follicular cysts and	0.
	follicular disorders	
M00-03	Infectious arthropathies	M0013, M0023, M0167, M020
M60	Myositis	M60.1-M6099
N10-11	Tubulo-interstitial nephritis	
N30	Cystitis	
N34	Urethritis and urethral syndrome	
N34Orethnis and drethna syndromeN39.0Urinary tract infection, site not		
	specified	
N41	Inflammatory diseases of prostate	
N45	Orchitis and epididymitis	
N48-49	Other disorders of male genital organs N48.9	
N61	Inflammatory disorders of breast	1110.5
N70-76	Inflammatory diseases of female pelvic	
1470-70		
	organs	

008.0	Genital tract and pelvic infection	
	following abortion and ectopic and	
	molar pregnancy	
023	Infections of genitourinary tract in	
	pregnancy	
O85-86	Puerperal sepsis and other puerperal	
	infections	
P35-9	Infections specific to the perinatal	
	period	
R05	Cough	
R11	Nausea and vomiting	
R30	Pain associated with micturition	
R36	Urethral discharge	
R50	Fever	
Fable S1: ICD 10	codes for infection used for the inclusion criteria	

Total initial	Antibiotic prescription	
presentations	during the illness episode	
29,246/82,976 (35.3%)	11,725/29,246 (40.1%)	
10,508/76,644 (13.7%)	5,003/10,508 (47.6%)	
70,137/83,338 (84.2%)	27,234/70,137 (38.8%)	
37,011/83,661 (44.2%)	39,242/83,661 (46.9%)	
	presentations 29,246/82,976 (35.3%) 10,508/76,644 (13.7%) 70,137/83,338 (84.2%)	

Table S2: the number of initial presentations for each inclusion criteria and the percentage prescribed antibiotics during their illness episode

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Age (years)	Number of presentations n/N (%)	Number of patients receiving an antibiotic prescription n/N
0-4	18,073/83,659 (21.6)	(%) 6,110/18,073 (33.8)
5-11	13,775/83,659 (16.5)	6,318/13,775 (45.9)
12-24	10,533/83,659 (12.6)	5,888/10,533 (55.9)
25-39	11,025/83,659 (13.2)	6,167/11,025 (55.9)
40-64	23,134/83,659 (27.7)	11,843/23,134 (51.2)
65 or over	7,119/83,659 (8.5)	2,915/7,119 (41)
Total	83,659 (100)	39,241/83,659 (46.9)
able S3: the number of	f presentations per age group and the perce	entage of each group prescribed a

Table S3: the number of presentations per age group and the percentage of each group prescribed an antibiotic

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Diagnosis	Number of	Number of antibiotic
	presentations n/N (%)	prescriptions during the
		illness episode n/N (%)
Respiratory		
Common cold	34,549/53,819 (64.2)	3,643/34,549 (10.5)
Acute sinusitis	30/53,819 (0.1)	25/30 (83.3)
Acute pharyngitis	13,080/53,819 (24.3)	11,607/13,080 (88.7)
Acute tonsillitis	3,459/53,819 (6.4)	3,014/3,459 (87.1)
Other URTIs	357/53,819 (0.7)	278/357 (77.9)
Acute LRTIs	663/53,819 (1.2)	541/663 (81.6)
Chronic bronchitis,	60/53,819 (0.1)	10/60 (16.7)
emphysema &		
bronchiectasis		
Cough	1,621/53,819 (3)	99/1,621 (6.1)
Sub total	53,819 (100)	19,217/53,819 (35.7)
Gastrointestinal		
Bacterial intestinal	199/2,706 (7.4)	127/199 (63.8)
infections or intoxications		
Viral enteritis	46/2,706 (1.7)	4/46 (8.7)
GE & colitis	2,412/2,706 (89.1)	1,614/2,412 (66.9)
Appendicitis	21/2,706 (0.8)	2/21 (9.5)
Other	9/2,706 (0.3)	2/9 (22.2)
Sialoadenitis	19/2,706 (0.7)	16/19 (84.2)
Sub total	2,706 (100)	1,765/2,706 (65.2)
Skin		
Infective dermatitis	85/4,060 (2.1)	70/85 (82.4)
Dermatophytosis	902/4,060 (22.2)	92/902 (10.2)
Other superficial mycoses	197/4,060 (4.9)	14/197 (7.1)
Candidiasis	101/4,060 (2.5)	23/101 (22.8)
Other	64/4,060 (1.6)	52/64 (81.3)
Scabies & infestations	52/4,060 (1.3)	8/52 (15.4)
Cellulitis & abscesses	841/4,060 (20.7)	618/841 (73.5)
Bacterial skin infections	533/4,060 (13.1)	464/533 (87.1)
Furuncles, caruncles &	947/4,060 (23.3)	780/947 (82.4)
cysts		
Other local infection of the	338/4,060 (8.3)	290/338 (85.8)
skin & subcutaneous tissue		
Sub total	4,060 (100)	2,411/4060 (59.4)
Eye		
Conjunctivitis	2,097/2,698 (77.7)	330/2,097 (15.7)
Hordeolum & chalazion	319/2,698 (11.8)	256/319 (80.3)
Other inflammation of the	268/2,698 (9.9)	98/268 (36.6)
eyelid & orbit		
Trachoma	14/2,698 (0.5)	5/14 (35.7)
Sub total	2,698 (100)	689/2,698 (25.5)
Ear		

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2			
3	Otitis externa	464/753 (61.6)	369/464 (79.5)
4	Otitis media	243/753 (32.3)	197/243 (81.1)
5 6	Mastoiditis	16/753 (2.1)	9/16 (56.3)
7	Perforation of tympanic	30/753 (4)	25/30 (83.3)
8	membrane & other		
9	disorders		
10	Sub total	753 (100)	600/753 (79.7)
11	Urogenital		
12	Acute tubulo-interstitial	36/1,871 (1.9)	32/36 (88.9)
13	nephritis	50/1,071 (1.5)	52/50 (88.5)
14	Other	17/1,871 (0.9)	12/17 (70.6)
15 16	Cystitis, UTI, dysuria,		1,291/1,370 (94.2)
17	urethritis & urethral	1,370/1,871 (73.2)	1,291/1,370 (94.2)
18			
19	syndrome	22/1 071 (1 7)	20/22/22 5
20	Other disorders of male	32/1,871 (1.7)	20/32 (62.5)
21	genital organs		
22	Other inflammatory	148/1,871 (7.9)	115/148 (77.7)
23	disorders of female pelvic		
24	organs		
25	Other inflammatory	268/1,871 (14.3)	149/268 (55.6)
26 27	disorders of the vagina &		
27 28	vulva		
29	Sub total	1,871 (100)	1,619/1,871 (86.5)
30	Other		
31	Bacterial	85/3,208 (2.7)	28/85 (32.9)
32	Unknown aetiology	33/3,208 (1)	14/33 (42.4)
33	Viral	728/3,208 (22.7)	153/728 (21)
34	Fungal	36/3,208 (1.1)	2/36 (5.6)
35	Protozoal	10/3,208 (0.3)	0/10 (0)
36	Parasitic	1,880/3,208 (58.6)	99/1,880 (5.3)
37 38	Nausea & vomiting	268/3,208 (8.4)	30/268 (11.2)
30 39	Fever of unknown or other	168/3,208 (5.2)	10/168 (6)
40	origin		-, (-)
41	Sub total	3,208 (100)	336/3,208 (10.5)
42			nd system and whether antib

Table S4: the number of presentations per diagnosis and system and whether antibiotics were prescribed for that illness episode

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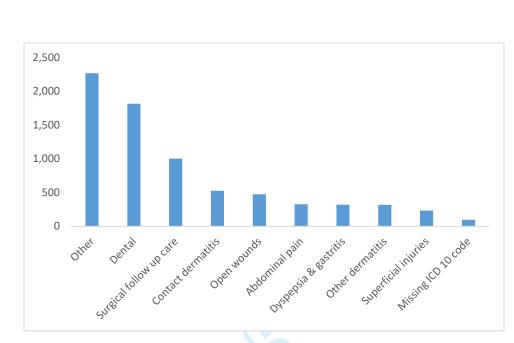


Figure S1: Single diagnoses used for antibiotic prescriptions without a history of fever, temperature or ICD 10 code for infection

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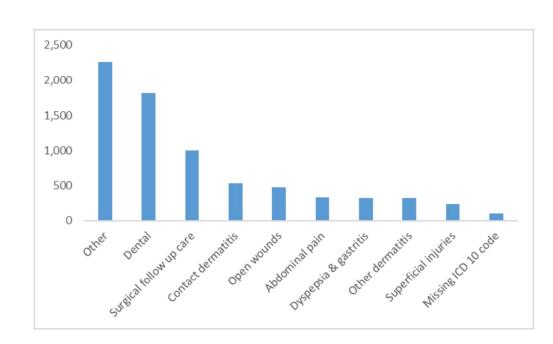


Figure S1: Single diagnoses used for antibiotic prescriptions without a history of fever, temperature or ICD 10 code for infection

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A Retrospective Review of the Management of Acute Infections and the Indications for Antibiotic Prescription in Primary Care in Northern Thailand

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Complete List of Authors:		
Primary Subject Heading :	Infectious diseases	
Secondary Subject Heading:	General practice / Family practice	
Keywords:	antibiotic use, PRIMARY CARE, Thailand, fever, Respiratory infections < THORACIC MEDICINE	

SCHOLARONE[™] Manuscripts

A RETROSPECTIVE REVIEW OF THE MANAGEMENT OF ACUTE INFECTIONS AND THE INDICATIONS FOR ANTIBIOTIC PRESCRIPTION IN PRIMARY CARE IN NORTHERN THAILAND

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Word count: 4002

ABSTRACT

Introduction Antibiotic use in low and middle income countries continues to rise despite the knowledge that antibiotic overuse can lead to antimicrobial resistance. There is a paucity of detailed data on the use of antibiotics in primary care in low resource settings.

Objective Describe the presentation of acute infections and the indications for antibiotic prescription.

Design A two year retrospective review of routinely collected data.

Setting All 32 primary care units in one district in northern Thailand.

Participants Patients attending primary care with a history of fever, documented temperature, ICD 10 code for infection or prescribed a systemic antibiotic. Patients attending after the initiation of a study on C-reactive protein testing in four centres were excluded.

Outcome measures The proportion of patients prescribed an antibiotic and the frequency of clinical presentations.

Results 762,868 patients attended the health centers, of whom 103,196 met the inclusion criteria, 5,966 were excluded resulting in 97,230 attendances consisting of 83,661 illness episodes.

46.9% (39,242) of patients were prescribed an antibiotic during their illness. Indications for antibiotic prescription in the multivariable logistic regression analysis included male sex (aOR 1.21 [Cl 1.16-1.28], p <0.001), adults (aOR 1.77 [Cl 1.57-2, p <0.001]) and a temperature >37.5°C (aOR 1.24 [Cl 1.03-1.48, p 0.020]). 77.9% of the presentations were for respiratory related problems, of which 98.6% were upper respiratory tract infections. The leading infection diagnoses were common cold (50%), acute pharyngitis (18.9%) and acute tonsillitis (5%), which were prescribed antibiotics in 10.5%, 88.7% and 87.1% of cases respectively. Amoxicillin was the most commonly prescribed antibiotic.

Conclusions Nearly half of the patients received an antibiotic, the majority of whom had a respiratory infection. The results can be used to plan interventions to improve the rational use of antibiotics. Further studies in private facilities, pharmacies and dental clinics are required.

