C H A R L E S U N I V E R S I T Y

FACULTY OF PHARMACY IN HRADEC KRÁLOVÉ

DEPARTMENT OF SOCIAL AND CLINICAL PHARMACY

Non-prescribed antibiotic use in some developing countries and its association with drug resistance

Thesis submitted for the degree of Doctor of Philosophy

Hradec Králové, 2017 Tatiana Belkina, MSc

Declaration

"I declare the experiments and composition of this thesis are my original work developed personally under the guidance from my supervisor.
The experimental work conducted in collaboration is stated below.

Chapter 4.3: The original design of the experiment was established by myself, Jiří Vlček and Abdullah Al Warafi and was conducted by Mohamed E. El Zowalaty in our close collaboration. I performed all the analyses presented here, and wrote the subsequent chapter of the manuscript with contribution by Jurjen Duintjer Tebbens and Jiří Vlček.
All literature and other sources used are included in the list of references and properly cited in the thesis.

This work has not been submitted for any other degree or professional qualification."

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Hradec Králové 12 February 2017

The work has been supported by the grant of Charles University (SVV 260 295).

Acknowledgements

I would firstly like to thank my supervisor, doc. RNDr. Jozef Kolář, CSc., and my consultant Head of the Department of Social and Clinical Pharmacy prof. RNDr. Jiří Vlček, CSc., for their continued support and encouragement throughout the course of my PhD. Thank you for allowing me the freedom and independence to pursue my research.

My thanks to Abdullah Al Warafi for the scientific ideas and help in taking the first steps toward my research goals and dreams.

My greatest gratitude to Erik Jurjen Duintjer Tebbens for the invaluable contribution to the work presented here. Jurjen- thank you, you opened up a world and beauty of statistics to me.

I am greatful to department's research group members Kateřina Ládová and Stanislava Kalafutová for all their practical help and endless support as well as the good company in our office.

I also owe thanks to the people who dedicated time to discuss different scientific aspects with me, and giving me wise counsels: Mohamed E. El Zowalaty, Petra Matoulková, Josef Malý, Jan Kostřiba, František Dohnal, Jana Kotlářová, Helena Marešová, Jan Babica, Martin Doseděl, Magda Vytřísalová and Jitka Pokladníková.

Thank you to everyone in the Department of Social and Clinical Pharmacy for shared experience and the great atmosphere which made me feel like at home.

Finally, I would like to thank my friends and family for their support and encouragement. There were times when you believed in me more than I believed in myself.

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Abstract

Charles University, Faculty of Pharmacy in Hradec Králové

Department of	Social and Clinical Pharmacy
Candidate	Tatiana Belkina, MSc
Supervisor	doc. RNDr. Jozef Kolář, CSc.
Title of Doctoral Thesis	Non-prescribed antibiotic use in some developing countries and its association with drug resistance

Background and Aims:

The global emergence and spread of antimicrobial resistance remain a major challenge to infection control and a predominant reason for therapy failure. Non-prescription access to antimicrobials is common, and self-prescribing is increasingly popular in a society with non-regulated access to antimicrobials. It is crucial to avoid self-medication in order to combat antimicrobial resistance. This research need has been addressed within 4 scientific projects with the following aims:

P1: We examined knowledge, attitude and practices of antibiotic use in 3 Asian countries and estimated the frequency and reasons for self- medication. **P2:** This study aimed to evaluate the extent of delay in diagnosis and treatment of tuberculosis in Uzbekistan and identify associated risk factors. **P3:** To evaluate knowledge of antibiotics, race, gender and age as independent risk factors for self-medication. **P4:** The aim of this study was to assess the attitudes of community pharmacists regarding antibiotic use and self-medication in Saint Petersburg, the Russian Federation.

Methods:

P1: A nationwide cross-sectional study was conducted with 1 200 adults of well-educated population segment in large cities in Yemen, Saudi Arabia and Uzbekistan. Data were analyzed using descriptive statistics.

P2: A cross-sectional study was performed on hospital patients with newly diagnosed TB in Tashkent and Aral Sea region, Uzbekistan. The time between the onset of respiratory symptoms and initiation of anti-tuberculosis treatment was assessed and delays were divided into patient, health system and total delays. Univariable and multivariable logistic regression analysis was used to evaluate determinants of diagnostic and treatment delay.

P3: A cross-sectional survey study was conducted among residents and population from different regions of Saudi Arabia. There were 1 310 participants, whose data were recorded anonymously. The questionnaire was distributed randomly in person interview of participants and included sociodemographic characteristics, antibiotics knowledge, attitudes and behavior with respect to antibiotics usage. Population aggregate scores on questions and data were analyzed using univariate logistic regression to evaluate the influence of variables on self-prescription of antibiotics.

P4: We conducted a cross-sectional study of community pharmacists in the Saint-Petersburg and Leningrad region, Russia. A self-administered questionnaire was used to assess antibiotic use and self-medication practices. The data were analysed using logistic regression and Pearson chi-squared tests.

Results:

P1: We identified socio-demographic factors associated with inappropriate use of antibiotics. The prevalence of non-prescription use was high and ranged from 48% in Saudi Arabia to 78% in Yemen and Uzbekistan. Pharmacies were the main source of non-prescribed antibiotics. In all 3 countries studied together the most common indication for antibiotic use was cough (40%) and influenza (34%); 49% stop taking antibiotics when feel better. Although awareness of the dangers of antibiotic use correlated with decreasing self-medication, understanding about the appropriate use of antibiotics was limited and associated with older age and higher education.

P2: Among 538 patients enrolled, the median delay from onset of symptoms until treatment with anti-tuberculosis drugs was 50 days. Analysis of the factors affecting health-seeking behaviour and timely treatment showed the presence of the patient factor. Self-medication was the first health-seeking action for 231 (43%) patients and proved to be a significant predictor of delay ($p = 0.005$), as well as coughing ($p = 0.009$), loss of weight ($p = 0.001$), and visiting private and primary health care facilities ($p = 0.03$ and $p = 0.02$, respectively).

P3: The response rate was 87.7%. Alarmingly, 63.6 % of participants reported to have purchased antibiotics without a prescription from pharmacies; 71.1% reported that they did not finish the antibiotic course as they felt better. The availability of antibiotics without prescription was found to be positively associated with self-medication (OR 0.238, 95% CI 0.17- 0.33). Of those who used prescribed or non-prescribed antibiotics, 44.7% reported that they kept left-over antibiotics from the incomplete course of treatment for future need. Interestingly, 62% of respondents who used antibiotics without prescription agreed with the statement that antibiotics should be access-controlled prescribed by physician. We also found significant association between storage, knowledge/attitudes and education.

P4: Of the 316 pharmacists (77.07%) who completed the questionnaire, 230 (72.8%) self-medicated with antibiotics. Antibiotics were mostly used to self-treat upper (53.3%) and lower respiratory tract infections (19.3%), relying on their own knowledge (81.5%), previous treatment experience (49%) and patients' prescriptions (17%). The most commonly used antibiotics were macrolides (33.2%). Characteristics such as age, education and experience were related to antibiotic use and self-medication.

Conclusions:

P1: The prevalence of self-medication with antibiotics in adult people in the studied 3 Asian countries is alarmingly high. Educational interventions involving health professionals and the public can help reduce inappropriate use of antibiotics.

P2: Tuberculosis diagnostic and treatment delay was mainly contributed to by patient delay and should be reduced through increasing public awareness of tuberculosis symptoms and improving public health-seeking behaviour for timely initiation of anti-tuberculosis treatment. Efforts should be made to minimise irrational use of antibiotics and support interventions to restrict over-the-counter availability of antibiotics in order to contain the spread of infection.

P3: The overall level of awareness on antibiotics use among residents in Saudi Arabia is low. This mandates public health awareness intervention programs to be implemented on the use of antibiotics.

P4: The study confirmed that self-prescription of antibiotics is a common practice amongst pharmacists in Saint Petersburg and also identified personal and professional characteristics of pharmacists strongly associated with self-medication.

