Obtaining antibiotics online from within the United Kingdom: a cross-sectional study

Sara Elizabeth BOYD [1,2*]

Luke Stephen Prockter MOORE [1,2]

Mark GILCHRIST [1,2]

Ceire COSTELLOE [2]

Enrique CASTRO-SÁNCHEZ [2]

Bryony Dean FRANKLIN [3,4]

Alison Helen HOLMES [1,2]

Affiliations:

1. Imperial College Healthcare NHS Trust, Du Cane Road, London.W12 0HS. United Kingdom.

2. National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, Imperial College London, Du Cane Road, London. W12 0HS. United Kingdom.

3. Centre for Medication Safety and Service Quality, Imperial College Healthcare NHS Trust, London, United Kingdom

4. Research Department of Practice and Policy, UCL, School of Pharmacy, Mezzanine Floor, BMA House, Tavistock Square, London, United Kingdom

***Corresponding author**

Dr Sara E Boyd, National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, Commonwealth Building, Imperial College London, Hammersmith Campus, Du Cane Road, London. W12 0NN. United Kingdom. Email: s.boyd@imperial.ac.uk Telephone: 02033132732

Running title: Obtaining antibiotics online from within the United Kingdom

Structured Synopsis

Background

Improved antibiotic stewardship (AS) and reduced prescribing in primary care, with a parallel increase in personal Internet use, could lead citizens to obtain antibiotics from alternative sources online.

Objectives

A cross-sectional analysis was performed to: a) determine the quality and legality of online pharmacies selling antibiotics to the UK public; b) describe processes for obtaining antibiotics online from within the UK; and c) identify resulting AS and patient safety issues.

Method

Searches were conducted for 'buy antibiotics online' using 'Google' and 'Yahoo'. For each search engine, data from the first 10 websites with unique URL addresses were reviewed. Analysis was conducted on evidence of appropriate pharmacy registration, prescription requirement, whether antibiotic choice was 'prescriber-driven' or 'consumer-driven', and whether specific information was required (allergies, comorbidities, pregnancy) or given (adverse effects) prior to purchase.

Results

Twenty unique URL addresses were analysed in detail. Online pharmacies evidencing their location in the UK (n=5; 25%) required a prescription before antibiotic purchase, and were appropriately registered. Online pharmacies unclear about the location they were operating from (n=10; 50%) had variable prescription requirements, and no evidence of appropriate registration. Nine (45%) online pharmacies did not require a prescription prior to purchase. For 16 (80%) online pharmacies, decisions were initially consumer-driven for antibiotic choice, dose, and quantity.

Conclusions

Wide variation exists among online pharmacies in relation to antibiotic practices, highlighting considerable patient safety and AS issues. Improved education, legislation, regulation, and new best practice stewardship guidelines are urgently needed for online antibiotic suppliers.

Introduction

Antimicrobial stewardship (AMS) is recognised as the organisational or healthcare-system-wide approach to promoting and monitoring the judicious use of antimicrobials,[1] such as antibiotics. Co-ordinated interventions within antibiotic stewardship (AS) programmes are designed to achieve optimal clinical outcomes whilst minimising adverse events and antibiotic resistance.[2] AS is a key priority within the United Kingdom (UK),[3] and globally,[4] as antimicrobial resistance (AMR) poses a profound threat to health security, healthcare quality and patient safety. The WHO global action plan for tackling AMR has specific objectives for international AS. These objectives include strengthening international regulations on the distribution, quality and use of antibiotics with emphasis placed on those obtained through Internet sales.[4] Within the UK National Health Service (NHS), local antibiotic guidelines, a variety of hospital-based restrictive and persuasive interventions,[5] community-based social norm feedback,[6] and national stewardship guidelines[1,7] encourage judicious antibiotic prescribing. However, antibiotics may be acquired in much of the world without a prescription, despite being illegal in many of the countries concerned.[8–15] Within the UK, patient safety and current AS strategies may be threatened due to antibiotics being available to purchase online, without a prescription, from a variety of vendors globally.[16] In 2013 a European survey reported that the use of the Internet to resolve healthcare needs within the UK was modest.[17] However, it is expected that the use of the Internet within the UK, for both consumer and healthcare needs, will continue to rise based on the current trajectory.