Word count: 299

Keywords: antibiotic use, primary care, Thailand, fever, respiratory infections

ARTICLE SUMMARY

Strengths and limitations of this study

- Over 80,000 illness episodes reviewed from all primary care units in a district, over a two year time period
- Wide range of infections included rather than focusing on one specific infection
- Use of routine electronic data (no Hawthorne Effect), making this work reproducible
- Only included public healthcare facilities
- Reliant on the correct coding and clinical diagnoses of illnesses

BACKGROUND

The proportion of global deaths attributable to communicable diseases has greatly reduced in recent years. Despite these improvements, 10.6% of deaths worldwide in 2015 were thought to be caused by lower respiratory tract infections (LRTIs), diarrhoea, and tuberculosis (TB).¹ In under five year olds, 51.8% of deaths worldwide were due to infectious causes in 2013, with pneumonia causing 14.8% of the deaths overall.² In Thailand in 2010, respiratory infections were the leading cause of hospitalisations and deaths in children under the age of five.³ Prompt access to appropriate antibiotics is vital to prevent many of these unnecessary deaths.⁴ But while inappropriate or no treatment remains a clear cause for concern, the global antibiotic consumption rate increased by 39% between 2000 and 2015, fueled by low and middle income countries (LMIC),⁵⁶ with the majority of antibiotics being consumed in the community.⁷

Overuse and misuse of antibiotics have been linked to the development of antimicrobial resistance (AMR).⁷⁻⁹ Antibiotics prescribed to individuals in primary care have been associated with bacterial resistance in that individual for up to 12 months, and longer and more frequent antibiotic courses are more likely to cause resistance.¹⁰ The World Health Organization has described AMR in Southeast Asia as a 'burgeoning and often neglected' issue, stating that a 'post-antibiotic era' may become reality, resulting in common infections and minor injuries being untreatable.¹¹ In Thailand in 2010, there were an estimated 19,122 deaths attributable to multidrug resistant hospital-acquired infections.¹² Thailand has been making sustained efforts to reduce inappropriate antibiotic use; its Antibiotic Smart Use program started in 2007 and targets three conditions which are unlikely to require antibiotic treatment but for which they are commonly prescribed: upper respiratory tract infections (URTIs), acute diarrhoea and simple wounds.¹³ Prescribing targets have been incorporated into the public health system's pay for performance criteria. In August 2016 the Thai government endorsed a national strategic plan for AMR which aims to optimize antimicrobial drug use and reduce the mean consumption of antimicrobials in humans by 20% by 2021.¹⁴

To appreciate the scale of the problem and to target future interventions, a greater understanding of the acute infections presenting to primary care and the conditions for which antibiotics are used in LMICs is required. Such data, however, are limited,¹⁵ with most studies deriving their estimates from small samples of health providers and over a limited timeframe, therefore neglecting possible seasonal and spatial variation and other secular trends. In this paper we describe the indications for antibiotic prescription in 32 primary care units (PCUs) across a district in northern Thailand over a two year period.

Study sites

Thailand is an upper-middle income country. In 2016 its gross domestic product (GDP) was 406.8 billion USD. The average life expectancy at birth is 75 years.¹⁶ Chiangrai is the most northern province in Thailand and shares borders with Laos and Myanmar. It has a population of 1,282,544, of whom 241,436 reside in Mueang Chiangrai District.^{17 18} Thailand has three seasons, the wet season typically runs from July to October, the cool season from November to February and the hot season from March to June.

Thailand's healthcare system is made up of public and private providers. Universal health coverage was established in 2002 following significant investment in the healthcare system and infrastructure since the 1970s. In rural and poorer areas primary healthcare is predominantly provided by the public healthcare system whereas in urban areas hospitals and private clinics play a larger role.¹⁹

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Antibiotics can be bought directly from pharmacies and local stores as well as being prescribed by healthcare workers. Community antibiotic guidelines exist for some but not all common infections, including assessment criteria (e.g. the Centor criteria for acute tonsillitis), first line antibiotics, their dose and duration. There are prescribing restrictions in place for some broad spectrum antibiotics such as amoxicillin and clavulanic acid (Co-amoxiclav), which cannot be prescribed by nurses working in the public primary care system. More comprehensive hospital based guidelines are available.

In Mueang Chiangrai District family medicine doctors based at the provincial hospital oversee 32 public PCUs which are staffed primarily by two to five nurses and public health officers. On average PCUs look after 5000 patients each.¹⁹ They provide care for acute and chronic conditions as well as providing preventative services such as immunisations, cervical screening and health education. Dental and traditional medicine services are also available. The furthest PCU is two hours' drive through the mountains from the provincial hospital in Chiangrai city (see figure 1). Finger-prick blood glucose tests are the only investigations routinely available on site.

METHOD

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55 56 A retrospective computerised search of routinely collected data from primary care units in Mueang Chiangrai District between January 2015 and December 2016 was carried out.

Inclusion criteria

Patients were identified with at least one of the following:

- Systemic antibiotic prescription
- International Statistical Classification of Diseases (ICD) 10 code for infection (see supplementary material, table S1)
- Fever as the chief complaint •
- Documented temperature >37.5°C at the PCU •

We excluded patients attending PCUs used as study sites during or after a recent trial on the use of Creactive protein (CRP) point of care tests

(https://www.clinicaltrials.gov/ct2/show/NCT02758821?term=NCT02758821&rank=1).

Study outcomes

The primary outcome was the overall proportion of illness episodes prescribed an antibiotic. Risk factors for antibiotic use are reported as well as the percentages of patients receiving antibiotics according to their diagnosis, percentages of individual antibiotics used and the frequency and type of acute infection presentations.

Data collection

With the approval of the Chiangrai Provincial and Public Health Office (PHO), a research data manager accessed the PHO's routine medical records database to search for relevant patients and extract the pre-specified variables. Data collected consisted of the PCU attended, patients' number, age, sex, date of visit, chief complaint, temperature, ICD 10 code, and drug prescriptions.

Data cleaning and coding

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Each inclusion criteria was classified as being present, absent or that the data were missing. Antibiotics were searched for in the prescription field (free text) and coded as prescribed (yes or no). A predefined antibiotic list (see supplementary material) was generated using the formulary. All medications prescribed in the dataset were reviewed to ensure no antibiotics were omitted due to spelling errors or their absence from our original list. If no prescription was recorded we made the assumption that this was because no medication was given rather than the data being missing.

Our predefined list of ICD 10 codes for infection (see supplementary material, table S1) were searched for in the diagnosis field (free text field, containing ICD 10 codes only) and then coded as present or absent. Our list of ICD 10 codes were reviewed with the other variables to ensure their appropriateness.

We searched for the word 'fever' in Thai in the chief complaint field (free text). In some cases 'no fever' was recorded, or the word 'fever' was present but part of a phrase alluding to a patient more generally, or 'influenza vaccine'. This field was checked manually with the help of two native northern Thai speaking study nurses. History of fever in the chief complaint was then coded as yes or no. Documented temperatures over 37.5°C at the PCU were searched for in the temperature field and then coded as temperature >37.5°C yes or no.

Repeat attendances within one month were classed as one illness episode allowing for the detection of subsequent antibiotics or treatment changes. All other indications such as the chief complaint and temperature were taken from the initial presentation. Children were defined as being under 12 years of age. The ICD 10 codes were grouped into gastrointestinal, respiratory, skin, urogenital, eye, ear and other categories. Each category was further broken down into conditions such as acute sinusitis and acute pharyngitis. The respiratory category was also grouped into upper and lower respiratory tract infections.

Statistical analyses

Descriptive statistics

Categorical variables were summarised using counts and percentages. Non-normally distributed data were described using medians and interquartile ranges and compared using the ranksum test. The proportions of patients prescribed an antibiotic in different demographic groups were summarised and compared using the chi-square test.

Logistic and Poisson regression models

A logistic regression model was used to model the binary outcome of antibiotic prescription (yes or no); both unadjusted and adjusted models were fitted and accounted for clustering of patients attending the same PCU. The odds ratios for the indications of antibiotic prescription were first obtained from univariate logistic regression models and then considered in a multivariable model if they had a p value of <0.05. Indications included sex, age category and documented temperature. The main purpose of this model was to identify risk factors that were independently associated with antibiotic prescription. A temperature of >37.5°C was used rather than the more subjective history of fever. ICD 10 codes were not included because of their strong association with antibiotic prescriptions (e.g. a health worker's diagnosis of acute pharyngitis and its affiliated ICD 10 code was inherently associated with antibiotic prescription, as opposed to a diagnosis of 'common cold'). Furthermore a Poisson regression model of the monthly number of antibiotic prescriptions over the 24 month period was produced to obtain the Incidence Rate Ratios and 95% confidence intervals.

Time-series analysis

Monthly antibiotic prescriptions were weighted by the number of contributing PCUs per month and modelled over the two year period. When time-series analysis is used for forecasting, it is common to apply it to periods of five years or more, however, our aim was not to forecast into the future but to simply describe the current trends in antibiotic prescription.^{20 21} We used a time-series analysis to separate long-term trends from seasonal variations.^{22 23} Symmetric Locally Weighted Moving Averages (MA) were used. In this procedure, less weight was applied to time points (in months) furthest away from the present time point. The data was available on a monthly basis, however, a quarterly window

was used to identify seasonality as follows: $\hat{X}_t = \frac{1}{9}(X_{t-2} + 2X_{t-1} + 3X_t + 2X_{t+1} + X_{t+2})$

Similarly a 12-month time-series window was used to obtain a trend line that would be sensitive to monthly changes but with reduced noise from seasonal variation:

$$\hat{X}_{t} = \frac{1}{24}(X_{t-6} + X_{t+6}) + \frac{1}{12}(X_{t} + X_{t-1} + X_{t+1} + X_{t-2} + X_{t+2} + X_{t-3} + X_{t+3} + X_{t-4} + X_{t+4} + X_{t-5} + X_{t+5})$$

Where \hat{X}_t is the time-series modelled monthly prevalence of antibiotic prescription. Statistical significance was declared at alpha=0.05. Data analyses were performed with STATA version 14 (College Station, Texas, USA).

Ethical approval

Ethical approval was obtained from Chiangrai's Provincial and Public Health Office IRB (number 56/2560). Exemption was given by the Oxford Tropical Research Ethics Committee (OxTREC).

Patient and public involvement

Patients were not involved in the design of the study. Due to the study's retrospective nature patients were not involved in the recruitment processes. Study results will be disseminated through community presentations as well as educational updates for the healthcare workers and community volunteers.

RESULTS

762,868 patients attended the PCUs between the 1st of January 2015 and the 31st of December 2016. The majority of patients' attendances included a chronic disease review or screening, the most common being screening for diseases such as diabetes, hypertension, mental health and dental disorders (145,410), essential hypertension reviews (98,822) and routine child health examinations (75,701).

The appropriateness of the ICD 10 codes for infection used in our inclusion criteria were reviewed alongside the other variables. For example, we found that patients with TB, HIV and Hepatitis B were only attending for regular medications rather than for acute illnesses so they were removed from the ICD 10 inclusion list. Mass head lice treatment at schools is carried out by the PCUs so these codes were also removed. The ICD 10 code 'K05' (dental) was also removed because it transpired that these patients are seen by dentists or dental nurses at the PCUs rather than by the regular PCU staff. All ICD 10 codes for myositis were removed from the inclusion criteria apart from M60.0 (infective myositis) because the other codes were being used for muscle pain or myalgia (see supplementary material, table S1).

In total 103,196 attendances met our inclusion criteria; 5,966 were then excluded because the PCUs they attended were involved in the CRP study before or during their attendance, resulting in 97,230 attendances (12.7%) meeting our inclusion and exclusion criteria. 13,569 repeat attendances within one month were classed as a single illness episode, leaving 83,661 illness episodes.

Patient characteristics

The median age was 24 years old with an interquartile range of 6 to 51 years old. Two patients had no age recorded. 54.7% of the patients were female (45,779) compared to 45.3% males (37,882) (p<0.001).

The proportion of patients meeting each inclusion criteria is shown in figure 2 and supplementary material table S2. 29,246 (35.3%) patients presented with a history of fever, while 10,508 (13.7%) had a temperature of more than 37.5°C at presentation. 8,871 (11.6%) patients had both a history of fever and a temperature.