Abstrakt

Univerzita Karlova, Farmaceutická fakulta v Hradci Králové

Katedra	sociální a klinické farmacie
Kandidát	Mgr. Tatiana Belkina
Školitel	doc. RNDr. Jozef Kolář, CSc.
Název disertační práce	Používání antibiotik bez lékařské preskripce v některých rozvojových zemích ve vztahu k lékové rezistenci

Úvod a cíle:

Celosvětový výskyt a šíření rezistentních mikroorganismů zůstává hlavní výzvou kontroly bakteriálních infekcí a důležitou příčinou selhávání farmakoterapie. Antibiotika bez lékařského předpisu jsou dostupná a stále více vyhledávaná ve společnostech s nižší úrovní antibiotické politiky. Proto byly připraveny 4 projekty:

P1: Sledovat znalosti, přístupy a způsob, jakým jsou antibiotika používána ve třech asijských zemí a důvody, které vedou k samoléčbě antibiotiky. **P2:** Vliv samoléčby a dalších rizikových faktorů na oddálení stanovení diagnózy onemocněním tuberkulózou u nemocných v Uzbekistánu. **P3:** Zhodnotit význam potenciálních nezávislých rizikových faktorů pro samoléčbu – jako jsou znalosti o antibioticích, a dále vliv rasy, pohlaví a věku u respondentů ze Saudské Arábie. **P4:** Analýza přístupů veřejných lékárníků k užívání antibiotik a jejich vztah k samoléčbě.

Metodika:

P1: Průřezová studie zahrnovala 1200 dospělých respondentů – učitelů z velkých měst v Jemenu, Saudské Arábii a Uzbekistánu. Data byla analyzována pomocí deskriptivní statistiky.

P2: Průřezová studie provedená u pacientů s nově diagnostikovanou tuberkulózou v Uzbekistánu v Taškentu a v oblasti Aralského moře. Byla sledována doba od začátků respiračních problémů do stanovení diagnózy a byla zjišťována délka prodlevy celkové, zdravotního systému a pacienta. Jedno-faktoriální a multifaktoriální logistická regresní analýza byla použita k detekci faktorů předurčujících diagnostickou a léčebnou prodlevu.

P3: Průřezová studie provedená u občanů z různých regionů Saudské Arábie. Anonymní data byla získána dotazníkovou metodou od 1310 respondentů. Dotazník zjišťoval sociodemografické charakteristiky, znalosti o antibioticích, postoje a chování týkající se užívání antibiotik. K hodnocení proměnných ovlivňující samoléčbu antibiotiky byla využita jednofaktorová logistická regrese.

P4: Byla provedena průřezová studie mezi veřejnými lékárníky z Petrohradu (Ruská federace). Respondenti sami vyplňovali dotazník o užívání antibiotik a využívání samoléčby antibiotiky. Ke statistickému zpracování byla použita logistická regrese a Pearson $\chi 2$ test.

Výsledky:

P1: Identifikovali jsme sociodemografické faktory, které korelovaly s užívání antibiotik. Prevalence užití antibiotik bez receptu se pohybovala od 48% v Saudské Arábii do 78% v Jemenu a Uzbekistánu. Většina respondentů získávala antibiotika od přímo lékárníků v lékárně. Nejčastější důvody pro použití antibiotik byly kašel (40%) a chřipka (34%). 49% respondentů ukončilo užívání antibiotik, když se cítili lépe. Míra povědomí o rizikovosti antibiotik korelovala s poklesem ve využívání samoléčby. Respondenti neměli dostatečné povědomí o správném užívání antibiotik. Při analýze podskupin lepší výsledky vykazovali starší respondenti a respondenti s vyšším vzděláním.

P2: Do analýzy bylo zahrnuto 538 pacientů a medián prodlení diagnózy od prvních symptomů onemocnění do zahájení léčby antituberkulotiky byl 50 dnů. Významnou roli hrál pacient. Předcházející samoléčba (43% respondentů) (p=0,005), stejně tak jako kašel (p=0,009), pokles hmotnosti (p=0,001) a návštěva ambulantních zdravotnických zařízení včetně privátních (p= 0,02 a 0,03) byly signifikantně asociovány s oddálením diagnózy onemocnění tuberkulózou.

P3: V projektu 3 byla návratnost dotazníků 87,7%, přičemž 63,6% respondentů nakupovalo antibiotika přímo v lékárně. 71,1% respondentů potvrdilo, že ukončují antibiotickou kůru, pokud se zlepší jejich zdravotní stav. Dostupnost antibiotik byla asociována s mírou samoléčení (0R 0,238; 95% CI 0,17-0,33). 44,7% uživatelů antibiotik uvádělo, že antibiotika, která nespotřebují v průběhu jedné kůry, využívá při další potřebě. 62% respondentů užívajících antibiotika bez receptu souhlasí s opatřením, že by dostupnost- či kontrola užití antibiotik měla být v gesci lékaře. Významné korelace byly zjištěny mezi zásobami, znalostmi/přístupem k léčbě a dosaženým vzděláním.

P4: 77,07% (316) z oslovených farmaceutů vyplnilo dotazník a z nich 72,8% (230) mělo zkušenost se samoléčbou antibiotiky. Nejčastěji respondenti užívali antibiotika pro infekce horních dýchacích cest (53,3%) a dolních dýchacích cest (19,3%). Způsob terapie byl volen na základě vlastních znalostí (81,5%), dřívějších zkušeností s léčbou (49%) a zkušeností z preskripce pacientů (17%). Respondenti nejčastěji v samoléčbě uváděli užívání makrolidů (33,2%). Užití antibiotik a samoléčba korelovaly s věkem, dosaženým vzděláním a profesními zkušenostmi.

Závěr:

P1: Prevalence samoléčení antibiotiky u dospělých ve 3 asijských zemích je velmi vysoká. Nutno se více zaměřit na edukaci zdravotníků a občanů a snížit tento nevýhodný stav.

P2: Oddálení léčby tuberkulózy je především způsobeno samotnými pacienty. Bylo by vhodné zlepšit povědomí o symptomech tuberkulózy. Ve zdravotnictví by se měly zefektivnit metody identifikace nových pacientů s tuberkulózou a tak umožnit pacientům rychleji nastoupit léčbu a snížit kontakt infikovaných pacientů se zdravým obyvatelstvem.

P3: Mezi občany Saudské Arábie je malé povědomí o antibiotické léčbě. Tyto informace je nutno začlenit do intervenčních programů týkající se především užívání antibiotik a ochrany před infekčními chorobami.

P4: Studie potvrdila, že samoléčení antibiotiky je mezi farmaceuty Petrohradu běžnou záležitostí a je potřeba diskutovat tuto praxi i s těmito zdravotnickými pracovníky.

Acronyms and abbreviations

ACTs	artemisinin-based combination therapies
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
AMR	antimicrobial resistance
ART	antiretroviral therapy
BCG	bacille Calmette-Guerin
CAESAR	Central Asian and Eastern European Surveillance of Antimicrobial Resistance Network
cART	combination antiretroviral therapy
CI	confidence interval
DOTS	directly observed treatment, short-course
DRSP	drug-resistant *Streptococcus pneumoniae*
DST	drug susceptibility testing
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
ESCM	Electronic Surveillance Case-based Management System
EU/EEA	European Union/European Economic Area
Euro-GASP	The European Gonococcal Antimicrobial Surveillance Programme
GBD	Global Burden of Disease
HIV	human immunodeficiency virus
IPTi	intermittent preventive treatment in infants
IPTp	intermittent preventive treatment in pregnancy
IRS	indoor residual spraying
ITNs	insecticide-treated mosquito nets
MDR	multidrug-resistant
MEMS	Medication Event Monitoring System
MRSA	methicillin-resistant *Staphylococcus aureus*
NRTI	nucleotide reverse-transcriptase inhibitor
NNRTI	non-nucleoside reverse-transcriptase inhibitor

OR	odds ratio
PCR	polymerase chain reaction
RNA	ribonucleic acid
RTIs	respiratory tract infections
SD	standard deviation
SMC	seasonal malaria chemoprevention
SP	sulfadoxine-pyrimethamine
TB	tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
USA	United States of America
WHO	World Health Organization
XDR-TB	extensively drug-resistant TB

Contents

1 Introduction

The discovery of penicillin in 1928 by Alexander Fleming was one of the greatest scientific achievements of the 20th century (1). Many infectious diseases that used to pose immediate threats to human life are now readily treated (2). However, the decreasing effectiveness of antibiotics in treating common infections has quickened in recent years, and with the arrival of untreatable strains of carbapenem-resistant Enterobacteriaceae, we are at the dawn of a postantibiotic era (3, 4).