Prescribing by healthcare professionals, all practices conducted within registered pharmacies, and any advertisements for medicinal products are closely monitored and regulated within the UK. The General Medical Council (GMC) advises on remote and electronic prescribing decisions;[18] and dentists, nurses, pharmacists, optometrists, and midwives, who may also issue antibiotic prescriptions, have similar regulatory bodies. In Great Britain (GB), the General Pharmaceutical Council (GPhC) registers practising pharmacists, as well as pharmacy premises and online pharmacies. Guidance for providing services online is also

distributed by the Royal Pharmaceutical Society (RPS) in GB,[19] and by the Pharmaceutical Society of Northern Ireland (PSNI). The UK Medicines and Healthcare products Regulatory Agency (MHRA) also provides registration for online pharmacies, investigates websites that are suspected of operating illegally and considers advertisements for prescription-only medicines (POMs) acceptable only on websites whose content is directed at healthcare professionals.[20] Formal MHRA registration for all online vendors selling medicines to UK consumers was mandated in 2015, with every webpage legally required to display the EU common logo containing a hyperlink directing users to a list of registered online pharmacies.[21] In contrast to the EU common logo, the GPhC logo is a voluntary scheme applicable only to pharmacies registered in GB.[22]

Currently, patients may obtain antibiotics online through legal registered pharmacy platforms, or through illegal websites, which expose them to a variety of potential risks. These risks may include: no verbal or physical review prior to antibiotic supply; inappropriate choice, dose, or duration; poor quality medication; pressured antibiotic advertising, or payment information fraud. In November 2015 the Review on Antimicrobial Resistance, commissioned by the UK government, highlighted the risks of online antibiotic sales and emphasised the need for a safe, secure and controlled antibiotic supply chain.[23] However, the extent of the problems associated is largely unknown.[23]

We report here an exploratory cross-sectional analysis of a representative sample of online pharmacies with the overarching objective being to improve understanding of the current state of online antibiotic sales in the UK. The specific aims of this cross-sectional analysis were: 1) to assess the quality and legality of online pharmacies identified (using registration status as a proxy indicator for quality and legality), 2) to analyse the processes (whether prescriber-driven or consumer-driven) for purchasing an antibiotic online and, 3) to identify any resulting AS or patient safety issues.

Methods

A multidisciplinary working group (AH, SB, MG, LM, CC), which included both healthcare professionals and academics with expertise in AS agreed a study protocol and data collection tool by Delphi consensus. One researcher (SB) completed data collection based on the pre-agreed protocol using a computer for which the cached search history was cleared prior to the study.

Choice of search engine

The popularity of specific Internet search engines will vary depending on the preference and geographical location of searchers. 'Google' and 'Yahoo,' widely recognised as two of the most popular search engines in the world play a major role in how people address medical needs[24] and were both used to reduce bias in the way that individual search engines may retrieve and rank results.[25] Due to varying degrees of overlap in the way these search engines present results,[26] websites that were duplicated were only included once. The Google search was completed first.

Choice of search term

Simple queries and keyword searches dominate when purchasing products online with searchers viewing fewer result pages.[27] Consumer time-pressure and cognitive-resource limitations have been hypothesised to account for this.[28] Search engine queries were therefore conducted with the search term 'buy antibiotics online.'

Choice of sample size

In their default setting the search engines selected typically respond to queries with a ranked list of 10 websites on the first page, with searchers being heavily influenced by the order in which they are presented.[29] The first position in an Internet search contributes to more traffic than the second and subsequent positions,[29,30] with products or websites at the top of a list being more likely to become part of a consumer's consideration set.[31] The first page of a

Google search generates approximately 92% of traffic from an average search, when moving from the first to second page traffic drops by 95%, and by 78% and 58% for subsequent pages.[30] When presented with options, consumers typically undergo a two-stage process by screening products or websites, and subsequently reviewing a more relevant subset in detail before making a purchase decision.[32] A sample size of 20, to include the first 10 unique webpages identified from each search engine, meeting the inclusion and exclusion criteria, was subsequently pre-determined.