Antibiotics

Medications were prescribed for 81,691 (97.7%) illness episodes. 37,011 (44.2%) patients were prescribed an antibiotic during their first visit, and this increased to 39,242 (46.9%) throughout their illness episodes.

Antibiotics were prescribed to:

- 49.2% of men compared to 45% of women (p<0.001)
- 39% of children compared to 51.8% of adults (p <0.001)
- 40.1% of those with a history of fever
- 47.6% with a temperature >37.5°C
- 38.8% with an ICD 10 code for infection

The proportion of patients within each age group prescribed an antibiotic varied, with the lowest rates in young children (0-4 year olds, 33.8%), peaking in adults (12-39 year olds, 55.9%) and then diminishing in the elderly (aged 65 years and older, 41%, see supplementary material, table S3).

The odds ratios for the univariate and multivariable logistic regression analyses are shown in table 1. All variables entered into the univariate model were significant so were added to the multivariable analysis. Indications for antibiotic prescription in the adjusted multivariable logistic regression analysis were male sex (aOR 1.21 [Cl 1.16-1.28], p <0.001), patients aged 12 years of age or older (compared to those less than 12 years old) (aOR 1.77 [Cl 1.57-2, p <0.001]) and having a temperature of more than 37.5°C (aOR 1.24 [Cl 1.03-1.48, p 0.02]).

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Variable	OR (confidence interval)	p value	aOR (confidence interval)	p value	
Univariate analysis			Multivariable analysis		
Male sex	1.18 (1.12-1.25)	<0.001	1.21 (1.16-1.28)	<0.001	
Aged ≥ 12 years old	1.68 (1.48-1.90)	<0.001	1.77 (1.57-2)	<0.001	
Temperature >37.5°C	1.05 (0.85-1.30)	0.197	1.24 (1.03-1.48)	0.020	

Table 1: Univariate and multivariable logistic regression analyses accounting for clustering of patients attending the same PCU, showing all included variables and their association with antibiotic prescription

Figure 3 is a time series plot for the monthly prevalence of antibiotic prescriptions. Overall there was no significant trend; incidence rate ratio (IRR) =0.99, 95% CI (0.990, 1.007), p=0.796, although there is a suggestion of a downward trend beginning in the final 6 months The monthly prevalence of antibiotic prescriptions was at least 39% throughout the two year period. Patients attending in the wet season (July-October) were more likely to receive antibiotics (47.4%) than those attending in the hot and cold seasons (46.6%) p value 0.029. Overall prescription rates varied greatly between the PCUs from 8 to 71.6%, with prescribing consistently higher in adults than in children.

The majority of patients prescribed an antibiotic received amoxicillin (56.7%) or dicloxacillin (25.1%). Other antibiotics prescribed include norfloxacin (8.9%), co-trimoxazole (4.2%), penicillin V (1.2%), roxithromycin (1.2%), metronidazole (1.2%), erythromycin (0.7%), cephalexin (0.4%) and tetracycline (0.2%).

Presentations and antibiotic prescriptions

The number of acute presentations with ICD 10 codes for infection related to a single system are shown in figure 4. 77.9% of these presentations were for respiratory related problems. 98.6% of these were diagnosed with an URTI, 1.1% with an acute LRTI and 0.3% with a chronic LRTI, of these 36.1%, 81.8% and 53.5% were prescribed antibiotics respectively. The most common single infection diagnoses were common cold (34,549, 50%), acute pharyngitis (13,080, 18.9%) and acute tonsillitis (3,459, 5%), antibiotics were prescribed to 10.5%, 88.7% and 87.1% of the cases respectively (see table 2).

Diagnosis					
	Number of presentations n/N (%)	Episode antibiotics prescribed n/N (%)	Commonest antibiotic prescribed (%)		
Common cold	34,549/69,115 (50)	3,643/34,549 (10.5)	Amoxicillin (71.7)		
Acute pharyngitis	13,080/69,115 (18.9)	11,607/13,080 (88.7)	Amoxicillin (91.5)		
Acute tonsillitis	3,459/69,115 (5)	3,014/3,459 (87.1)	Amoxicillin (93.4)		
Gastroenteritis & colitis unspecified	2,412/69,115 (3.5)	1,614/2,412 (66.9)	Norfloxacin (68.8)		
Conjunctivitis	2,097/69,115 (3.0)	330/2,097 (15.7)	Amoxicillin (56.4)		
Other helminthiases	1,231/69,115 (1.8)	65/1,231 (5.3)	Amoxicillin (41.5)		
Cystitis	1,230/69,115 (1.8)	1,165/1,230 (94.7)	Norfloxacin (75.9)		

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Table 2: Common diagnoses in patients with one single ICD 10 code for infection, whether antibiotics were prescribed and which antibiotic was mostly commonly used

Supplementary table S4 shows the number of individual infection diagnoses by systems and the rates of antibiotic prescriptions. Antibiotics were prescribed to 59.4% of skin infections, 81.1% of otitis media, 79.5% of otitis externa, 94.7% of cystitis, 80.3% of hordeolum (styes) and chalazions as well as 15.7% of conjunctivitis cases. Of the total antibiotics prescribed almost a third (29.6%) were given to those with acute pharyngitis, followed by common cold (9.3%), acute tonsillitis (7.7%), gastroenteritis and colitis (4.1%) and cystitis (3%) as the single infection diagnoses.

13.8% of patients (11,547) were prescribed antibiotics without a temperature, history of fever or ICD 10 code for infection. Of those who had a single ICD 10 code recorded 1,815 (24.6%) of these antibiotics were for dental reasons, 1,002 (13.6%) for surgical follow up care, 526 (7.1%) for contact dermatitis and 473 (6.4%) for open wounds (see supplementary material, figure S1). These patients were more likely to be male (54.3%, p value <0.001) and older (median age of 41 compared to 24 years old) than the main patient group.

DISCUSSION

To the best of our knowledge this is the largest review of acute illness presentations and community antibiotic prescribing in a LMIC. Over a two year period there were more than 97,000 attendances to 32 PCUs for acute infections and nearly half these patients received an antibiotic, with no significant change in prescribing levels over the two year study period. Studies of this magnitude are required to increase our knowledge of the scale of antibiotic prescribing as well as the common conditions they are used for.^{24 25} Thailand's 2016 national strategic plan on AMR also highlighted the importance of monitoring and reporting antimicrobial consumption.²⁶

Comparing overall antibiotic prescribing rates with other studies is challenging because of varying definitions of acute illnesses and the different patient populations. However the antibiotic prescribing rate in our study is more than double the prescribing in a Malaysian study but similar to studies in India and Laos.²⁷⁻²⁹ A third of our patients had a history of fever, which is similar to a point prevalence study in India where fever was the most common symptom.³⁰ Almost 80% of the ICD 10 codes for infection were related to respiratory infections, which is consistent with respiratory infections being the leading cause of hospitalisations and deaths in Thai under five year olds³ but is higher than the proportion of respiratory presentations in other South and Southeast Asian countries.^{30 31} Antibiotic prescribing in Thailand for tonsillitis and pharyngitis remains high despite Group A beta-haemolytic Streptococci being isolated in only 3.8-7.9% of those with URTI.^{32 33}

In the first phase of Thailand's Antibiotic Smart Use program overall antibiotic use in PCUs was reduced by between 39% and 46%. Prescriptions for the three target conditions (URTI, acute diarrhoea and simple wounds) reduced from 54.5% to 25.4%.³⁴ Despite the lower prescribing levels of 10.5% for common colds in our review, there were still 3,643 antibiotic prescriptions for this condition, alongside 88.7% of those with acute pharyngitis, 87.1% with acute tonsillitis and 66.9% with gastroenteritis and colitis receiving antibiotics; this is likely to represent the overuse of antibiotics. Open wounds and superficial injuries were common diagnoses in those prescribed an antibiotic without a history of fever, temperature, or ICD 10 code for infection. The results reveal the ongoing high levels of prescribing for these conditions and present an opportunity to further reduce antibiotic use. Since late 2016 an antibiotic prescribing target of less than 20% for these three conditions has been incorporated into Thailand's rational drug use service plan as well as the pay for performance health criteria, and financial incentives are given to the PCUs achieving this target. A review of the long term effectiveness of this policy including any impact on patient safety is required.

Our study also identifies high levels of prescribing for skin infections, otitis media, otitis externa, cystitis, hordeolum (styes) and chalazions. A lack of available topical antibiotics may account for the high prescribing for skin infections as well as for otitis externa. However, despite antibacterial eye drops being available, 15.7% of conjunctivitis cases were still prescribed a systemic antibiotic. Urine dipstick tests are not available on site to assess patients with cystitis or suspected urinary tract infections. Introduction of these simple tests may help to rationalize prescribing for these conditions in a setting where urine cultures are not readily available or achievable.

While we did not set out to review dental prescribing, this area accounted for 25% of the antibiotics prescribed to those without a history of fever, temperature or ICD 10 code for infection, which warrants further investigation.

Some of the variation in antibiotic prescribing rates between PCUs may be accounted for by the degree of staff training. Two out of the three highest prescribing PCUs are staffed only by public health officers. The study findings are being used to guide educational updates and training for the PCU staff, with priority being given to those PCUs without nurses and with high prescription rates for conditions unlikely to require antibiotics.

A wide range of antibiotics are prescribed in the PCUs. Restrictions are in place for some broadspectrum antibiotics such as amoxicillin and clavulanic acid (Co-amoxiclav) which cannot be prescribed. One area of concern is that less than 1% of the antibiotics being prescribed have activity against scrub typhus, which is the leading cause of hospital admission with acute undifferentiated fever in this region.³⁵

Strengths and limitations

The main strength of this study is the large number of illness episodes included. The two year time period should allow for seasonal variations and disease epidemics. We reviewed prescribing in all of the PCUs in Mueang Chiangrai District which covers a large geographical area and has a range of rural and urban facilities, making the results generalizable to the region more broadly. Many studies have focused on prescribing for specific conditions such as URTIs but our study covers a wide range of infections that present in the community. Having research staff on site has been shown to influence healthcare workers' prescribing habits (the Hawthorne Effect), but due to the retrospective nature of the study this was not a source of bias. The use of routinely collected data means that this methodology could be repeated in other districts and provinces in Thailand, although a lot of the data are entered as free text which presents challenges for analysis. Searching for patients with a history of fever, for instance, was problematic because the Thai word "la" or fever is also part of the Thai words for patient, influenza, antipyrexials, etc.

Limitations of this study are that we only included public PCUs and have no data on antibiotic use by private clinics, pharmacies or family medicine doctors based at the provincial hospital, which requires further study. The PCU data is taken from routine electronic records and in some instances there were tranches of missing data (five PCUs had no recorded data for several months). Verifying the quality of some data is also challenging; coding of clinical diagnoses for instance using ICD 10 could be inconsistent between healthcare workers and in primary care the majority of infections are diagnosed clinically without any laboratory tests. However we used data from a subsample of patients enrolled in a clinical trial in four PCUs and compared them to their respective routine medical records. While minor discrepancies were found in their precise age and temperature the diagnoses and antibiotic prescribing data were consistent. Our decision to class all attendances within a one month period as a single illness episode means that we may have incorrectly classed some new illnesses as a repeat attendance but did allow us to review antibiotic prescribing over the course of the illness. The time series analysis was carried out using data from a two year time period, more definitive conclusions and trends may have become apparent if further time points and data were available.

CONCLUSIONS

This study provides much needed insight into the use of antibiotics in primary care in northern Thailand, allowing targeting of interventions to improve the rational use of antibiotics. Nearly half of all patients attending with an acute illness received an antibiotic. The majority of presentations were for respiratory infections. Further education and resources are required to support clinicians in the targeting of antibiotics. This could include the introduction of clinical algorithms and point of care tests such as CRP and urine dipsticks. Antibiotic guidelines are required for common conditions seen in primary care outside of the current Antibiotic Smart Use policy. Further studies including qualitative work are required to appreciate the use of antibiotics in other settings such as private facilities, pharmacies and dental clinics.