The global emergence and spread of antimicrobial resistance (AMR) remain a major infection control challenge and a predominant reason for therapy failure, which, in turn, results in high rates of morbidity and mortality. It is widely recognised that increasing use of antimicrobials is an important contributor to growth of resistance (5-7). In the past decade, worldwide consumption of antibiotic drugs increased substantially. Non-prescription access to antimicrobials, including antituberculosis drugs, is common and self-prescribing is increasingly popular in many developing countries where the conditions for mandatory dispensation of antibiotics according to prescription are not explicitly defined by legislation.

The great clinical success of antibiotics changed the attitude of the medical profession toward bacterial infections. This is reflected in a statement from 1969 by the Surgeon General, William H. Steward, to the U.S. Congress: "It is time to close the book on infectious diseases" (8). Irrational and inadequate prescription by physicians uncertain of diagnosis or treating largerly self-limiting bacterial or viral infections, wrong antibiotic choice in incorrect dosage regimen or treatment duration. Pharmacists, whose primary role in over-the-counter dispensation of antibiotics offsets with imperfect enforcement and who often mimic prescription patterns of physicians and unwittingly copy both desirable and undesirable practices (4). Moreover, in an environment of relatively low level of public trust in physicians and the lack of a formal need for doctor office visit, the pharmacist become the main alternative for patients not only in providing proper counselling, but substituting a physician in antibiotic selection, administration of antibiotic regimen and the course of therapy.

Patients may store antimicrobials from uncompleted courses, even beyond the expiration date, and later self-administer these drugs for self-diagnosed conditions or dispense them to family members and friends (9, 10).

The desire to self-medicate is present in developed countries, however the means for that are limited since the regulations of prescription-only use are enforced (11-15). In countries where antibiotics are freely available, the problem cannot only be solved by enforcement of prescription legislation, but also through the education and consultation among all interest groups (16, 17).

The causes of antibiotic resistance are complex and include human behaviour at many levels of society. The consequences affect everybody in the world (4). Although it is hardly possible to prevent the spread of AMR, but we could inhibit the further resistance emergence.

2 Hypothesis and Aims

A hypothesis of our project is based on the following well-known postulates:

1. Inappropriate use of antibiotics contributes to the emergence of drug resistance.
2. Knowledge and skills of people that are involved in decision making on how to use antibiotics attribute to inappropriate use.
3. Access to antibiotics should be regulated in the frame of medicines policy and interventions on appropriate use of antibiotics.
4. Global drug resistance to bacteria has no borders.
5. Medicines policy is not always properly followed, particularly in developing countries.

The aim of our project was:

To examine the practice of self-medication with antibiotics in some developing countries.

- To investigate the level of self-medication with antibiotics and to define the risk factors for self-medication;
- To define association between self-medication and diagnostic delay of tuberculosis;
- To examine knowledge, practice and awareness towards antibiotics use among particular consumers of antibiotics in selected countries.

3 Theoretical part – Overview of the problem

3.1 The emergence of antimicrobial resistance

The evolving public health threat of AMR is driven by both appropriate and inappropriate use of anti-infective medicines for human and animal health and food production, together with inadequate measures to control the spread of infections (18).

AMR is a main hindrance to the treatment of infectious diseases worldwide and the cause of increased morbidity and mortality. Organ transplants, cancer chemotherapy and care of preterm neonates rely on the availability of effective antibacterial drugs. The rapid emergence of AMR to antibiotics threatens the treatment of both hospital- and community-acquired bacterial infections and jeopardize effective medical practices. This situation is further aggravated by a sharp decline in the discovery of new antimicrobial drugs needed to overcome drug resistance. Such developments represent a looming crisis for the healthcare system (19).

Until 1970s single resistant strains were surmounted by a wave of novel classes of antibacterial drugs, but since 1987 the successful discoveries of novel agents have slowed (20-22).

Figure 1 **Dates of discovery of distinct classes of antibacterial drugs**

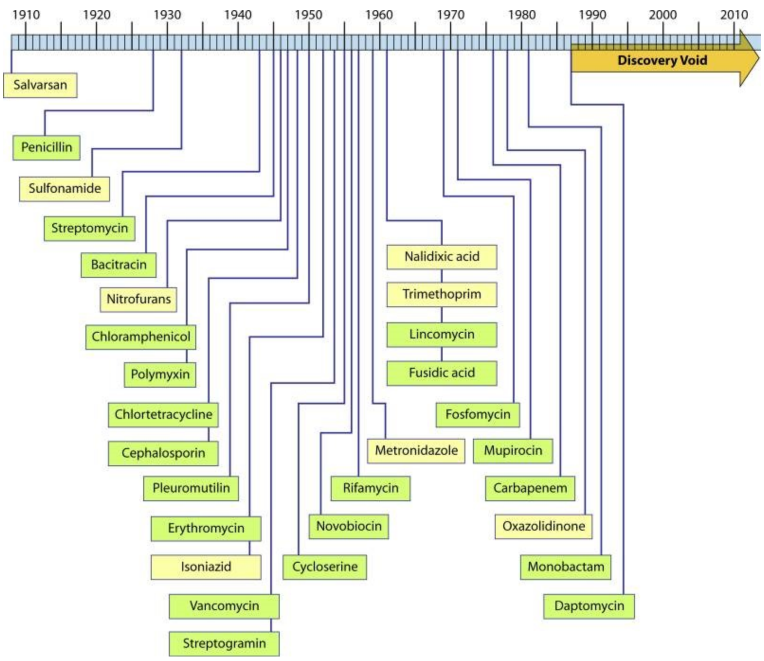


Illustration of the "discovery void." Dates indicated are those of reported initial discovery or patent.

Source: Silver 2011 (20)

The problem is exacerbated in developing countries. AMR is a major problem for a wide range of infectious diseases, including the poverty-related diseases HIV/AIDS, TB and malaria, as well as for many multidrug-resistant (MDR) bacterial, viral, protozoan and fungal infections (23).

The prevalence of health-care associated infections in resource-limited countries (15·5 per 100 patients) was twice the average prevalence in Europe (7·1 per 100 patients) (4, 24). Incidence of infections acquired in intensive care units in developing countries (pooled density 47·9 per 1000 patient-days) was three times the rate in the USA (13·6 per 1000 patient-days) (4). Health-care associated infections in neonatal intensive care units in some countries (15·2–62·0 infections per 1000 patient-days) are up to nine times more common than in the USA (6·9 infections per 1000 patient-days) (4). The burden of resistance and antibiotics consumption tend to be increased with the rate of health-care associated infections in developing countries.

3.2 Surveillance of antimicrobial resistance

Comprehensive national plans, based on a multisectoral approach and with sustainable financing, are regarded as one of the main ways to fight AMR globally (25).

A national surveillance mechanism and the necessary laboratory capacity are essential to detect, analyse and track resistant microorganisms. Surveillance can reveal the presence of patterns of resistant microorganisms and identify trends and outbreaks (26). Many countries established national coordination mechanism in place, introduces national strategies and policies to address AMR. However, poor laboratory capacity, infrastructure and data management can prevent effective surveillance (26). To strengthen networks of public health laboratories in order to contribute to effective monitoring of AMR, WHO represented worldwide implemented regional surveillance divided into six regions: the African Region, the Region of the Americas, the Eastern Mediterranean Region, the European Region, the South-East Asia Region and the Western Pacific Region. Laboratory capacity varied by country in all regions, but at least one country in each of the six regions had a national reference laboratory capable of testing for antibiotic sensitivity and subject to external quality assessment (26). All countries are required to report monitoring of AMR in humans (26).