Inclusion and exclusion criteria

Websites were included if they were English-language vendors selling antibiotics online, for human use, to consumers within the UK. Websites were excluded if they were advertisement links, primarily for veterinary medicine, did not ship to the UK, or were inactive when attempts were made to proceed to checkout. In some cases different Uniform Resource Locator (URL) addresses were linked to a common stem vendor (CSV) selling antibiotics. Each CSV was included only once. The first 10 websites from each search engine with a unique URL address, that fitted the criteria specified, were analysed in detail. Data were collected to meet the objectives, and the process for purchasing an antibiotic followed until the point of payment. Purchasing an antibiotic was defined as a payment transaction.

The first objective was to assess the quality and legality of online pharmacies identified. Registration with the MHRA, evidenced by the presence of the mandatory EU common logo, was used as a proxy indicator of the quality and legality of the pharmacy. Evidence of accreditation and registration with the GPhC (or PSNI) was also recorded. All websites displaying accreditation logos were cross-referenced with the relevant online register (MHRA and GPhC/PSNI), to ensure the validity of the logo displayed. Each website was further studied to identify the location from where it was operating.

The second objective was to analyse the processes for purchasing an antibiotic online. Data were collected on prescription requirements and whether information for safe prescribing (allergies, comorbidities, pregnancy) were required prior to the purchase of an antibiotic. Websites were thoroughly reviewed to identify statements on prescription requirements. All webpages specifying the sale of antibiotics were analysed in detail and the process for obtaining an antibiotic was followed up to the point of inputting payment information for each website. In addition, the term 'prescription' was searched for and the 'frequently asked questions' section, or equivalent, was reviewed in detail for each online pharmacy included. Initial decisions regarding the choice of antibiotic were defined as being 'prescriber-driven' or 'consumer-driven'. A 'prescriber-driven' process was when the consumer was first directed through an online consultation after clicking on a specific ailment, and if appropriate, a prescription for an antibiotic was subsequently selected by the prescriber. A 'consumer-driven' process was when the consumer initiated the antibiotic purchase by first selecting an antibiotic of their choice for placement in their 'shopping basket'. Data were also collected on whether any safety information on adverse effects was provided to patients during the online process, whether oral or intravenous (IV) antibiotics were available for purchase, the standard delivery time to the UK, and whether an express delivery option was available. Each website was explored in detail and data collected on the name of all antibiotics which appeared available for purchase online.

The third objective was to identify any resulting antibiotic stewardship and patient safety issues; this was met through integration of the above findings.

After completion of data collection all vendors identified as illegally selling antibiotics to patients within the UK were reported to the MHRA. Ethics approval was not required for this study of open source data.

Results

Results of the searches performed on 28 February 2016 are shown in Figure 1. Twenty-eight websites were screened. Of the websites analysed in detail (n=20), five (25%) websites showed evidence of operating from within GB. All 5 displayed appropriate evidence of registration with both the MHRA and the GPhC. Table 1 shows the locations and registration status of the 15 other websites analysed.

Figure 2 summarises the prescription requirements and different processes for providing a prescription to the vendor prior to online purchase. All 5 GB-based online pharmacies required a prescription before an antibiotic would be delivered. For 16 (80%) websites, decisions regarding antibiotic choice, dose and duration were initially consumer-driven, with only four (20%) online pharmacies utilising a prescriber-driven pathway (Table 2). All four of these were based in GB and registered with both the MHRA and GPhC. A further GB-based pharmacy, registered with both the MHRA and GPhC, permitted a consumer-driven process prior to the point of payment through which consumers were directed to an antibiotic choice depending on the syndrome they clicked on the webpage. However, despite initially adopting a consumer-driven approach, this pharmacy described a pathway whereby a health questionnaire would be made available after payment was received to allow a doctor to assess an individual's suitability for an antibiotic. Six websites (30%) did not issue online prescriptions and instead required that a prescription be faxed or posted before an antibiotic would be delivered. One of these websites did not specify the location from where they were operating and it was not clear if an address would have been provided to allow a consumer to post the prescription after a payment transaction. Figure 3 correlates the requirement for prescription through each individual online pharmacy with the information that was requested, prior to antibiotic purchase. All pharmacies offered oral antibiotics, one non-EU based website also advertised IV antibiotics for sale. The cumulative frequency of all types of antibiotic available from the 20 pharmacies is presented in Table 3. Standard delivery time to the UK varied from 1 to 14 days (mean: 10.5, median: 14, interquartile range: 6.75 – 14).