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Competing interests

None declared

Author contribution statement

All authors were involved in the design of the study. PW collected the data. RCG carried out the analysis with support from YL. MM provided statistical support. RCG, YL, DI, SN interpreted the data. RCG wrote

the first draft of the paper. YL, NPJD and MM reviewed subsequent drafts. All authors approved the final draft for publication.

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Data sharing statement

We are unable to share additional unpublished data which falls under the jurisdiction of the Chiang Rai PHO.

Ethical approval

Ethical approval was obtained from Chiangrai's Provincial and Public Health Office IRB (number 56/2560). Exemption was given by the Oxford Tropical Research Ethics Committee (OxTREC). Individual informed consent was not required.

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7	utility of biomarkers in Chiangrai, northern Thailand. Submitted
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10	Figure 1: Chiangrai and the 32 PCUs
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12	Figure 2: A Venn diagram to show the inclusion criteria
13	Figure 3: Trend and seasonality of antibiotic prescriptions overlaid by mean antibiotic prescription
14	rates per PCU
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16	Figure 4: Number of acute presentations by single systems and whether antibiotics were prescribed
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21	Figure 3: Trend and seasonality of antibiotic prescriptions overlaid by mean antibiotic prescription rates per PCU Figure 4: Number of acute presentations by single systems and whether antibiotics were prescribed
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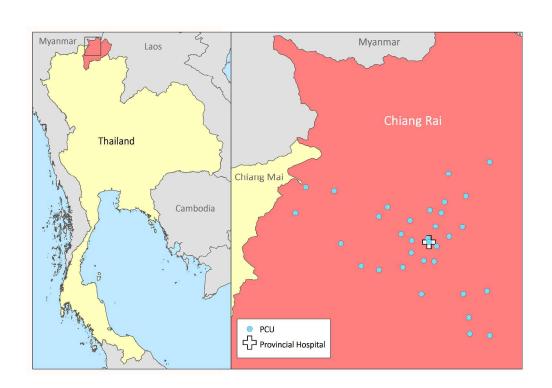
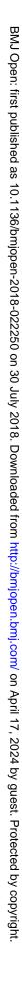


Figure 1: Chiangrai and the 32 PCUs

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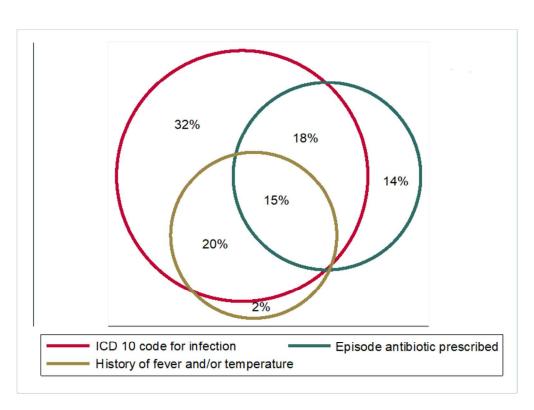


Figure 2: A Venn diagram to show the inclusion criteria

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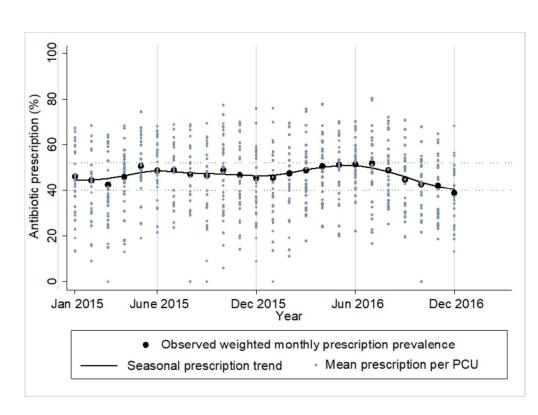
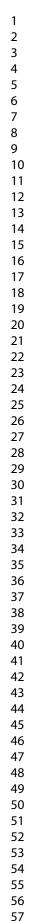


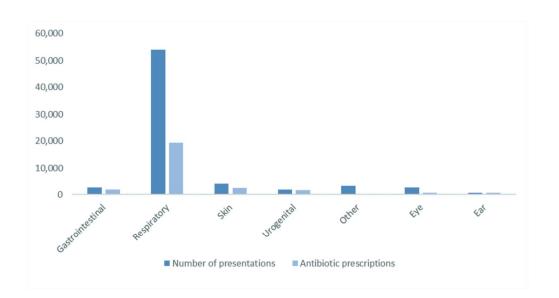
Figure 3: Trend and seasonality of antibiotic prescriptions overlaid by mean antibiotic prescription rates per PCU

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Supplementary material

Antibiotic search list

- Amoxicillin
- Cefixime
- Ceftriaxone
- Cephalexin
- Ciprofloxacin
- Co-amoxiclav/ augmentin
- Co-trimoxazole/bactrim
- Dicloxacillin
- Doxycycline
- Erythromycin
- Metronidazole
- Norfloxacin
- Penicillin V
- Roxithromycin
- TC mycin/ tetracycline

Table S1: ICD 10 codes for infection used for the inclusion criteria

Code	Description	Excluded code (number)	
A00-B99	Certain infectious and parasitic 🔨	A15 (167), A16 (29), A18 (7),	
	diseases	A31.9 (1), B18 (18), B24 (85),	
		B85 (671)	
G00-G07	Inflammatory diseases of the central		
	nervous system		
H00-01	Hordeolum, chalazion and other	H01.1 (35)	
	inflammation of the eyelid		
H05.0	Acute inflammation of orbit		
H10	Conjunctivitis		
H60-H70	Otitis externa, otitis media and	H61 (112)	
	mastoiditis		
H72-73	Perforation and other disorders of the	H73.9 (2)	
	tympanic membrane		
J00-43	Respiratory tract infections	J30 (150), J31 (8), J33 (1), J35.1	
		(1)	
J47	Bronchiectasis		
К05	Gingivitis and periodontal diseases	Exclude all (9,469)	
K11-12	Diseases of salivary glands, stomatitis	K11.1 (3), K11.88 (2), K11.9 (1)	
	and related lesions	K12.0 (682), K12.1 (716)	
K35-37	Appendicitis		
K57	Diverticulitis	K57 (2)	

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K61	Abscess of anal and rectal regions				
K81	Cholecystitis	Cholecystitis			
K83-85	Cholangitis and pancreatitis				
L00-08	Infections of the skin and				
	subcutaneous tissue				
L20-22	Dermatitis L20 (23), L21 (19),	L22 (5)			
L30.3	Infective dermatitis				
L70-73.2	Acne, rosacea follicular cysts and				
	follicular disorders				
M00-03	Infectious arthropathies M0013 (1), M0023	3 (1) <i>,</i> M0167			
	(1), M020 (1)				
M60	Myositis M60.1-M6099 (3,	504)			
N10-11	Tubulo-interstitial nephritis				
N30	Cystitis				
N34	Urethritis and urethral syndrome				
N39.0	Urinary tract infection, site not				
	specified				
N41	Inflammatory diseases of prostate				
N45	Orchitis and epididymitis				
N48-49	Other disorders of male genital organs N48.9 (1)				
N61	Inflammatory disorders of breast				
N70-76	Inflammatory diseases of female pelvic				
	organs				
008.0	Genital tract and pelvic infection				
	following abortion and ectopic and				
	molar pregnancy				
023	Infections of genitourinary tract in				
	pregnancy				
O85-86	Puerperal sepsis and other puerperal				
	infections				
P35-9	Infections specific to the perinatal				
	period				
R05	Cough				
R11	Nausea and vomiting				
R30	Pain associated with micturition				
R36	Urethral discharge				
R50	Fever				

Table S2: The number of initial presentations for each inclusion criteria and the percentage prescribed antibiotics during their illness episode

Age (years)	Number of presentations n/N (%)	Number of patients receiving an antibiotic prescription n/N (%)
0-4	18,073/83,659 (21.6)	6,110/18,073 (33.8)
5-11	13,775/83,659 (16.5)	6,318/13,775 (45.9)
12-24	10,533/83,659 (12.6)	5,888/10,533 (55.9)
25-39	11,025/83,659 (13.2)	6,167/11,025 (55.9)
40-64	23,134/83,659 (27.7)	11,843/23,134 (51.2)
65 or over	7,119/83,659 (8.5)	2,915/7,119 (41)
Total	83,659 (100)	39,241/83,659 (46.9)

Table S3: The number of presentations per age group and the percentage of each group prescribed an antibiotic

unubiotic		
Inclusion criteria	Total initial presentations	Antibiotic prescription during the illness episode
History of fever n/N (%)	29,246/82,976 (35.3%)	11,725/29,246 (40.1%)
Temperature >37.5°C n/N (%)	10,508/76,644 (13.7%)	5,003/10,508 (47.6%)
ICD 10 code for infection n/N (%)	70,137/83,338 (84.2%)	27,234/70,137 (38.8%)
Antibiotic prescription n/N (%)	37,011/83,661 (44.2%)	39,242/83,661 (46.9%)

Diagnosis	Number of presentations n/N (%)	Number of antibion prescriptions duri illness episode n/
Respiratory		
Common cold	34,549/53,819 (64.2)	3,643/34,549 (10.
Acute sinusitis	30/53,819 (0.1)	25/30 (83.3)
Acute pharyngitis	13,080/53,819 (24.3)	11,607/13,080 (88
Acute tonsillitis	3,459/53,819 (6.4)	3,014/3,459 (87.1
Other URTIs	357/53,819 (0.7)	278/357 (77.9)
Acute LRTIs	663/53,819 (1.2)	541/663 (81.6)
Chronic bronchitis,	60/53,819 (0.1)	10/60 (16.7)
emphysema &		
bronchiectasis		
Cough	1,621/53,819 (3)	99/1,621 (6.1)
Sub total	53,819 (100)	19,217/53,819 (35
Gastrointestinal		
Bacterial intestinal	199/2,706 (7.4)	127/199 (63.8)
infections or intoxications		
Viral enteritis	46/2,706 (1.7)	4/46 (8.7)
GE & colitis	2,412/2,706 (89.1)	1,614/2,412 (66.9
Appendicitis	21/2,706 (0.8)	2/21 (9.5)
Other	9/2,706 (0.3)	2/9 (22.2)
Sialoadenitis	19/2,706 (0.7)	16/19 (84.2)
Sub total	2,706 (100)	1,765/2,706 (65.2
Skin		
Infective dermatitis	85/4,060 (2.1)	70/85 (82.4)
Dermatophytosis	902/4,060 (22.2)	92/902 (10.2)
Other superficial mycoses	197/4,060 (4.9)	14/197 (7.1)
Candidiasis	101/4,060 (2.5)	23/101 (22.8)
Other	64/4,060 (1.6)	52/64 (81.3)
Scabies & infestations	52/4,060 (1.3)	8/52 (15.4)
Cellulitis & abscesses	841/4,060 (20.7)	618/841 (73.5)
Bacterial skin infections	533/4,060 (13.1)	464/533 (87.1)
Furuncles, caruncles & cysts	947/4,060 (23.3)	780/947 (82.4)
Other local infection of the skin & subcutaneous tissue	338/4,060 (8.3)	290/338 (85.8)
Sub total	4,060 (100)	2,411/4060 (59.4)
Eye		
Conjunctivitis	2,097/2,698 (77.7)	330/2,097 (15.7)
Hordeolum & chalazion	319/2,698 (11.8)	256/319 (80.3)
Other inflammation of the eyelid & orbit	268/2,698 (9.9)	98/268 (36.6)
Trachoma	14/2,698 (0.5)	5/14 (35.7)