All European Union countries, Iceland and Norway are united into the international surveillance system called the European Antimicrobial Resistance Surveillance Network-EARS-Net coordinated by the European Centre for Disease Prevention and Control (ECDC) and supported by the WHO Regional Office for Europe (27). The network performs surveillance of antimicrobial susceptibility of seven bacterial pathogens of public health importance (28):

- *Escherichia coli*
- *Klebsiella pneumonia*
- *Staphylococcus aureus*
- *Streptococcus pneumonia*
- *Pseudomonas aeruginosa*
- *Enterococcus faecalis*
- *Enterococcus faecium*
- *Neisseria gonorrhoeae*

To support countries that are not part of EARS-Net the network for the Central Asian and Eastern European Surveillance of Antimicrobial Resistance – CAESAR (29) was established. Currently, 19 countries are participating in CAESAR. These countries are: Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, the Republic of Moldova, the Russian Federation, Serbia, Switzerland, Tajikistan, the former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine and Uzbekistan, as well as Kosovo. CAESAR initiative adopted the EARS-Net methodology will help to strength AMR epidemiology and laboratory capacity in those countries.

3.3 Resistance in selected bacteria

3.3.1 Escherichia coli

Escherichia coli is a gram-negative bacteria, part of the normal flora in the intestines of people and animals. It is the most frequent cause of bloodstream infections, community- and hospital-acquired urinary tract infections; it is associated with spontaneous and post-surgical peritonitis and with skin and soft tissue infections of polymicrobial aetiology, causes neonatal meningitis and is one of the leading causative agents in food-borne infections worldwide (31). *E. coli* can be transmitted through contaminated water or food chain, through contact with animals or individuals.

Therapeutic options vary depending on the type of infection (32). For urinary tract infections, trimethoprim/sulfamethoxazole and fluoroquinolones are treatments of choice (33), whereas for Shiga toxin–producing *E. coli* infections, antimicrobial drug therapy is not recommended (34). *E. coli* is sometimes used as a sentinel for monitoring antimicrobial drug resistance in fecal bacteria because it is found more frequently in a wide range of hosts, acquires resistance easily (35), and is a reliable indicator of resistance in *Salmonellae* (36).

Surveillance data demonstrate that resistance in *E. coli* is consistently highest for antimicrobial agents that have been in use a very long time in human and veterinary medicine (32, 37). The past 2 decades have witnessed major increases in emergence and spread of MDR bacteria and increasing resistance to newer compounds, such as fluoroquinolones and certain cephalosporins (38).

Significantly increasing reported trends of AMR in *E. coli* to third-generation cephalosporins or fluoroquinolone will require the use of broader therapy, higher involved costs and a risk of further expansion of resistant strains. One review of community-acquired neonatal and infant sepsis in developing countries concluded that, because of resistance, a significant proportion of the causal bacteria were treatable neither by the recommended first-line regimen nor by alternative cephalosporin treatment (39).

3.3.2 Klebsiella pneumoniae

Klebsiella is a gram-negative bacteria found in the human intestines that can cause different types of healthcare-associated infections, including pneumonia, bloodstream infections, wound or surgical site infections, and meningitis (40).

Infections with *K. pneumoniae* are particularly common in hospitals among vulnerable individuals such as pre-term infants and patients with impaired immune systems, diabetes or alcohol-use disorders, and those receiving advanced medical care (41). The recent emergence of AMR of *K. pneumonia* to carbapenems has now been reported in many regions, thereby rendering almost all available treatment options ineffective (41).

3.3.3 *Staphylococcus aureus*

S. aureus is a gram-positive bacterium that can be a part of the normal flora or on the skin. *S. aureus* can cause a variety of infections, most notably skin, soft tissue, bone and bloodstream infections. *Staphylococci* can cause many forms of infection, most notably superficial skin lesions and localized abscesses in other sites, bone and bloodstream infections. *S. aureus* is a major cause of hospital acquired (nosocomial) infection of surgical wounds. *S. aureus* causes toxic shock syndrome by release of superantigens into the blood stream and food poisoning by releasing enterotoxins into food (42).

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major pathogen worldwide; MRSA infections are associated with increased morbidity and mortality, in comparison with other *S. aureus* infections may require second-line antibacterials (43). The possable increasing prevalence of heterogeneous vancomycin-intermediate *S. aureus* (hVISA) and vancomycin-intermediate *S. aureus* (VISA) MRSA strains in Europe, Asia, and the United States is a matter of concern (44).

3.3.4 *Streptococcus pneumoniae*

Streptococcus pneumoniae is the most common cause of community-acquired pneumonia, meningitis, and acute otitis media mostly in young children, elderly people and patients with compromised immune systems (45).

The association between community-wide use of antibiotics and the emergence of pneumococcal resistance has been demonstrated for β-lactams, macrolides, and fluoroquinolones (46). Recent antibiotic use has been shown repeatedly to be the strongest risk factor for the carriage and spread of resistant pneumococci, at both the individual and the community levels (47). It is also associated with invasive disease caused by drug-resistant *S. pneumoniae* (DRSP) (47).

3.3.5 *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a non-fermentative gram-negative bacterium that is ubiquitous in aquatic environments in nature (28). It is an opportunistic pathogen, is an important cause of infection in patients with impaired immune systems, being a common cause of hospital-acuired pneumonia, bloodstream and urinary tract infections (48).

P. aeruginosa is intrinsically resistant to the majority of antimicrobial agents due to its selective ability to prevent various antibiotic molecules from penetrating its outer membrane or extruding them if they enter the cell (31). The antimicrobial groups that remain active include some fluoroquinolones (e.g. ciprofloxacin and levofloxacin), aminoglycosides (e.g. gentamicin, tobramycin and amikacin), some beta-lactams (piperacillin-tazobactam, ceftazidime, cefepime, imipenem, doripenem and meropenem) and polymyxins (polymyxin B and colistin) (28). Resistance in *P. aeruginosa* isolates to colistin is emerging in many countries (49). Significantly increasing trends of extensively-drug-resistant ST235 *P aeruginosa* were observed for Russia, Belarus and Kazakhstan via clonal dissemination (50).

3.3.6 Enterococci

Enterococci are gram-positive aerobic organisms belonging to the normal intestinal flora. *Enterococcus faecalis* and *E. faecium* cause a variety of infections, including endocarditis, urinary tract infections, prostatitis, intra-abdominal infection, cellulitis, and wound infection as well as concurrent bacteremia (51).

Enterococci are intrinsically resistant to many commonly used antimicrobial agents including cephalosporins, all penicillins with extended spectrum, sulphonamides and clinically achievable concentrations of aminoglycosides (52).

An increasing number of European countries report significantly increasing trends in vancomycin-resistant *E. faecium* that may indicate a changing epidemiology for this pathogen in Europe (31). The EU/EEA population-weighted mean percentage for vancomycin resistance in *E. faecium* also showed a significantly increasing trend for the period 2011-2014 (28,31).

3.3.7 Neisseria gonorrhoeae

Neisseria gonorrhoeae is bacteria which causes a sexually transmitted infection Gonorrhoea. Urethral infections in men and uro-genital infections in women are the main presenting feature, but a broad spectrum of clinical presentations can occur, including systemic dissemination with fever and skin and joint involvement, and also throat and ano-rectal infections (41).

The therapeutic agents currently recommended in Europe (53), extended-spectrum cephalosporins, are the last remaining options for effective empiric first-line antimicrobial monotherapy. Susceptibility to these antimicrobials has decreased in the past (54), which is why the current European treatment guidelines recommend combination treatment with azithromycin in an attempt to slow down the development of resistance to these antimicrobials (53, 55).