Thirteen websites (65%) had a standard delivery time of 14 days. An express option was available on request for all 20 websites.

Discussion

This study raises several important issues regarding AS and patient safety with online pharmacies. Concerning heterogeneity was observed in the legality and quality of online pharmacies, the processes for obtaining an antibiotic, and in other safety procedures prior the point of payment.

Assessing the quality and legality of online pharmacies

A similar study, carried out by Mainous *et al* in the United States, found that 36.2% of 138 online pharmacies sold antibiotics without prescription,[16] a figure slightly below the 45% identified in our sample. The relative paucity of published literature around selling antibiotics via the Internet is contrasted with numerous studies relating to other classes of medication. A systematic review published in 2011 assessed 193 relevant studies and aimed to determine the characteristics and quality of online pharmacies.[33] The authors reported a wide variety of prescription-only medicines available with inconsistent prescription requirements and that the presence of at least one quality certification ranged from between 12-28% depending on the study in question.[33] Among the 20 online pharmacies analysed in the present study, those that were operating from within the UK (25%) evidenced registration with both the MHRA and the GPhC. Confirming the registration status was facilitated by a user-friendly hyperlink, enabling potential consumers to check the legitimacy of a website. However, this mechanism to reassure the public on quality and safety relies on consumers understanding what the logos represent. A concerning number of pharmacies within our sample (75%) lacked evidence of registration required by current UK and European legislation. This may be because some of the identified pharmacies were operating outside of Europe, with three based in India. There was no information provided on where ten (50%) of the pharmacies were operating from. Regardless of where they are based, vendors providing antibiotics to patients within the UK,

are subject to UK legislation. While non-prescription antibiotics are recognised as an important means for access in resource-poor settings,[34] this is unlikely to be a concern within the UK where healthcare is free at the point of need. This study raises concerns on the effectiveness of current legislation, licensing and regulation for platforms selling antibiotics via the Internet to UK consumers.

The processes for obtaining antibiotics online from within the UK

We have identified heterogeneity in the processes for obtaining antibiotics online, including in the safety assessments made to determine if antibiotics were required, and if so, the most appropriate and safe antibiotic choice, dose and duration. Overall, 16 (80%) of the pharmacies reviewed required that consumers directly select an antibiotic before proceeding to checkout. Health questionnaires were utilised in only six (30%) online pharmacies. These lacked consistency and often came subsequent to a consumer-driven choice on requirement and type of antibiotic. A systematic review of online pharmacies reported use of an online questionnaire during the purchasing process to be between 10-81%, depending on the study in question.[33] We observed variation in the information sought via health questionnaires, and the methods used to collect this information. Some questionnaires comprised drop-down boxes, some free-text boxes, and others a mixture of both. Additionally, it was not clear whether there would be feedback from the prescriber/dispenser if a mismatch was subsequently identified between the consumer-selected choice and the most appropriate course of action, taking into account the information in the questionnaire.

Opinion is mixed regarding whether antibiotics should be available without prescription.[35,36] However, in line with current UK legal requirements[37] and National Institute for Health and Care Excellence (NICE) guidance for AS,[1] decision processes should be shared and crucially underpinned by prescriber-driven rationale. In addition, a uniform, consistent and thorough health questionnaire should be mandatory. This tool should be developed through

collaboration with key UK stakeholders to ensure that online patient safety and antibiotic stewardship is consistent with national best practice. Key stakeholders may include representatives from Public Health England, the GMC, GPhC, RPS, PSNI, MHRA, Royal College of General Practitioners, NICE, the Department of Health Advisory Committee for Antimicrobial Resistance and Healthcare-Associated Infection, patient representatives, and the public.

We identified a median delivery time of 14 days, representing a potential risk to patients acquiring antibiotics to treat an acute infection. Mainous *et al* also analysed shipping times for antibiotic delivery.[16] These authors suggested, based on similar results to our findings, that the prolonged "interval between ordering and receiving the medication suggest that these transactions will likely be used by individuals storing the drugs for future self-diagnosis and treatment or for sale."