Sub total	2,698 (100)	689/2,698 (25.5)
Ear		
Otitis externa	464/753 (61.6)	369/464 (79.5)
Otitis media	243/753 (32.3)	197/243 (81.1)
Mastoiditis	16/753 (2.1)	9/16 (56.3)
Perforation of tympanic membrane & other disorders	30/753 (4)	25/30 (83.3)
Sub total	753 (100)	600/753 (79.7)
Urogenital		
Acute tubulo-interstitial nephritis	36/1,871 (1.9)	32/36 (88.9)
Other	17/1,871 (0.9)	12/17 (70.6)
Cystitis, UTI, dysuria, urethritis & urethral syndrome	1,370/1,871 (73.2)	1,291/1,370 (94.2)
Other disorders of male genital organs	32/1,871 (1.7)	20/32 (62.5)
Other inflammatory disorders of female pelvic organs	148/1,871 (7.9)	115/148 (77.7)
Other inflammatory disorders of the vagina & vulva	268/1,871 (14.3)	149/268 (55.6)
Sub total	1,871 (100)	1,619/1,871 (86.5)
Other		
Bacterial	85/3,208 (2.7)	28/85 (32.9)
Unknown aetiology	33/3,208 (1)	14/33 (42.4)
Viral	728/3,208 (22.7)	153/728 (21)
Fungal	36/3,208 (1.1)	2/36 (5.6)
Protozoal	10/3,208 (0.3)	0/10 (0)
Parasitic	1,880/3,208 (58.6)	99/1,880 (5.3)
Nausea & vomiting	268/3,208 (8.4)	30/268 (11.2)
Fever of unknown or other origin	168/3,208 (5.2)	10/168 (6)
Sub total	3,208 (100)	336/3,208 (10.5)

Table S4: The number of presentations per diagnosis and system and whether antibiotics were prescribed for that illness episode

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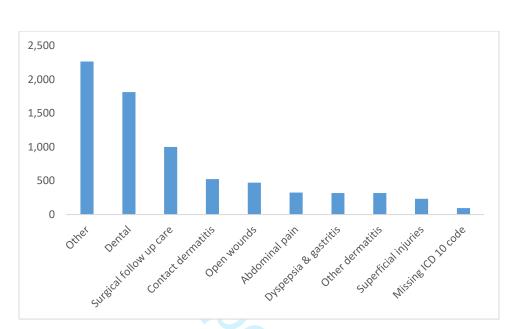


Figure S1: Single diagnoses used for antibiotic prescriptions without a history of fever, temperature or ICD 10 code for infection

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PRD statement – checklist of items, extended from the STROBE statement, that should be reported in observationa	ıl stud
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Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location manuscri where reported
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1	 (a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found 		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe	Abstræt r 11 10.1136/bmjopetr
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A Retrospective Review of the Management of Acute Infections and the Indications for Antibiotic Prescription in Primary Care in Northern Thailand

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Keywords:	antibiotic use, PRIMARY CARE, Thailand, fever, Respiratory infections < THORACIC MEDICINE

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A RETROSPECTIVE REVIEW OF THE MANAGEMENT OF ACUTE INFECTIONS AND THE INDICATIONS FOR ANTIBIOTIC PRESCRIPTION IN PRIMARY CARE IN NORTHERN THAILAND

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Word count: 4008

ABSTRACT

Introduction Antibiotic use in low and middle income countries continues to rise despite the knowledge that antibiotic overuse can lead to antimicrobial resistance. There is a paucity of detailed data on the use of antibiotics in primary care in low resource settings.

Objective Describe the presentation of acute infections and the indications for antibiotic prescription.

Design A two year retrospective review of routinely collected data.

Setting All 32 primary care units in one district in northern Thailand.

Participants Patients attending primary care with a history of fever, documented temperature, ICD 10 code for infection or prescribed a systemic antibiotic. Patients attending after the initiation of a study on C-reactive protein testing in four centres were excluded.

Outcome measures The proportion of patients prescribed an antibiotic and the frequency of clinical presentations.

Results 762,868 patients attended the health centers, of whom 103,196 met the inclusion criteria, 5,966 were excluded resulting in 97,230 attendances consisting of 83,661 illness episodes.

46.9% (39,242) of patients were prescribed an antibiotic during their illness. Indications for antibiotic prescription in the multivariable logistic regression analysis included male sex (aOR 1.21 [Cl 1.16-1.28], p <0.001), adults (aOR 1.77 [Cl 1.57-2, p <0.001]) and a temperature >37.5°C (aOR 1.24 [Cl 1.03-1.48, p 0.020]). 77.9% of the presentations were for respiratory related problems, of which 98.6% were upper respiratory tract infections. The leading infection diagnoses were common cold (50%), acute pharyngitis (18.9%) and acute tonsillitis (5%), which were prescribed antibiotics in 10.5%, 88.7% and 87.1% of cases respectively. Amoxicillin was the most commonly prescribed antibiotic.

Conclusions Nearly half of the patients received an antibiotic, the majority of whom had a respiratory infection. The results can be used to plan interventions to improve the rational use of antibiotics. Further studies in private facilities, pharmacies and dental clinics are required.

Word count: 299

Keywords: antibiotic use, primary care, Thailand, fever, respiratory infections

ARTICLE SUMMARY

Strengths and limitations of this study

- Over 80,000 illness episodes reviewed from all primary care units in a district, over a two year time period
- Wide range of infections included rather than focusing on one specific infection
- Use of routine electronic data (no Hawthorne Effect), making this work reproducible
- Only included public healthcare facilities
- Reliant on the correct coding and clinical diagnoses of illnesses

BACKGROUND

The proportion of global deaths attributable to communicable diseases has greatly reduced in recent years. Despite these improvements, 10.6% of deaths worldwide in 2015 were thought to be caused by lower respiratory tract infections (LRTIs), diarrhoea, and tuberculosis (TB).¹ In under five year olds, 51.8% of deaths worldwide were due to infectious causes in 2013, with pneumonia causing 14.8% of the deaths overall.² In Thailand in 2010, respiratory infections were the leading cause of hospitalisations and deaths in children under the age of five.³ Prompt access to appropriate antibiotics is vital to prevent many of these unnecessary deaths.⁴ But while inappropriate or no treatment remains a clear cause for concern, the global antibiotic consumption rate increased by 39% between 2000 and 2015, fueled by low and middle income countries (LMIC),⁵⁶ with the majority of antibiotics being consumed in the community.⁷

Overuse and misuse of antibiotics have been linked to the development of antimicrobial resistance (AMR).⁷⁻⁹ Antibiotics prescribed to individuals in primary care have been associated with bacterial resistance in that individual for up to 12 months, and longer and more frequent antibiotic courses are more likely to cause resistance.¹⁰ The World Health Organization has described AMR in Southeast Asia as a 'burgeoning and often neglected' issue, stating that a 'post-antibiotic era' may become reality, resulting in common infections and minor injuries being untreatable.¹¹ In Thailand in 2010, there were an estimated 19,122 deaths attributable to multidrug resistant hospital-acquired infections.¹² Thailand has been making sustained efforts to reduce inappropriate antibiotic use; its Antibiotic Smart Use program started in 2007 and targets three conditions which are unlikely to require antibiotic treatment but for which they are commonly prescribed: upper respiratory tract infections (URTIs), acute diarrhoea and simple wounds.¹³ Prescribing targets have been incorporated into the public health system's pay for performance criteria. In August 2016 the Thai government endorsed a national strategic plan for AMR which aims to optimize antimicrobial drug use and reduce the mean consumption of antimicrobials in humans by 20% by 2021.¹⁴

To appreciate the scale of the problem and to target future interventions, a greater understanding of the acute infections presenting to primary care and the conditions for which antibiotics are used in LMICs is required. Such data, however, are limited,¹⁵ with most studies deriving their estimates from small samples of health providers and over a limited timeframe, therefore neglecting possible seasonal and spatial variation and other secular trends. In this paper we describe the proportion of patients receiving an antibiotic prescription and indications for antibiotic use in 32 primary care units (PCUs) across a district in northern Thailand over a two year period.

METHOD

A retrospective computerised search of routinely collected data from primary care units in Mueang Chiangrai District between January 2015 and December 2016 was carried out.

Study setting

Thailand is an upper-middle income country. In 2016 its gross domestic product (GDP) was 407 billion USD. The average life expectancy at birth is 75 years.¹⁶ Chiangrai is the most northern province in Thailand and shares borders with Laos and Myanmar. It has a population of 1,282,544, of whom 241,436

reside in Mueang Chiangrai District.^{17 18} Thailand has three seasons; the wet season typically runs from July to October, the cool season from November to February and the hot season from March to June.

Thailand's healthcare system is made up of public and private providers. Universal health coverage was established in 2002 following significant investment in the healthcare system and infrastructure since the 1970s. In rural and poorer areas primary healthcare is predominantly provided by the public healthcare system whereas in urban areas hospitals and private clinics play a larger role.¹⁹

Antibiotics can be bought directly from pharmacies and local stores as well as being prescribed by healthcare workers. Community antibiotic guidelines exist for some but not all common infections, including assessment criteria (e.g. the Centor criteria for acute tonsillitis), first line antibiotics, their dose and duration. There are prescribing restrictions in place for some broad spectrum antibiotics such as amoxicillin and clavulanic acid (Co-amoxiclav), which cannot be prescribed by nurses working in the public primary care system. More comprehensive hospital based guidelines are available.

In Mueang Chiangrai District family medicine doctors based at the provincial hospital oversee 32 public PCUs which are staffed primarily by two to five nurses and public health officers. On average PCUs look after 5000 patients each.¹⁹ They provide care for acute and chronic conditions as well as providing preventative services such as immunisations, cervical screening and health education. Dental and traditional medicine services are also available. The furthest PCU is two hours' drive through the mountains from the provincial hospital in Chiangrai city (see figure 1). Finger-prick blood glucose tests are the only investigations routinely available on site.

Inclusion criteria

Patients were identified with at least one of the following:

- Systemic antibiotic prescription
- International Statistical Classification of Diseases (ICD) 10 code for infection (see supplementary material, table S1)
- Fever as the chief complaint
- Documented temperature >37.5°C at the PCU

We excluded patients attending PCUs used as study sites during or after a recent trial on the use of C-reactive protein (CRP) point of care tests

(https://www.clinicaltrials.gov/ct2/show/NCT02758821?term=NCT02758821&rank=1).

Study outcomes

The primary outcome was the overall proportion of illness episodes prescribed an antibiotic. Risk factors for antibiotic use are reported as well as the percentages of patients receiving antibiotics according to their diagnosis, percentages of individual antibiotics used and the frequency and type of acute infection presentations.

Data collection

With the approval of the Chiangrai Provincial and Public Health Office (PHO), a research data manager accessed the PHO's routine medical records database to search for relevant patients and extract the

pre-specified variables. Data collected consisted of the PCU attended, patients' number, age, sex, date of visit, chief complaint, temperature, ICD 10 code, and drug prescriptions.

Data cleaning and coding

The inclusion criteria were classified as being present, absent or that the data were missing. Antibiotics were searched for in the prescription field (free text) and coded as prescribed (yes or no). A predefined antibiotic list (see supplementary material) was generated using the formulary. All medications prescribed in the dataset were reviewed to ensure no antibiotics were omitted due to spelling errors or their absence from our original list. If no prescription was recorded we made the assumption that this was because no medication was given rather than the data being missing.

Our predefined list of ICD 10 codes for infection (see supplementary material, table S1) were searched for in the diagnosis field (free text field, containing ICD 10 codes only) and then coded as present or absent. Our list of ICD 10 codes were reviewed with the other variables to ensure their appropriateness.

We searched for the word 'fever' in Thai in the chief complaint field (free text). In some cases 'no fever' was recorded, or the word 'fever' was present but part of a phrase alluding to a patient more generally, or 'influenza vaccine'. This field was checked manually with the help of two native northern Thai speaking study nurses. History of fever in the chief complaint was then coded as yes or no. Documented temperatures over 37.5°C at the PCU were searched for in the temperature field and then coded as temperature >37.5°C yes or no.