In 2013, The European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) coordinated by ECDC ran a sentinel surveillance programme in 21 EU countries to control and manage the threat of MDR *N. gonorrhoeae* in Europe. The major findings were (55, 56):

- Cefixime resistance was observed in 4.7% of tested isolates. This represented a 0.8% increase compared to 2012, prior to which there had been a decreasing trend since 2010.
- Seven isolates resistant to ceftriaxone were detected in Euro-GASP, compared to three in 2012.
- Rates of ciprofloxacin and azithromycin resistance increased slightly compared to 2012. The proportion of isolates resistant to ciprofloxacin remained very high (52.9%); azithromycin resistance remained close to 5% (5.4%).

The emergence and spread of AMR in *Neisseria gonorrhoeae* is of global concern because there will be a major impact on disease control efforts due to increased prevalence of serious complications, and separate gonococcal entities such as neonatal infections and disseminated gonococcal infections will become much more common, as in the era before antibacterial treatment was available (41). In addition, untreated gonococcal infection is associated with an increased risk of acquisition and transmission of HIV infection (41). Given the global nature and large burden of gonorrhea, the high-level and frequently uncontrolled usage of antimicrobials, suboptimal control and monitoring of AMR and treatment failures, slow update of treatment guidelines in most geographical settings, and the extraordinary capacity of the gonococci to develop and retain AMR, the global problem of gonococcal AMR will likely worsen in the foreseeable future, and the severe complications of gonorrhea will emerge as a silent epidemic (54).

3.4 Disease burden

Current estimates show the infectious disease burden specific to drug resistance is high and can be defined as the number of deaths attributable to the failure of antibiotic therapy due to antibiotic resistance (30). Resistance has emerged in TB, malaria, HIV and other bacterial infections that together constitute a significant proportion of the burden disease in developing countries (6).

3.4.1 Tuberculosis

Tuberculosis (TB) is caused by bacteria *Mycobacterium tuberculosis.* TB has many manifestations, affecting bone, the central nervous system, and many other organ systems, but it is primarily a pulmonary disease that is initiated by the deposition of *M. tuberculosis*, contained in aerosol droplets, onto lung alveolar surfaces (57). Inhaled infectious droplets lodge in the alveoli, and bacilli are taken up there by macrophages, beginning a series of events that results in either the containment of infection or the progression to active disease (58). Following uptake by macrophages, *M. tuberculosis* replicates slowly but continuously and spreads through the lymphatic system to hilar lymph nodes (59). In most infected people, cell-mediated immunity, associated with a positive tuberculin test, develops two to eight weeks after infection, but if the immune system response cannot suppress replication, primary infection leads to active TB (59). The risk of progressing to active disease is relatively high in infancy and lower in older children; it increases quickly during adolescence (earlier in girls) and then more slowly throughout adulthood (60-63).

TB burden estimates (incidence, prevalence and mortality)

In 2014, there were an estimated 9.6 million new TB cases: 5.4 million men, 3.2 million women and 1.0 million children; and 1.5 million deaths (64). Globally, 12% of the 9.6 million new TB cases in 2014 were HIV-positive (64). The TB epidemic has been fueled by a surge in HIV–TB co-infection and compounded by the growing emergence of multi- and extensively drug resistant (M/XDR) TB strains, with a high prevalence in the former Soviet Union countries (65, 66).

TB has increased in Eastern European countries because of economic decline and the general failure of TB control and other health services since 1991 (67). Periodic surveys indicate that more than 10 percent of new TB cases in Estonia, Latvia, and some parts of the Russian Federation are MDR - that is, resistant to at least isoniazid and rifampicin, the two most effective anti-TB drugs (68, 69). Drug resistance is likely to be a by-product of the events that led to TB resurgence in these countries, not the primary cause of it, for three reasons (59). First, resistance is generated initially by inadequate treatment caused, for example, by interruption of the treatment schedule or use of low-quality drugs (59). Second, resistance tends to build up over many years, and yet TB incidence increased suddenly in Eastern European countries after 1991 (59). Third, although formal calculations have not been done, resistance rates are probably too low to attribute all of the increase in caseload to excess transmission from treatment failures (59).

The alarmingly high prevalence of MDR-TB in most of the countries of eastern Europe and central Asia is one of the main challenges for TB control. Of the 480 000 cases of MDR-TB estimated to have occurred in 2014, only about a quarter of these – 123 000 – were detected and reported (64). Over 50% of the estimated MDR-TB cases emerging in the world in 2014 were in China, India and the Russian Federation (64). An estimated 190 000 deaths were caused by MDR-TB globally in 2014, including patients with concomitant HIV infection (64).

The proportion of new TB cases with MDR-TB is high in Belarus (34%), Kazakhstan, Kyrgyzstan (26% each) and Moldova (24%) (70). Levels of drug resistance remain very low (<3% in new cases) in most western European countries (70). The proportion of previously-treated TB cases with MDR-TB ranged from 0% to 69%. Countries with the highest proportion of MDR-TB among previously-treated cases are Belarus (69%), Moldova and Uzbekistan (62% each) (70). When data from all countries of the Region are combined, 15% (range 10–20%) of new and 48% (range 43–53%) of previously-treated TB cases are estimated to have had MDR-TB in 2014 (70).

XDR-TB had been reported by 105 countries by 2015 and an estimated 9.7% of people with MDR-TB have XDR-TB (64).

Interventions

TB can be controlled by preventing infection, by stopping progression from infection to active disease, and by treating active disease (59). The main intervention is the directly observed treatment, short-course (DOTS) strategy resting on the rapid diagnosis and treatment of smear-positive and MDR-TB forms, but also smear-negative and extrapulmonary TB cases.

The main components of DOTS strategy are political commitment, case detection among self-reporting patients with symptoms using sputum smear microscopy, short-course chemotherapy under proper management, including directly observed therapy, assurance of a regular drug supply, and a strong surveillance and monitoring system (71, 72). The need for directly observed treatment as a universal requirement is controversial, since the success of some TB control programmes is attributed to other programme elements (73-77). The importance given to monitoring treatment outcomes is non-controversial. The DOTS strategy aims at detecting at least 70% of new smear-positive cases and successfully treating 85% of them (71, 78).

The limited number of available anti-tuberculosis medications imposes particular constraints on the use of the most efficacious drugs (79). The correct regimens and administration should be designed to prevent the emergence of MDR-TB.

The 6-month regimen includes rifampin, isoniazid, pyrazinamide, and ethambutol given daily or intermittently for two months, followed by rifampin and isoniazid for four months (Table 1) (81).

Anti-TB agents for treatment of drug-susceptible and MDR TB

• Isoniazid, the hydrazide of isonicotinic acid, is highly bactericidal against replicating tubercle bacilli and the cornerstone of every first-line regimen. It rarely causes adverse drug events, the most important of which is hepatic injury, which may result in hepatitis in a small fraction of patients (79). It interacts with several medications, but the single most important is its enhancement of the effect of anti-epileptics (79). Since isoniazid interacts with anticonvulsants used for epilepsy, it may be necessary to reduce the dosage of these drugs during treatment with isoniazid (80).

• Rifampicin is a complex macrocyclic antibiotic that inhibits ribonucleic acid synthesis in a broad range of microbial pathogens (80). It has unique relapse-preventing properties that allowed the duration of chemotherapy to be shortened to nine months or fewer (79). It is a superbly tolerated drug that may, however, complicate isoniazid-associated hepatitis, mainly by supporting cholestasis (79). Immunologically-linked events might be serious and life-threatening, but are very rare. Rifampicin interacts with a multitude of other medications: the most important interactions in practice are reduction of the efficacy of oral contraceptives and anti-retroviral medications, which preclude any such combination. Since resistance readily develops, rifampicin must always be administered in combination with other effective anti-TB agents (80).