Consumers accessing health websites have relatively high levels of digital health literacy,[17] but there remains a need for a formal assessment of websites to ensure uniform standards for user-friendly platforms, readability, and that important health messages are conveyed. If antibiotics are to be sold online, advice to see a healthcare provider promptly if an adverse reaction occurs or if presenting symptoms do not improve must be at the forefront of the antibiotic purchasing process.

Additional concerns for antimicrobial stewardship and patient safety

Antibiotics were advertised directly to patients on several websites, and although direct-to-consumer marketing may be permitted in other healthcare settings, this practice is incongruous with current MHRA regulations.[20] The prevalence of antibiotic advertising was not a primary outcome measure in this study, but is raised as a concern on both ethical and

safety grounds. Given the significant volume of funding and effort to develop effective strategies for antibiotic stewardship in the UK, further research should be conducted to determine the frequency with which this advertising occurs, the effect it has on patients' expectation for antibiotics, and subsequent antibiotic-seeking behaviours. Recognition that inappropriate antibiotic prescribing is correlated with public expectation has been the focus of several educational campaigns led by the UK Department of Health and Public Health England.[7,38] Technical solutions that prevent advertisement links should be implemented, with consideration to financial penalties for websites who are in breach of MHRA regulations or who are supplying antibiotics outwith national stewardship guidelines, which are 'Start Smart Then Focus' and 'TARGET,' within England.[39,40]

This research raises a question on the potential unintended consequences of stewardship initiatives that improve and reduce antibiotic prescribing through traditional routes.[5] If the risks of inappropriate antibiotic use are not conveyed to patients there is concern that, as consumers, they may seek to obtain antibiotics from an alternative source. At present there is no way to estimate the acquisition of antibiotics through legal or illegal online pharmacies. Education and public awareness campaigns should encourage prescribers to identify patients' ideas, concerns and expectations, whilst fully explaining why they do not need an antibiotic. Although the gains of this strategy have been modest to date, the prospect that a patient may seek to obtain an antibiotic from an alternative source, such as online, reinforces its importance. Practitioners should seek to address the issues surrounding obtaining medicines online with those felt most likely to engage in this behaviour, although further research is urgently required to understand who they may be. It seems likely that they represent a 'hard-to-reach' group through traditional healthcare given their preference to seek healthcare through non-traditional routes. A snowball approach that actively seeks to engage online healthcare communities may prove useful to identify these consumers. Facilitated small group or one-to-one sessions using formal qualitative behavioural research methods, aiming to understand how to engage their desire for self-management in a safe manner, is required. In

addition to these strategies, the issues surrounding obtaining a variety of medicines online, including antibiotics, should be integrated into the curricula for all prescribers in order to raise awareness.

Strengths and limitations

This is the first analysis looking specifically at issues pertaining to the availability of antibiotics online to patients within the UK. Websites were identified using a method felt to be widely representative of how consumers search for and buy products online. By using two popular search engines we identified a broad range of relevant websites.

This study had limitations inherent to the constantly evolving online consumer domain. A Google or Yahoo search is not identical when different browsers are used for the same search, or when the same search is performed at different times. Different consumers may be faced with different purchasing options. However, it is widely accepted that the most popular sites will be placed higher on the result list for all searchers. Illegal vendors may also masquerade, and change their domain name frequently in order to remain operational. There is a possibility that if this occurred, the same vendor may have been included twice, although this is unlikely given the cross-sectional nature of the study. In addition, one researcher analysed all websites and would have most likely noticed any striking similarities among them.

When antibiotics are dispensed in person, an opportunity to ensure patient safety exists when handing over a prescription. Actually purchasing antibiotics was beyond the scope of our analysis, and in not proceeding to payment, we may have missed any patient safety prompts that occur only after a monetary transaction. Statements on websites were sought to determine whether antibiotic prescriptions were required. However, by not proceeding through a payment transaction we cannot be certain whether websites that made no statement on prescription requirement would subsequently refuse to process an order without a valid

prescription, or whether websites which had statements on prescription requirement would subsequently dispense antibiotics without a valid prescription. We did not explore whether or not information was sought on concomitant medications that may affect antibiotic suitability; collecting this additional data would be a valuable focus for future research.