Repeat attendances within one month were classed as one illness episode allowing for the detection of subsequent antibiotics or treatment changes. All other indications such as the chief complaint and temperature were taken from the initial presentation. Children were defined as being under 12 years of age. The ICD 10 codes were grouped into gastrointestinal, respiratory, skin, urogenital, eye, ear and other categories. Each category was further broken down into conditions such as acute sinusitis and acute pharyngitis. The respiratory category was also grouped into upper and lower respiratory tract infections.

Statistical analyses

Descriptive statistics

Categorical variables were summarised using counts and percentages. Non-normally distributed data were described using medians and interquartile ranges and compared using the ranksum test. The proportions of patients prescribed an antibiotic in different demographic groups were summarised and compared using the chi-square test.

Logistic and Poisson regression models

A logistic regression model was used to model the binary outcome of antibiotic prescription (yes or no); both unadjusted and adjusted models were fitted and accounted for clustering of patients attending the same PCU. The odds ratios for the indications of antibiotic prescription were first obtained from univariate logistic regression models and then considered in a multivariable model if they had a p value of <0.05. Indications included sex, age category and documented temperature. The main purpose of this model was to identify risk factors that were independently associated with antibiotic prescription. A temperature of >37.5°C was used rather than the more subjective history of fever. ICD 10 codes were not included because of their strong association with antibiotic prescriptions (e.g. a health worker's diagnosis of acute pharyngitis and its affiliated ICD 10 code was inherently associated with antibiotic prescription, as opposed to a diagnosis of 'common cold'). Furthermore a Poisson regression model of the monthly number of antibiotic prescriptions over the 24 month period was produced to obtain the Incidence Rate Ratios and 95% confidence intervals.

Time-series analysis

Monthly antibiotic prescriptions were weighted by the number of contributing PCUs per month and modelled over the two year period. When time-series analysis is used for forecasting, it is common to apply it to periods of five years or more, however, our aim was not to forecast into the future but to simply describe the current trends in antibiotic prescription.^{20 21} We used a time-series analysis to separate long-term trends from seasonal variations.^{22 23} Symmetric Locally Weighted Moving Averages (MA) were used. In this procedure, less weight was applied to time points (in months) furthest away from the present time point. The data was available on a monthly basis, however, a quarterly window

was used to identify seasonality as follows: $\hat{X}_t = \frac{1}{9}(X_{t-2} + 2X_{t-1} + 3X_t + 2X_{t+1} + X_{t+2})$

Similarly a 12-month time-series window was used to obtain a trend line that would be sensitive to monthly changes but with reduced noise from seasonal variation:

$$\hat{X}_{t} = \frac{1}{24}(X_{t-6} + X_{t+6}) + \frac{1}{12}(X_{t} + X_{t-1} + X_{t+1} + X_{t-2} + X_{t+2} + X_{t-3} + X_{t+3} + X_{t-4} + X_{t+4} + X_{t-5} + X_{t+5})$$

Where \hat{X}_{t} is the time-series modelled monthly prevalence of antibiotic prescription. Statistical significance was declared at alpha=0.05. Data analyses were performed with STATA version 14 (College Station, Texas, USA).

Ethical approval

Ethical approval was obtained from Chiangrai's Provincial and Public Health Office IRB (number 56/2560). Exemption was given by the Oxford Tropical Research Ethics Committee (OxTREC).

Patient and public involvement

Patients were not involved in the design of the study. Due to the study's retrospective nature patients were not involved in the recruitment processes. Study results will be disseminated through community presentations as well as educational updates for the healthcare workers and community volunteers.

RESULTS

762,868 patients attended the PCUs between the 1st of January 2015 and the 31st of December 2016. The majority of patients' attendances included a chronic disease review or screening, the most common

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being screening for diseases such as diabetes, hypertension, mental health and dental disorders (145,410), essential hypertension reviews (98,822) and routine child health examinations (75,701).

The appropriateness of the ICD 10 codes for infection used in our inclusion criteria were reviewed alongside the other variables. For example, we found that patients with TB, HIV and Hepatitis B were only attending for regular medications rather than for acute illnesses so they were removed from the ICD 10 inclusion list. Mass head lice treatment at schools is carried out by the PCUs so these codes were also removed. The ICD 10 code 'K05' (dental) was also removed because it transpired that these patients are seen by dentists or dental nurses at the PCUs rather than by the regular PCU staff. All ICD 10 codes for myositis were removed from the inclusion criteria apart from M60.0 (infective myositis) because the other codes were being used for muscle pain or myalgia (see supplementary material, table S1).

In total 103,196 attendances met our inclusion criteria; 5,966 were then excluded because the PCUs they attended were involved in the CRP study before or during their attendance, resulting in 97,230 attendances (12.7%) meeting our inclusion and exclusion criteria. 13,569 repeat attendances within one month were classed as a single illness episode, leaving 83,661 illness episodes.

Patient characteristics

The median age was 24 years old with an interquartile range of 6 to 51 years old. Two patients had no age recorded. 54.7% of the patients were female (45,779) compared to 45.3% males (37,882) (p<0.001).

The proportion of patients meeting each inclusion criterion is shown in figure 2 and supplementary material table S2. 29,246 (35.3%) patients presented with a history of fever, while 10,508 (13.7%) had a temperature of more than 37.5°C at presentation. 8,871 (11.6%) patients had both a history of fever and a temperature.

Antibiotics

Medications were prescribed for 81,691 (97.7%) illness episodes. 37,011 (44.2%) patients were prescribed an antibiotic during their first visit, and this increased to 39,242 (46.9%) throughout their illness episodes.

Antibiotics were prescribed to:

- 49.2% of men compared to 45% of women (p<0.001)
- 39% of children compared to 51.8% of adults (p <0.001)
- 40.1% of those with a history of fever
- 47.6% with a temperature >37.5°C
- 38.8% with an ICD 10 code for infection

The proportion of patients within each age group prescribed an antibiotic varied, with the lowest rates in young children (0-4 year olds, 33.8%), peaking in adults (12-39 year olds, 55.9%) and then diminishing in the elderly (aged 65 years and older, 41%, see supplementary material, table S3).

The odds ratios for the univariate and multivariable logistic regression analyses are shown in table 1. All variables entered into the univariate model were significant so were added to the multivariable analysis. Indications for antibiotic prescription in the adjusted multivariable logistic regression analysis were male sex (aOR 1.21 [Cl 1.16-1.28], p <0.001), patients aged 12 years of age or older (compared to those less

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than 12 years old) (aOR 1.77 [Cl 1.57-2, p <0.001]) and having a temperature of more than 37.5°C (aOR 1.24 [Cl 1.03-1.48, p 0.02]).

Variable	OR (confidence interval)	p value	aOR (confidence interval)	p value
Univariate analysis			Multivariable analy	sis
Male sex	1.18 (1.12-1.25)	<0.001	1.21 (1.16-1.28)	<0.001
Aged ≥ 12 years old	1.68 (1.48-1.90)	<0.001	1.77 (1.57-2)	<0.001
Temperature >37.5°C	1.05 (0.85-1.30)	0.197	1.24 (1.03-1.48)	0.020

Table 1: Univariate and multivariable logistic regression analyses accounting for clustering of patients attending the same PCU, showing all included variables and their association with antibiotic prescription

Figure 3 is a time series plot for the monthly prevalence of antibiotic prescriptions. Overall there was no significant trend; incidence rate ratio (IRR) =0.99, 95% CI (0.990, 1.007), p=0.796, although there is a suggestion of a downward trend beginning in the final 6 months The monthly prevalence of antibiotic prescriptions was at least 39% throughout the two year period. Patients attending in the wet season (July-October) were more likely to receive antibiotics (47.4%) than those attending in the hot and cold seasons (46.6%) p value 0.029. Overall prescription rates varied greatly between the PCUs from 8 to 71.6%, with prescribing consistently higher in adults than in children.

The majority of patients prescribed an antibiotic received amoxicillin (56.7%) or dicloxacillin (25.1%). Other antibiotics prescribed include norfloxacin (8.9%), co-trimoxazole (4.2%), penicillin V (1.2%), roxithromycin (1.2%), metronidazole (1.2%), erythromycin (0.7%), cephalexin (0.4%) and tetracycline (0.2%).

Presentations and antibiotic prescriptions

The number of acute presentations with ICD 10 codes for infection related to a single system are shown in figure 4. 77.9% of these presentations were for respiratory related problems. 98.6% of these were diagnosed with an URTI, 1.1% with an acute LRTI and 0.3% with a chronic LRTI, of these 36.1%, 81.8% and 53.5% were prescribed antibiotics respectively. The most common single infection diagnoses were common cold (34,549, 50%), acute pharyngitis (13,080, 18.9%) and acute tonsillitis (3,459, 5%), antibiotics were prescribed to 10.5%, 88.7% and 87.1% of the cases respectively (see table 2).

Diagnosis	Number of presentations n/N (%)	Episode antibiotics prescribed n/N (%)	Commonest antibiotic prescribed (%)
Common cold	34,549/69,115 (50)	3,643/34,549 (10.5)	Amoxicillin (71.7)
Acute pharyngitis	13,080/69,115 (18.9)	11,607/13,080 (88.7)	Amoxicillin (91.5)
Acute tonsillitis	3,459/69,115 (5)	3,014/3,459 (87.1)	Amoxicillin (93.4)
Gastroenteritis & colitis unspecified	2,412/69,115 (3.5)	1,614/2,412 (66.9)	Norfloxacin (68.8)
Conjunctivitis	2,097/69,115 (3.0)	330/2,097 (15.7)	Amoxicillin (56.4)
Other helminthiases	1,231/69,115 (1.8)	65/1,231 (5.3)	Amoxicillin (41.5)
Cystitis	1,230/69,115 (1.8)	1,165/1,230 (94.7)	Norfloxacin (75.9)

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Table 2: Common diagnoses in patients with one single ICD 10 code for infection, whether antibiotics were prescribed and which antibiotic was mostly commonly used

Supplementary table S4 shows the number of individual infection diagnoses by systems and the rates of antibiotic prescriptions. Antibiotics were prescribed to 59.4% of skin infections, 81.1% of otitis media, 79.5% of otitis externa, 94.7% of cystitis, 80.3% of hordeolum (styes) and chalazions as well as 15.7% of conjunctivitis cases. Of the total antibiotics prescribed almost a third (29.6%) were given to those with acute pharyngitis, followed by common cold (9.3%), acute tonsillitis (7.7%), gastroenteritis and colitis (4.1%) and cystitis (3%) as the single infection diagnoses.

13.8% of patients (11,547) were prescribed antibiotics without a temperature, history of fever or ICD 10 code for infection. Of those who had a single ICD 10 code recorded 1,815 (24.6%) of these antibiotics were for dental reasons, 1,002 (13.6%) for surgical follow up care, 526 (7.1%) for contact dermatitis and 473 (6.4%) for open wounds (see supplementary material, figure S1). These patients were more likely to be male (54.3%, p value <0.001) and older (median age of 41 compared to 24 years old) than the main patient group.