• Pyrazinamide is a synthetic analogue of nicotinamide which is only weakly bactericidal against *M. tuberculosis* but has potent sterilizing activity, particularly in the relatively acidic intracellular environment of macrophages and in areas of acute inflammation (80). It is highly effective during the first 2 months of treatment while acute inflammatory changes persist, its use has enabled treatment regimens to be shortened and the risk of relapse to be reduced (80). Arthralgias are the most frequently reported adverse event that can be alleviated by the administration of acetylic salicylic acid or intermittent administration (79). There are no practically important interactions with other medications (79).

• Ethambutol is a synthetic congener of 1,2-ethanediamine, which is active against *M. tuberculosis, M. bovis* and some nonspecific mycobacteria (80). It is used in combination with other anti-TB drugs to prevent or delay the emergence of resistant strains (80). It is a very well tolerated drug, and optic neuritis, its main adverse drug event, occurs infrequently with the currently recommended dosages (79).

• Streptomycin might add bactericidal activity to a regimen in the intensive phase and may add additional protection against the emergence of drug resistance, particularly in patients receiving a re-treatment regimen (79). It is reasonably well tolerated by young patients, but its vestibulocochlear toxicity and hypersensitivity reactions make its prolonged use an unpleasant experience for many patients (79). The only potentially important interaction in daily practice is that its toxic effects are enhanced by some diuretics (79).

Table 1 Anti-tuberculosis agents for treatment of drug-susceptible and drug-resistant tuberculosis

Group	Drugs	Characteristics
Group 1	First-line oral agents – isoniazid, rifampicin, ethambutol, and pyrazinamide	The most potent and best tolerated agents to be used in combined 6-month chemotherapy – each should be used if there is laboratory evidence and clinical history to suggest that it is effective. For patients with strains resistant to low concentrations of isoniazid but susceptible to higher concentrations, the use of high-dose isoniazid may have some benefit (when isoniazid is used in this manner, it is considered a Group 5 drug; see below).
	New generation rifamycins – rifabutin and rifapentine	Rifabutin is used in place of rifampin under certain conditions such as treatment of TB in HIV patients on protease inhibitors.

		Rifapentine, a long-acting rifamycin, recommended by CDC for once-weekly continuation phase in low-risk, HIV-negative TB patients is presently in trials for treatment shortening, using higher or daily dosing. These two newer generation rifamycins have high cross-resistance to rifampin.
Group 2	Injectable agents – kanamycin, amikacin, capreomycin, and streptomycin	All patients with MDR-TB should receive a Group 2 injectable agent if susceptibility is suspected. Use of kanamycin or amikacin should be preferred, given the high rates of streptomycin resistance in MDR-TB patients and the fact that both these agents are low cost, have less toxicity than streptomycin, and have been used extensively for the treatment of MDR-TB.
Group 3	Fluoroquinolones – moxifloxacin, gatifloxacin, levofloxacin, and ofloxacin	All patients with MDR-TB should receive a Group 3 medication if the strain is susceptible or if the agent is thought to have efficacy. Currently, the most potent available fluoroquinolones in descending order based on *in-vitro* activity and animal studies are: moxifloxacin=gatifloxacin>levofloxacin>ofloxacin. If gatifloxacin is used, patients should undergo close monitoring and follow-up due to reports of severe dysglycaemia.
Group 4	Oral bacteriostatic second-line agents – thioamides (ethionamide and prothionamide), cycloserine, terizidone, and p-aminosalicylic acid	Group 4 medications are added based on estimated susceptibility, drug history, efficacy, side-effect profile, and cost.
Group 5	Agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients) – clofazimine, linezolid, amoxicillin/ clavulanate, thioacetazone, imipenem/cilastatin, high-dose isoniazida, and clarithromycin	Group 5 drugs are not recommended for routine use in MDR-TB treatment because their contribution to the efficacy of multidrug regimens is unclear. Although they have demonstrated some activity *in vitro* or in animal models, there is little or no evidence of their efficacy in humans for the treatment of MDR-TB. However, they can be used in patients in whom adequate regimens are impossible to design with the medicines from Groups 1 to 4.

CDC, Centers for Disease Control; MDR, multidrug resistant; TB, tuberculosis.

[a] High-dose isoniazid is defined as 16–20 mg/kg per day.

Adapted from Lienhardt 2010 (81)

Vaccination

The live attenuated vaccine BCG, or bacille Calmette-Guerin, is the only TB vaccine currently available, although there are other TB vaccines under development (82-87). It is accepted that BCG vaccine protects young children (age, <5 years) against more dangerous extrapulmonary forms of TB (88) and, thus, is given as a routine vaccination in many countries, as recommended by the WHO (89). However, BCG vaccine is only partially effective against pulmonary TB. Some studies have shown that BCG vaccine has a protective effect against pulmonary TB, and others have failed to show such benefits; in 2 studies, the vaccine appeared to enhance the risk of *M. tuberculosis* infection (89-92). A trial involving >10,000 infants that was performed by the South African TB Vaccine Initiative in the Western Cape province of South Africa found a 4.5% incidence of disease over 18 months, despite routine BCG vaccination (93). The most complete analysis of the effect of BCG vaccination suggests that BCG given to children born in 2002 prevents about 29,700 cases of childhood meningitis and 11,500 cases of miliary TB during the first five years of life, or one case for every 3,400 and 9,300 vaccinations (88).

A model by Abu-Raddad et al. (94) found that vaccination of neonates with a vaccine that is 60% effective before exposure to TB would lead to a 39% reduction in the incidence of TB by 2050 in southern Asia alone. Mass vaccination with such a preexposure vaccine would lead to an ~80% decrease in incidence by 2050 (89). A policy of mass vaccination, especially if combined with aggressive case finding and treatment, would, however, require sustained commitment from national and international bodies and significant financial resources (89).

3.4.2 Malaria

Malaria in humans is caused by five species of parasites belonging to the genus *Plasmodium*. Four of these – *P. falciparum, P. vivax, P. malariae* and *P. ovale* – are human malaria species that are spread from one person to another via the bite of female mosquitoes of the genus *Anopheles* (95). In the human body, parasites travel in the bloodstream to the liver, where they multiply and subsequently infect red blood cells (41). The most dangerous form of malaria, with the highest rates of complications and mortality, is caused by *P. falciparum* (41). *P vivax* is a major cause of morbidity, causing 72–390 million clinical cases of malaria worldwide each year (9-98). Vivax malaria is an important cause of morbidity, especially in young children, with adverse consequences for education, development, and wellbeing (98). Malaria in pregnancy (caused by both *P. falciparum* and *P. vivax*) causes indirect mortality from abortion and intrauterine growth retardation, which increases infant mortality (99).

Early and effective treatment is a key element of malaria control. There have been large reductions in the number of malaria cases and deaths for the last decade. By 2015, it was estimated that the number of malaria cases had decreased to 214 million (range: 149–303 million), and the number of deaths to 438 000 (range: 236 000–635 000) (95).

Substantial progress has been made in reduction of the global burden of malaria, much of which has been attributed to increases in access to health-care services, early diagnosis, treatment with highly effective antimalarial drug regimens, and deployment of insecticide-treated bednets (98). One of the greatest threats to control and elimination efforts is the emergence and spread of antimalarial drug resistance (98). Ineffective treatment resulting from drug resistance might lead more patients to rely on the unregulated private sector, increasing the risk of reliance on monotherapy, substandard and counterfeit medicines and subsequently leading to the emergence or further spread of drug resistance (100).

Vaccination

Despite many decades of intense research and development effort, there is no commercially available malaria vaccine at the present time (101). The RTS,S subunit vaccine, which targets the circumsporozoite protein of *P. falciparum* and is boosted with the potent ASO adjuvant, is the most advanced vaccine in development (99). More than 20 other vaccine constructs are currently being evaluated in clinical trials or are in advanced preclinical development (101). The results of a large multicentre study (102) of RTS,S/ASO1 in infants aged 6–12 weeks at first immunisation (deployed as a monthly dose for three months in conjunction with an Expanded Programme of Immunisation vaccines) showed good safety but only moderate efficacy, with 30% protection against clinical malaria and 26% protection against severe malaria in the 12 months after the last dose (99). Previously reported results (103) in slightly older children (aged 5–17 months) were better, with 55% protection against all falciparum malaria and 35% protection against severe malaria during 14 months (99). In July 2015, the European Medicines

Agency issued a positive scientific opinion on the RTS,S /ASO1 vaccine's risk-benefit balance (101).