Finally, the URL pages we identified may no longer be operational. All vendors identified as illegally selling antibiotics to patients within the UK were reported directly to the MHRA,[41] who promptly responded by email stating that all concerns had been passed to the Enforcement Team.

Conclusions

The way patients interact with healthcare is constantly evolving and shifts in consumer behaviour over the past decade mean increasing numbers are now opting to purchase products online. The availability of antibiotics online, or products being sold as such, poses a serious threat to patient safety and national antibiotic stewardship initiatives.

We make several key recommendations for stakeholders in the UK. GMC and RPS guidance for prescribers should be updated to reflect changes in healthcare seeking behaviour, the increasing demand for remote and online prescribing, and the importance of antibiotic stewardship in this environment. Display of the GPhC/PSNI logo should be made mandatory in line with the EU common logo. A best practice toolkit based on current NICE guidelines for antibiotic stewardship with a standardised health questionnaire developed by key stakeholders is recommended if the sale of antibiotics online is to continue in the UK. Emphasis should be placed on prescriber responsibility for follow-up to ensure infective symptoms improve and to monitor antibiotic-associated adverse events in line with current NICE guidance. We also evidence the urgent need to improve the surveillance of online antibiotic sales. Antibiotic distribution through online channels should be mandatory to report, in line with antibiotic consumption data for the UK National Health Service. Engaging

collaboration between international policy makers, governmental law enforcement agencies, pharmaceutical companies, individual prescribers and consumers will be a priority. In order to promote patient safety and preserve antibiotic therapy, an efficient and operational multidisciplinary taskforce is needed to address the issues we have identified.

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Transparency declarations

All authors have completed the ICMJE uniform disclosure form and declare: AHH has consulted for bioMérieux in 2013 and 2014. LSPM has consulted for bioMérieux in 2014, and DNA electronics in 2015. MJG reports attending advisory boards for Pfizer and MSD, in addition to receiving educational travel and speaker grants from Astellas Pharmaceuticals and Sanofi. SEB, CC, BDF, and ECS have no conflicts of interest to declare.

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Figure 1. Flow diagram displaying results from search performed on 28 February 2016