DISCUSSION

To the best of our knowledge this is the largest review of acute illness presentations and community antibiotic prescribing in a LMIC. Over a two year period there were more than 97,000 attendances to 32 PCUs for acute infections and nearly half these patients received an antibiotic, with no significant change in prescribing levels over the two year study period. Studies of this magnitude are required to increase our knowledge of the scale of antibiotic prescribing as well as the common conditions they are used for.^{24 25} Thailand's 2016 national strategic plan on AMR also highlighted the importance of monitoring and reporting antimicrobial consumption.²⁶

Comparing overall antibiotic prescribing rates with other studies is challenging because of varying definitions of acute illnesses and the different patient populations. However the antibiotic prescribing rate in our study is more than double the prescribing in a Malaysian study but similar to studies in India and Laos.²⁷⁻²⁹ A third of our patients had a history of fever, which is similar to a point prevalence study in India where fever was the most common symptom.³⁰ Almost 80% of the ICD 10 codes for infection were related to respiratory infections, which is consistent with respiratory infections being the leading cause of hospitalisations and deaths in Thai under five year olds³ but is higher than the proportion of respiratory presentations in other South and Southeast Asian countries.^{30 31} Antibiotic prescribing in Thailand for tonsillitis and pharyngitis remains high despite Group A beta-haemolytic Streptococci being isolated in only 3.8-7.9% of those with URTI.^{32 33}

In the first phase of Thailand's Antibiotic Smart Use program overall antibiotic use in PCUs was reduced by between 39% and 46%. Prescriptions for the three target conditions (URTI, acute diarrhoea and simple wounds) reduced from 54.5% to 25.4%.³⁴ Despite the lower prescribing levels of 10.5% for common colds in our review, there were still 3,643 antibiotic prescriptions for this condition, alongside 88.7% of those with acute pharyngitis, 87.1% with acute tonsillitis and 66.9% with gastroenteritis and colitis receiving antibiotics; this is likely to represent the overuse of antibiotics. Open wounds and superficial injuries were common diagnoses in those prescribed an antibiotic without a history of fever, temperature, or ICD 10 code for infection. The results reveal the ongoing high levels of prescribing for these conditions and present an opportunity to further reduce antibiotic use. Since late 2016 an antibiotic prescribing target of less than 20% for these three conditions has been incorporated into Thailand's rational drug use service plan as well as the pay for performance health criteria, and financial incentives are given to the PCUs achieving this target. A review of the long term effectiveness of this policy including any impact on patient safety is required.

Our study also identifies high levels of prescribing for skin infections, otitis media, otitis externa, cystitis, hordeolum (styes) and chalazions. A lack of available topical antibiotics may account for the high prescribing for skin infections as well as for otitis externa. However, despite antibacterial eye drops being available, 15.7% of conjunctivitis cases were still prescribed a systemic antibiotic. Urine dipstick tests are not available on site to assess patients with cystitis or suspected urinary tract infections. Introduction of these simple tests may help to rationalize prescribing for these conditions in a setting where urine cultures are not readily available or achievable.

While we did not set out to review dental prescribing, this area accounted for 25% of the antibiotics prescribed to those without a history of fever, temperature or ICD 10 code for infection, which warrants further investigation.

Some of the variation in antibiotic prescribing rates between PCUs may be accounted for by the degree of staff training. Two out of the three highest prescribing PCUs are staffed only by public health officers. The study findings are being used to guide educational updates and training for the PCU staff, with priority being given to those PCUs without nurses and with high prescription rates for conditions unlikely to require antibiotics.

A wide range of antibiotics are prescribed in the PCUs. Restrictions are in place for some broadspectrum antibiotics such as amoxicillin and clavulanic acid (Co-amoxiclav) which cannot be prescribed. One area of concern is that less than 1% of the antibiotics being prescribed have activity against scrub typhus, which is the leading cause of hospital admission with acute undifferentiated fever in this region.³⁵

Strengths and limitations

The main strength of this study is the large number of illness episodes included. The two year time period should allow for seasonal variations and disease epidemics. We reviewed prescribing in all of the PCUs in Mueang Chiangrai District which covers a large geographical area and has a range of rural and urban facilities, making the results generalizable to the region more broadly. Many studies have focused on prescribing for specific conditions such as URTIs but our study covers a wide range of infections that present in the community. Having research staff on site has been shown to influence healthcare workers' prescribing habits (the Hawthorne Effect), but due to the retrospective nature of the study this was not a source of bias. The use of routinely collected data means that this methodology could be repeated in other districts and provinces in Thailand, although a lot of the data are entered as free text which presents challenges for analysis. Searching for patients with a history of fever, for instance, was problematic because the Thai word "lot" or fever is also part of the Thai words for patient, influenza, antipyrexials, etc.

Limitations of this study are that we only included public PCUs and have no data on antibiotic use by private clinics, pharmacies or family medicine doctors based at the provincial hospital, which requires further study. The PCU data is taken from routine electronic records and in some instances there were tranches of missing data (five PCUs had no recorded data for several months). Verifying the quality of some data is also challenging; coding of clinical diagnoses for instance using ICD 10 could be inconsistent between healthcare workers and in primary care the majority of infections are diagnosed clinically without any laboratory tests. However we used data from a subsample of patients enrolled in a clinical trial in four PCUs and compared them to their respective routine medical records. While minor discrepancies were found in their precise age and temperature the diagnoses and antibiotic prescribing data were consistent. Our decision to class all attendances within a one month period as a single illness episode means that we may have incorrectly classed some new illnesses as a repeat attendance but did allow us to review antibiotic prescribing over the course of the illness. The time series analysis was carried out using data from a two year time period, more definitive conclusions and trends may have become apparent if further time points and data were available.

CONCLUSIONS

This study provides much needed insight into the use of antibiotics in primary care in northern Thailand, allowing targeting of interventions to improve the rational use of antibiotics. Nearly half of all patients attending with an acute illness received an antibiotic. The majority of presentations were for respiratory infections. Further education and resources are required to support clinicians in the targeting of antibiotics. This could include the introduction of clinical algorithms and point of care tests such as CRP and urine dipsticks. Antibiotic guidelines are required for common conditions seen in primary care outside of the current Antibiotic Smart Use policy. Further studies including qualitative work are required to appreciate the use of antibiotics in other settings such as private facilities, pharmacies and dental clinics.

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Competing interests

None declared

Author contribution statement

All authors were involved in the design of the study. PW collected the data. RCG carried out the analysis with support from YL. MM provided statistical support. RCG, YL, DI, SN interpreted the data. RCG wrote

the first draft of the paper. YL, NPJD and MM reviewed subsequent drafts. All authors approved the final draft for publication.

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Data sharing statement

We are unable to share additional unpublished data which falls under the jurisdiction of the Chiang Rai PHO.

Ethical approval

Ethical approval was obtained from Chiangrai's Provincial and Public Health Office IRB (number 56/2560). Exemption was given by the Oxford Tropical Research Ethics Committee (OxTREC). Individual informed consent was not required.

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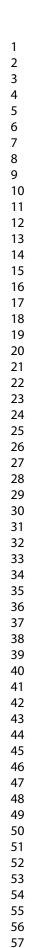
Figure 1: Chiangrai and the 32 PCUs

Figure 2: A Venn diagram to show the inclusion criteria

Figure 3: Trend and seasonality of antibiotic prescriptions overlaid by mean antibiotic prescription rates per PCU

Figure 4: Number of acute presentations by single systems and whether antibiotics were prescribed

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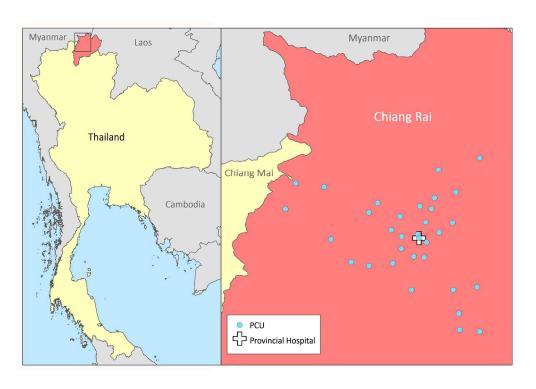
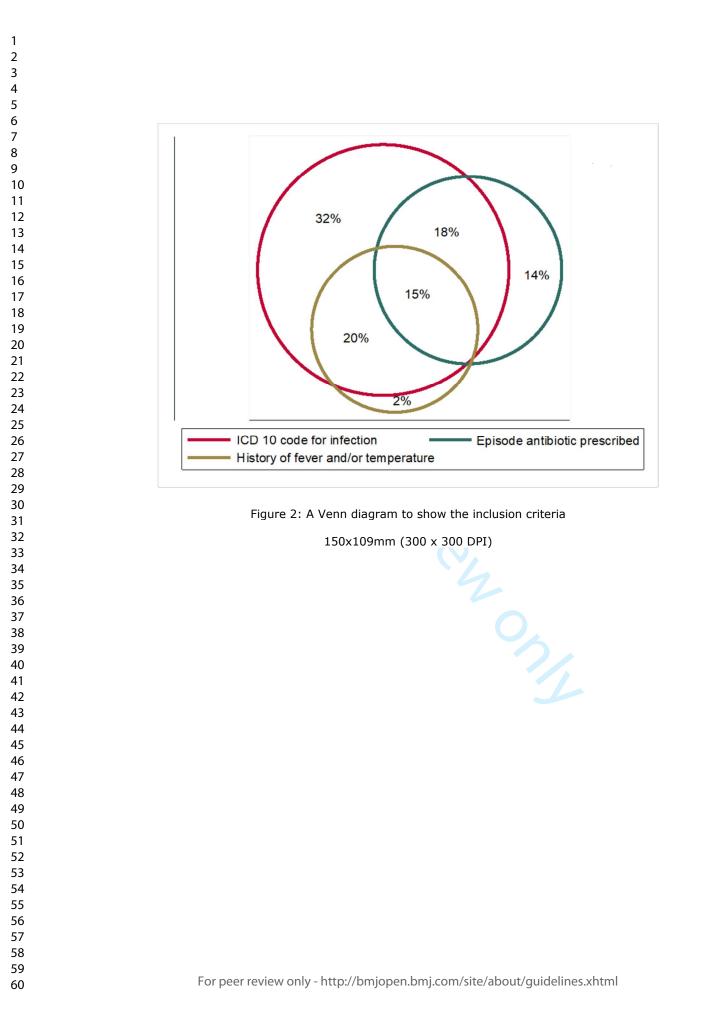
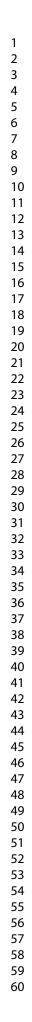


Figure 1: Chiangrai and the 32 PCUs

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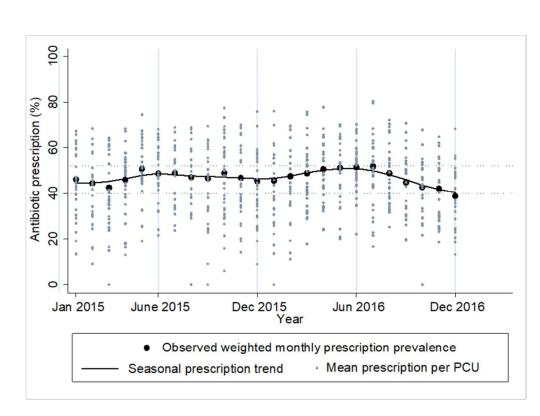
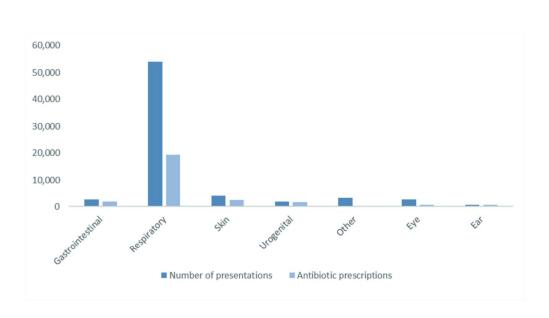


Figure 3: Trend and seasonality of antibiotic prescriptions overlaid by mean antibiotic prescription rates per PCU

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Supplementary material

Antibiotic search list

- Amoxicillin
- Cefixime
- Ceftriaxone
- Cephalexin
- Ciprofloxacin
- Co-amoxiclav/ augmentin
- Co-trimoxazole/bactrim
- Dicloxacillin
- Doxycycline
- Erythromycin
- Metronidazole
- Norfloxacin
- Penicillin V
- Roxithromycin
- TC mycin/ tetracycline