Vector control

Vector control is an essential part of prevention. It is achieved largely through use of insecticide-treated mosquito nets (ITNs) or indoor residual spraying (IRS) (95).

Use of ITNs reduces malaria mortality rates by an estimated 55% in children aged under 5 years in sub-Saharan Africa (104). Their public health impact is due to a reduction in malaria deaths, and also to reductions in child deaths from other causes that are associated with, or exacerbated by, malaria, such as acute respiratory infection, low birth weight and malnutrition (95).

Chemoprophylaxis and chemoprevention

Chemoprophylaxis is recommended for travellers during potential exposure to malaria (105). The need for chemoprophylaxis depends on local patterns of susceptibility to antimalarials and the probability of acquisition of malaria (99). When the risk exists, drugs that effectively prevent infection should be use - atovaquone–proguanil, doxycycline, primaquine, or mefloquine (99). Chemoprophylaxis is never completely reliable, and malaria should always be a possible diagnosis in febrile patients who have travelled to endemic areas (99).

Chemoprevention is effective in pregnant women and young children. Intermittent preventive treatment in pregnancy (IPTp) involves administration of sulfadoxine-pyrimethamine (SP) during antenatal clinic visits in the second and third trimesters of pregnancy (95). It has been shown to reduce severe maternal anaemia (106), low birth weight (107) and perinatal mortality (108). By maintaining therapeutic antimalarial drug concentrations in the blood during periods of greatest malaria risk, seasonal malaria chemoprevention (SMC) with amodiaquine plus SP (AQ+SP) for children aged 3–59 months has the potential to avert millions of cases and thousands of deaths in children living in areas of highly seasonal malaria transmission in the Sahel subregion (109). Intermittent preventive treatment in infants (IPTi) with SP, delivered at routine childhood immunization clinics (at 2, 3 and 9 months of age), provides protection in the first year of life against clinical malaria and anaemia; it reduces hospital admissions for infants with malaria and admissions for all causes (110).

Treatment

WHO has recommended artemisinin-based combination therapies (ACTs) as first-line treatment for uncomplicated *P. falciparum* malaria since 2001, and, during the past decade, most malaria-endemic countries shifted their national treatment policies to ACTs (100). Chloroquine remains the treatment of choice for *P. vivax* malaria in areas where it remains effective.

Resistance

Resistance to antimalarial drugs has threatened global malaria control since the emergence of resistance to chloroquine in the 1970s (41).

Key drivers of antimalarial drug resistance (111):

- Unusual genetic structure of malaria parasites in regions known for antimalarial drug resistance
- Counterfeit or substandard treatment
- Unregulated or poorly administered antimalarial drug use
- Artemisinin drug use without a complementary combination treatment, such as lumefantrine

WHO emphasizes the need for countries to conduct therapeutic efficacy studies of the antimalarial medicines being used as first- and second-line treatment as the information derived facilitates early detection and subsequent prevention of the spread of drug resistance (100). Monitoring the efficacy of chloroquine and ACTs is essential for timely changes to treatment policy and the importance is high as no other antimalarials are available that offer the same efficacy and tolerability as ACTs, and few alternatives exist for the immediate future (100).

3.4.3 Human immunodeficiency virus (HIV)

Human immunodeficiency virus (HIV) infects cells of the immune system, destroying or impairing their function (41). Infection with the virus results in the progressive deterioration of the immune system, eventually leading to the development of acquired immunodeficiency syndrome (AIDS) (112). Without antiretroviral therapy (ART), HIV ribonucleic acid (RNA) viral load drives sexual (113) and mother-to-child (114) transmission.

Vaccines remain a distant hope in HIV prevention, vaginal microbicides have been ineffective so far, and treatment of sexually transmitted diseases does not reduce HIV transmission in most settings (115).

According to the estimates by WHO there were approximately 36.7 (34.0–39.8) million people living with HIV at the end of 2015 with 2.1 (1.8–2.4) million people becoming newly infected with HIV in 2015 globally (116).

A comprehensive new analysis of HIV incidence, prevalence, deaths and coverage of ART at the global, regional, and national level for 195 countries between 1980 and 2015 from the Global Burden of Disease 2015 (GBD 2015) study (117) reveals the following findings:

- In 2015, three-quarters of new infections (1.8 million) were in sub-Saharan Africa. Outside of Africa, south Asia accounted for 8.5% (212 500), southeast Asia for 4.7% (117 500), and east Asia for 2.3% (57 500).
- Within European region, the highest number of new infections in 2015 were in Russia (57 340), Ukraine (13 490), Spain (2 350), Portugal (2 220), UK (2 060), Italy (1 960), and Germany (1 760).
- Between 2005 and 2015, 74 countries experienced a rise in age-standardised incidence rates, notably in Indonesia and the Philippines, north Africa and the Middle East, and eastern Europe, but also in some countries in western Europe (Spain and Greece).
- In 2015, especially high rates of incidence (new infections in 2015 divided by the total population) were recorded in southern Africa, with more than 1% of the population becoming infected with HIV in Botswana, Lesotho, and Swaziland, compared with around 39 per 100 000 in Ethiopia and 42 per 100 000 in Congo.
- In 2015, the highest incidence rates in European region were in Russia (exceeding 20 per 100 000), while Cambodia (above 46 per 100 000) had the highest rates in Asia. In parts of Latin America and the Caribbean (Belize, Guyana, and Haiti), rates exceed 50 per 100 000 people.
- No country has reached the UNAIDS 90-90-90 target of 81% of people living with HIV should be receiving ART by 2020 yet, Sweden (76%), the USA, Netherlands, and Argentina (all at about 70%) are close.

- ART coverage is highly variable and massive scale-up of treatment is needed in the Middle East, north Africa, eastern Europe, and east Asia where only around a fifth of people living with HIV receive ART, and in central Asia where treatment reaches less than a third of people with HIV.
- Although global HIV mortality has been declining at 5.5% a year since the mid-2000s, progress has been mixed between regions and countries. In sub-Saharan Africa, for example, mass scale-up of ART and interventions to prevent mother-to-child transmission have led to huge declines in HIV death rates over the past decade, while in many countries in north Africa and the Middle East like Morocco, Egypt, Iraq, Syria, and Tunisia, progress has been nonexistent.

Some of the most rapidly growing national epidemics with the greatest increases in incidence are occurring in eastern Europe and central Asia—a region dominated by Russia, where the number of people living with HIV tipped 1 million earlier in 2015 (118). This expansion in the epidemic is largely attributable to escalating injection drug use in both regions, reflecting central Asia's geographic position along major drug trafficking routes (119, 120).

TB is the most common presenting illness among people with HIV. It is fatal if undetected or untreated and is the leading cause of death among people with HIV- responsible for 1 of every 3 HIV-associated deaths (116). Management of TB in patients with HIV in eastern Europe is complicated by the high prevalence of MDR-TB, low rates of drug susceptibility testing, and poor access to ART (121). Early detection of TB and prompt linkage to TB treatment and ART can prevent these deaths and it is strongly advised that HIV testing services integrate screening for TB and that all individuals diagnosed with HIV and active TB urgently use ART (116).

Treatment

There is increasing evidence of the potential of ART to reduce HIV transmission by lowering viral load (123). ART does not cure HIV infection but controls viral replication within a person's body and allows an individual's immune system to strengthen and regain the capacity to fight off infections (116). Viral load is the single greatest determinant of the risk of HIV transmission and when someone is virally suppressed (viral load is undetectable), the risk of HIV transmission is significantly reduced (123). This evidence supports early initiation of ART in individuals, irrespective of CD4 count, for prevention of HIV transmission (124). The administration of combination antiretroviral therapy (cART) at the time individuals with HIV-1 are initially diagnosed prevents immunological deterioration as early as possible and interrupts the spread of HIV-1 from newly diagnosed individuals (125).