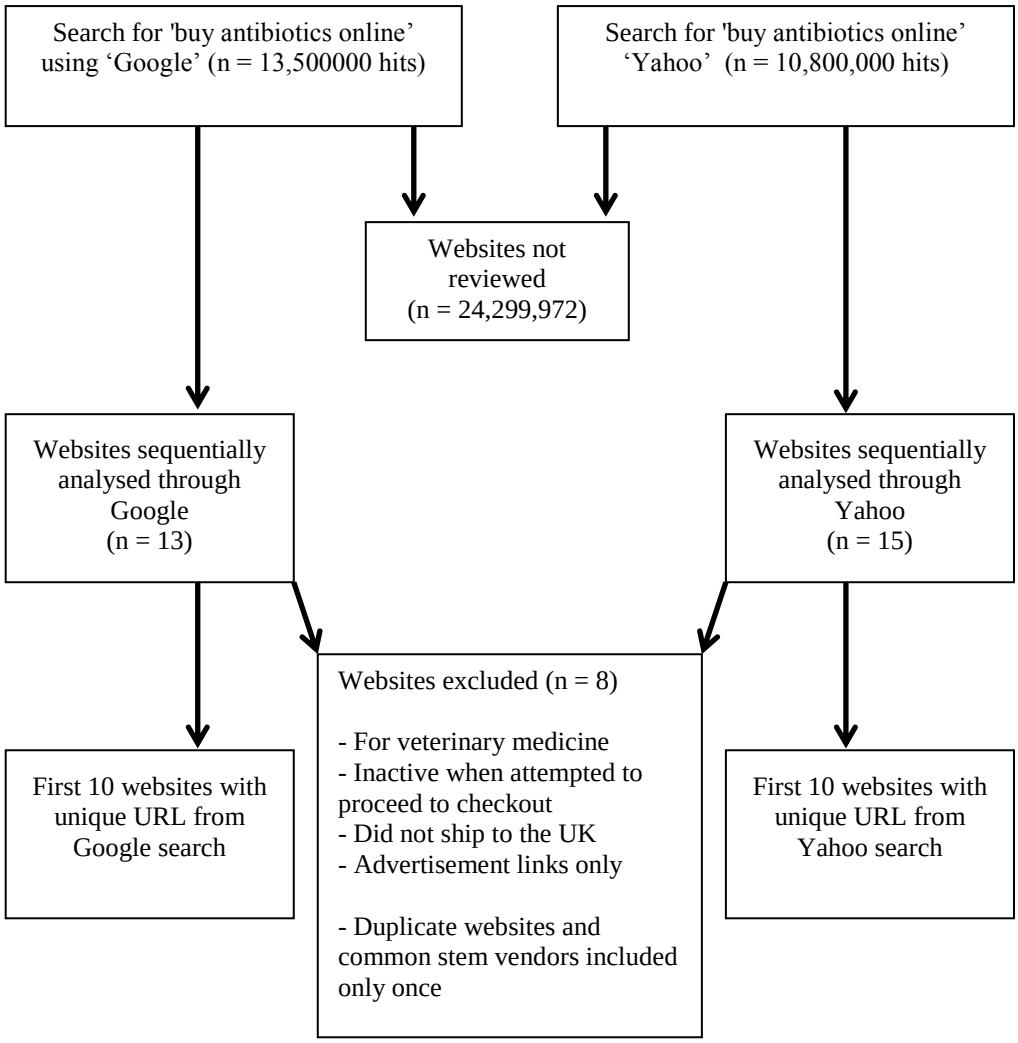

Figure 2. Prescription requirements and processes for obtaining an antibiotic among sampled online pharmacies (n=20)

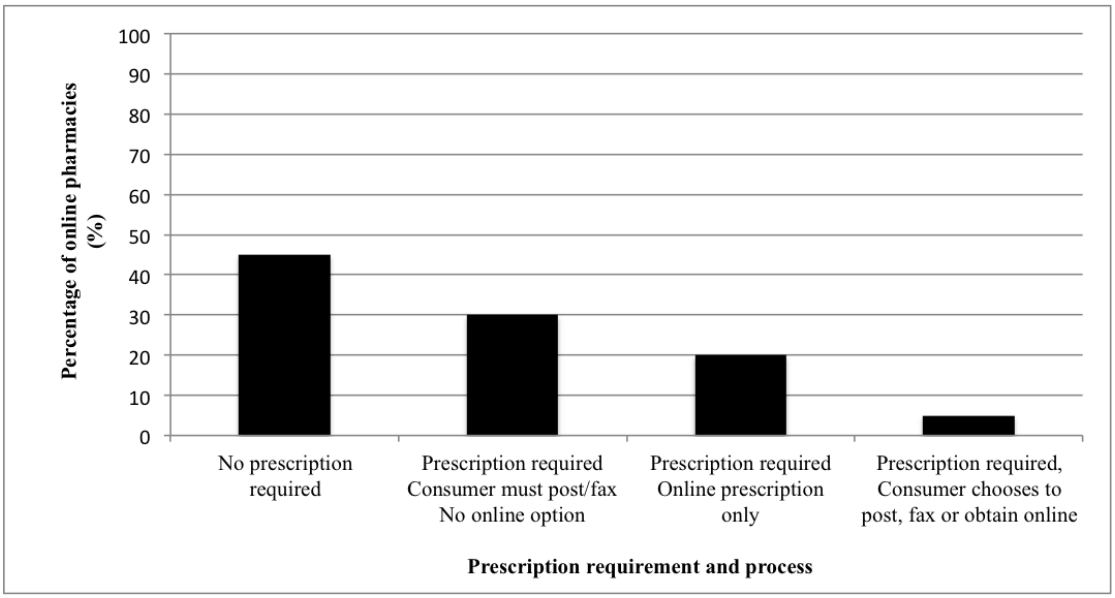

Figure 3. Prescription and information requirements for obtaining an antibiotic among the top twenty online pharmacies analysed