Table S1: ICD 10 codes for infection used for the inclusion criteria

Code	Description	Excluded code (number)
А00-В99	Certain infectious and parasitic 🔨	A15 (167), A16 (29), A18 (7),
	diseases	A31.9 (1), B18 (18), B24 (85),
		B85 (671)
G00-G07	Inflammatory diseases of the central	
	nervous system	
H00-01	Hordeolum, chalazion and other	H01.1 (35)
	inflammation of the eyelid	
H05.0	Acute inflammation of orbit	
H10	Conjunctivitis	
H60-H70	Otitis externa, otitis media and	H61 (112)
	mastoiditis	
H72-73	Perforation and other disorders of the	H73.9 (2)
	tympanic membrane	
J00-43	Respiratory tract infections	J30 (150), J31 (8), J33 (1), J35.1
		(1)
J47	Bronchiectasis	
К05	Gingivitis and periodontal diseases	Exclude all (9,469)
K11-12	Diseases of salivary glands, stomatitis	K11.1 (3), K11.88 (2), K11.9 (1)
	and related lesions	K12.0 (682), K12.1 (716)
K35-37	Appendicitis	
K57	Diverticulitis	K57 (2)



K61	Abscess of anal and rectal regions	
K81	Cholecystitis	
K83-85	Cholangitis and pancreatitis	
L00-08	Infections of the skin and	
	subcutaneous tissue	
L20-22	Dermatitis	L20 (23), L21 (19), L22 (5)
L30.3	Infective dermatitis	
L70-73.2	Acne, rosacea follicular cysts and	
	follicular disorders	
M00-03	Infectious arthropathies	M0013 (1), M0023 (1), M016
		(1), M020 (1)
M60	Myositis	M60.1-M6099 (3,604)
N10-11	Tubulo-interstitial nephritis	
N30	Cystitis	
N34	Urethritis and urethral syndrome	
N39.0	Urinary tract infection, site not	
	specified	
N41	Inflammatory diseases of prostate	
N45	Orchitis and epididymitis	
N48-49	Other disorders of male genital organs	N48.9 (1)
N61	Inflammatory disorders of breast	
N70-76	Inflammatory diseases of female pelvic	
	organs	
008.0	Genital tract and pelvic infection	
	following abortion and ectopic and	
	molar pregnancy	
023	Infections of genitourinary tract in	
	pregnancy	
O85-86	Puerperal sepsis and other puerperal	
	infections	<u> </u>
P35-9	Infections specific to the perinatal	
	period	
R05	Cough	
R11	Nausea and vomiting	
R30	Pain associated with micturition	
R36	Urethral discharge	
R50	Fever	

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Table S2: The number of initial presentations for each inclusion criteria and the percentage prescribed antibiotics during their illness episode

Age (years)	Number of presentations n/N (%)	Number of patients receiving an antibiotic prescription n/N (%)
0-4	18,073/83,659 (21.6)	6,110/18,073 (33.8)
5-11	13,775/83,659 (16.5)	6,318/13,775 (45.9)
12-24	10,533/83,659 (12.6)	5,888/10,533 (55.9)
25-39	11,025/83,659 (13.2)	6,167/11,025 (55.9)
40-64	23,134/83,659 (27.7)	11,843/23,134 (51.2)
65 or over	7,119/83,659 (8.5)	2,915/7,119 (41)
Total	83,659 (100)	39,241/83,659 (46.9)

Table S3: The number of presentations per age group and the percentage of each group prescribed an antibiotic

Inclusion criteria	Total initial presentations	Antibiotic prescription during the illness episode
History of fever n/N (%)	29,246/82,976 (35.3%)	11,725/29,246 (40.1%)
Temperature >37.5°C n/N (%)	10,508/76,644 (13.7%)	5,003/10,508 (47.6%)
ICD 10 code for infection n/N (%)	70,137/83,338 (84.2%)	27,234/70,137 (38.8%)
Antibiotic prescription n/N (%)	37,011/83,661 (44.2%)	39,242/83,661 (46.9%)

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Diagnosis	Number of presentations n/N (%)	Number of antibiotic prescriptions during the illness episode n/N (%
Respiratory		
Common cold	34,549/53,819 (64.2)	3,643/34,549 (10.5)
Acute sinusitis	30/53,819 (0.1)	25/30 (83.3)
Acute pharyngitis	13,080/53,819 (24.3)	11,607/13,080 (88.7)
Acute tonsillitis	3,459/53,819 (6.4)	3,014/3,459 (87.1)
Other URTIs	357/53,819 (0.7)	278/357 (77.9)
Acute LRTIs	663/53,819 (1.2)	541/663 (81.6)
Chronic bronchitis,	60/53,819 (0.1)	10/60 (16.7)
emphysema & bronchiectasis		
Cough	1,621/53,819 (3)	99/1,621 (6.1)
Sub total	53,819 (100)	19,217/53,819 (35.7)
Gastrointestinal	,	
Bacterial intestinal	199/2,706 (7.4)	127/199 (63.8)
infections or intoxications		· · · ·
Viral enteritis	46/2,706 (1.7)	4/46 (8.7)
GE & colitis	2,412/2,706 (89.1)	1,614/2,412 (66.9)
Appendicitis	21/2,706 (0.8)	2/21 (9.5)
Other	9/2,706 (0.3)	2/9 (22.2)
Sialoadenitis	19/2,706 (0.7)	16/19 (84.2)
Sub total	2,706 (100)	1,765/2,706 (65.2)
Skin		
Infective dermatitis	85/4,060 (2.1)	70/85 (82.4)
Dermatophytosis	902/4,060 (22.2)	92/902 (10.2)
Other superficial mycoses	197/4,060 (4.9)	14/197 (7.1)
Candidiasis	101/4,060 (2.5)	23/101 (22.8)
Other	64/4,060 (1.6)	52/64 (81.3)
Scabies & infestations	52/4,060 (1.3)	8/52 (15.4)
Cellulitis & abscesses	841/4,060 (20.7)	618/841 (73.5)
Bacterial skin infections	533/4,060 (13.1)	464/533 (87.1)
Furuncles, caruncles & cysts	947/4,060 (23.3)	780/947 (82.4)
Other local infection of the skin & subcutaneous tissue	338/4,060 (8.3)	290/338 (85.8)
Sub total	4,060 (100)	2,411/4060 (59.4)
Eye		
Conjunctivitis	2,097/2,698 (77.7)	330/2,097 (15.7)
Hordeolum & chalazion	319/2,698 (11.8)	256/319 (80.3)
Other inflammation of the eyelid & orbit	268/2,698 (9.9)	98/268 (36.6)
, Trachoma	14/2,698 (0.5)	5/14 (35.7)

Sub total	2,698 (100)	689/2,698 (25.5)
Ear	2,000 (200)	
Otitis externa	464/753 (61.6)	369/464 (79.5)
Otitis media	243/753 (32.3)	197/243 (81.1)
Mastoiditis	16/753 (2.1)	9/16 (56.3)
Perforation of tympanic membrane & other disorders	30/753 (4)	25/30 (83.3)
Sub total	753 (100)	600/753 (79.7)
Urogenital		
Acute tubulo-interstitial nephritis	36/1,871 (1.9)	32/36 (88.9)
Other	17/1,871 (0.9)	12/17 (70.6)
Cystitis, UTI, dysuria, urethritis & urethral syndrome	1,370/1,871 (73.2)	1,291/1,370 (94.2)
Other disorders of male genital organs	32/1,871 (1.7)	20/32 (62.5)
Other inflammatory disorders of female pelvic organs	148/1,871 (7.9)	115/148 (77.7)
Other inflammatory disorders of the vagina & vulva	268/1,871 (14.3)	149/268 (55.6)
Sub total	1,871 (100)	1,619/1,871 (86.5)
Other		
Bacterial	85/3,208 (2.7)	28/85 (32.9)
Unknown aetiology	33/3,208 (1)	14/33 (42.4)
Viral	728/3,208 (22.7)	153/728 (21)
Fungal	36/3,208 (1.1)	2/36 (5.6)
Protozoal	10/3,208 (0.3)	0/10 (0)
Parasitic	1,880/3,208 (58.6)	99/1,880 (5.3)
Nausea & vomiting	268/3,208 (8.4)	30/268 (11.2)
Fever of unknown or other origin	168/3,208 (5.2)	10/168 (6)
Sub total	3,208 (100)	336/3,208 (10.5)

Table S4: The number of presentations per diagnosis and system and whether antibiotics were prescribed for that illness episode

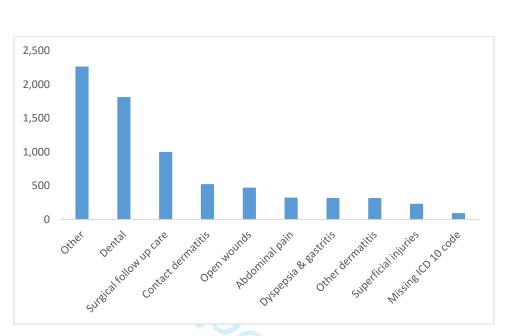


Figure S1: Single diagnoses used for antibiotic prescriptions without a history of fever, temperature or ICD 10 code for infection

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0 1 1 2 3 4	 (a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced 		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.	Abstra 11
5 6 7 8 9 0 1	summary of what was done and what was found	1	RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.	Abstra 11 Abstra 11&1
2 3 4 5 6			RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	NA 、
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8 2 9 0	Explain the scientific background and rationale for th investigation being reported	ne		Page 3 Backg section
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7 4 3 4 9 5	Present key elements of study design early in the paper		0	Page 3 pa pa
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	<u> </u>	follow-up, and data collection			<u> </u>
1	6	(a) Cohort study - Give the	1	RECORD 6.1: The methods of study	Page Page
'2 3	1	eligibility criteria, and the		population selection (such as codes or	page 4530
3 4		sources and methods of selection		algorithms used to identify subjects)	line 37
4 5		of participants. Describe		should be listed in detail. If this is not	n.
6	1	methods of follow-up		possible, an explanation should be	first
7	1	<i>Case-control study</i> - Give the		provided.	pu
8	1	eligibility criteria, and the			blis
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12 13	1	the choice of cases and controls		referenced. If validation was conducted	113
13 14		<i>Cross-sectional study</i> - Give the		for this study and not published	36/b
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24	1	unexposed		process, including the number of individuals with linked data at each) Ju
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28 29	7	controls per case		DECODD 7 1. A 1 (1' (C)	line 386n: first published as 10.1136/bmjopen-2018-022250 on 30 July 2018. Down
29 30	7	Clearly define all outcomes,		RECORD 7.1: A complete list of codes	rage ∑lir
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2	10	potential sources of bias			NA Page	BM
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б б	11	Explain how quantitative variables were handled in the			Page	<u>주</u> 111
7		analyses. If applicable, describe			page	<u>e</u>
8		which groupings were chosen,				blish
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10 11	12	(a) Describe all statistical			Page 15, 3 line 3	∜.lir
12	12	methods, including those used to			15 3	7≟n:
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19		were addressed				8-0
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12		individuals at each stage of the		selection of the persons included in the	48, page
13		study (e.g., numbers potentially		study (<i>i.e.</i> , study population selection)	Page 🛞
14 15		eligible, examined for eligibility,		including filtering based on data	page Z
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17		the study, completing follow-up,		The selection of included persons can	-ne
18		and analysed)		be described in the text and/or by	201
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20		participation at each stage.		_	222
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5		and, if applicable, confounder-			page	& lin
6		adjusted estimates and their				st p
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8 9		interval). Make clear which				lishe
9 10		confounders were adjusted for				ed o
10		and why they were included				as 1
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18		risk into absolute risk for a				201
19		meaningful time period			Page	8-0;
∕S @\$	17	Report other analyses done—			Page	&lin
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22		interactions, and sensitivity				on 3
23 		analyses			page	ľ 0
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26	18	Summarise key results with			Page	S lin
27		reference to study objectives			20	∞
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29		taking into account sources of		implications of using data that were not	54, pa	a ≩ e 1
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