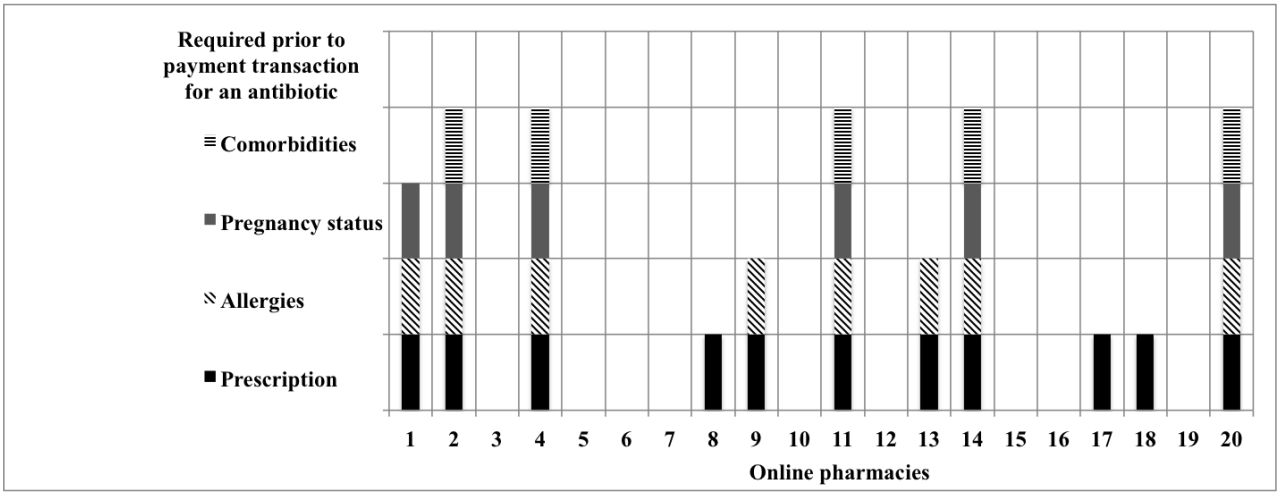

Table 1. Online pharmacies selling antibiotics to consumers within the United Kingdom

	Number of online pharmacies (n=20)
Registered with MHRA and GPhC	
Yes	5 (25%)
No	15 (75%)
Location operating from	
Great Britain	5 (25%) *
Unclear	10 (50%)
India	3 (15%)
Cyprus	2 (10%)

MHRA = Medicines and Healthcare products Regulatory Authority

GPhC = General Pharmaceutical Council

* All those operating from within Great Britain were registered with both the MHRA and GPhC

Table 2. Processes for obtaining an antibiotic online from within the United Kingdom

	Number of online pharmacies (n=20)
Consumer-driven versus prescriber-driven antibiotic choice	
Consumer–driven choice of drug, dose and quantity	16 (80%)
Prescriber-driven choice of drug, dose and quantity	4 (20%)
Use of an online health questionnaire during purchasing	
Yes	6 (30%)
No	14 (70%)
Safety information provided on contraindications or side effects prior to purchasing	
Yes	14 (70%)
No	6 (30%)

Table 3. Cumulative frequency of antibiotics available from online pharmacies analysed (n=20)

Antibiotic class Agent	Number of online pharmacies that made clear on website they were able to supply (n=20)
Penicillins	
Penicillin	3
Amoxicillin	17
Ampicillin	14
Flucloxacillin	3
Co-amoxiclav	16
Tetracyclines	
Doxycycline	19
Lymecycline	1
Oxytetracycline	8
Minocycline	14
Tetracycline	13
Macrolides	
Clarithromycin	12
Erythromycin	15
Azithromycin	19
Roxithromycin	9
Cephalosporins	
Cefalexin	13
Cefuroxime	10
Cefadroxil	13
Cefixime	16
Cefpodoxime	13
Cefaclor	9
Cefdinir	10
Cefipime	3
Cefprozil	2
Carbapenems	
Faropenem	2
Quinolones	
Ciprofloxacin	15
Ofloxacin	17
Levofloxacin	9
Moxifloxacin	9
Norfloxacin	11
Sparfloxacin	4
Nalidixic Acid	3
Sulfonamides and Trimethoprim	
Co-trimoxazole	10
Trimethoprim	8
Lincosamide	
Clindamycin	12
Lincomycin	7
Others	
Nitrofurantoin	14
Chloramphenicol	11
Linezolid	12
Metronidazole	14

Rifaximin	4
Rifampin	1
Cycloserine	4
Ethambutol	4
Ethionamide	5
Pyrazinamide	2