In 2015, WHO released a new "Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV", which recommend that anyone infected with HIV should begin ART as soon after diagnosis as possible (126).

Based on WHO's new recommendations, to treat all people living with HIV and offer antiretrovirals as an additional prevention choice for people at "substantial" risk, the number of people eligible for antiretroviral treatment increases from 28 million to all 36.7 million people (116). WHO treatment guidelines for adult HIV-1 infection recommend the nucleotide reverse-transcriptase inhibitor (NRTI) tenofovir for first-line ART, in combination with lamivudine or emtricitabine and the non-nucleoside reverse-transcriptase inhibitor (NNRTI) efavirenz (126). Data from clinical trials and cohorts in high-income settings using tenofovir combined with NNRTI have reported low prevalence of tenofovir resistance at viral failure, (127-129) in stark contrast with reports from low-income and middle-income countries where prevalence seems to be much higher (130-131). Likewise, high-level resistance to NNRTI and the cytosine analogue component (emtricitabine and lamivudine) arise through changes to one aminoacid, which suggests a low genetic barrier to resistance for these drugs as well (132).

As of 2015, 17 million people were receiving ART globally − this means that by 2020, an additional 15 million people must initiate and be successfully maintained on ART for life (133). The treatment of millions of people with antiretroviral drugs will inevitably be accompanied by the emergence and transmission of drug-resistant virus (122).

Understanding the emergence and transmission of HIV drug resistance at population level, and the interaction between its various determinants, requires routine monitoring of the performance of health services in delivering ART, and surveillance of HIV drug resistance in selected populations (41). High-quality treatment and care services are essential to limit the impact of HIV drug resistance on the effectiveness of ART (41).

3.5 Containment of antimicrobial resistance

There are many factors that contribute to AMR, but the use and misuse of antimicrobials are among the most important determinants of resistance. Overuse and misuse result from poor prescribing behaviour, uninformed patient demand and lack of adherence to the treatment regimen prescribed as well as low-quality drug formulations, inadequate dosage regimens and insufficient duration of therapy (134).

In 2001 WHO released the Global Strategy for Containment of Antimicrobial Resistance (135). The Global Strategy includes 14 priority interventions and 67 recommendations in the areas of advocacy, education, management and regulation of drug use (Table 2).

Table 2 Summary of WHO-recommended interventions to contain antimicrobial resistance

Target group	Recommended interventions
Patients and the public	Education to promote appropriate use and discourage self-medication
	Education on hygiene and disease transmission
Prescribers and dispensers	Education on appropriate use
	Education on promotion
	Professional regulation
	Monitoring and supervision
	Decision support tools (guidelines and formularies)
Health-care systems	Institution of therapeutic committees
	Institution of infection control committees
	Guidelines for antimicrobial use
	Antimicrobial use surveillance
	Antimicrobial resistance surveillance through laboratory networks
Government, policies, strategies, and regulations	Commitment to a national antimicrobial resistance task force with a budget
	National drug policies (essential drug lists, standard treatment guidelines)
	Registration and regulation of all drug outlets (dispensing of antimicrobials by prescription only and by licensed staff)
	Quality assurance for antimicrobials
	Required resistance data for drug licensing
	Undergraduate and continuing education on resistance
	Access to evidence-based drug information and monitoring of promotion
	Monitoring and linking of resistance and use data

Target group	Recommended interventions
Pharmaceutical industry	Incentives for research and development
	Production according to good manufacturing practice standards
	Monitoring and supervision of drug promotion
Non-human antimicrobial use	Surveillance of resistance and use
	Banning or phasing out of growth promoters
	Education of farmers and veterinary practitioners

Adapted from Okeke et al. (11)

Inappropriate antimicrobial use constitutes selective pressure without a corresponding benefit to individual or public health and this multifaceted problem arises from behaviors of prescribers, dispensers, and consumers (6). An important factor in overprescription is the issue of externalities; physicians, patients, and pharmacists have few incentives to consider the effects of their prescriptions or drug use on overall levels of resistance and the burden imposed on the rest of society, and physicians, both in private practice and in hospital settings, may also derive income from drugs sold and may, therefore, prescribe antibiotics more frequently than is desirable (6).

Healthcare providers-targeted interventions

Successful educational programmes for prescribers in developing countries have resulted in improving diagnostic quality, dispelling perceptions of patient pressure, reducing unjustified antimicrobial prescription (136-142) and reducing polypharmacy (136, 138) among private as well as public providers, including non-physicians (142-145).

Prescription guidelines, essential drug lists, and formularies are essential for defining policy and provide a useful framework on which educational interventions can be based (146). Important components of educational interventions are long-term commitment and refresher courses, and complementary interventions are also desirable (147).

However, despite several recommendations for the treatment of common infections, as respiratory tract infections (RTIs) (148), there is no universally accepted, validated definition of prudent prescribing (149). Different groups often have different perspectives on what constitutes prudent antibiotic prescribing as for example, diagnostic criteria developed by microbiologists and infectious disease specialists may seem unrealistic or unacceptable to primary care physicians (149). Generally, prudent prescribing involves a dynamic assessment of the benefits of therapy (improved clinical outcomes) and the risks (contribution to antibiotic resistance and adverse events) based on a dialogue between the physician and the patient (149).

Patient-targeted interventions

Patient-related factors that are thought to contribute to the problem of AMR include the following (135):

- patients' misperceptions
- self-medication
- poor adherence to dosage regimens.

Patients' misperceptions

Many patients believe that most infections, regardless of etiology, respond to antimicrobials and thus expect to receive a prescription from their physician for any perceived infection (135). In several studies, patients expecting an antibiotic prescription—or patients whose physician anticipates such an expectation—are more likely to be prescribed one (150-154).

There have been various attempts to educate the public about appropriate use of antibiotics (155). Several clinical trials at the community level have shown at least moderate benefits of patient education on the use of antibiotics (156-160). In several countries, public campaigns have been done on a larger scale (161). In Europe, numerous new national campaigns were launched on the occasion of the first European Antibiotic Awareness Day on November 18, 2008 (162).

Self-medication

Enforcement of prescription-only regulations for most antimicrobials reduces self-medication in developed countries (163-165). However, such a strategy may be difficult to implement in developing countries. There have been only rare reports of reduction in antibiotic use following blanket enforcement of prescription supply legislation in areas where antibiotics are freely available (166). Opponents to enforcement demand a heavy financial and political investment, implying that a black market for medicines could emerge, particularly if the demand for these drugs is not lowered (147, 167). The sale of antimicrobials is a lucrative business, even when illegal, because of high demand (6).

Adherence to dosage regimens

Adherence to medications has long been a concern because it often affects the outcome of treatment (168). Non-adherence to antibiotics might lead to the storing of antibiotics at home, which induces self-medication, leading to a vicious circle, and thereby favoring the emergence of bacterial resistance (169). Patients who fail to complete therapy have a higher likelihood of relapse, development of resistance and need for re-treatment; this applies especially to those patients requiring prolonged treatment, e.g. those with TB or HIV infection (135). Previous antimicrobial treatment and excessive duration of treatment are considered two of the most important factors in the selection of resistant microorganisms (170, 171). The methods ensuring adherence to antimicrobial therapy include the use of fixed dose combinations to minimize the number of tablets or capsules, special calendars, blister packing, DOTS for TB (172-174), other course-of-therapy, packaging using symbols in labelling.

The gold standard for the measurement of adherence is the Medication Event Monitoring System (MEMS) (175-177). MEMS have been used to monitor adherence mainly with long-term medications, and in the case of infectious diseases, this technology has particularly been used to track medication adherence with antiretroviral agents and with anti-TB drugs (168). With the use of MEMS the adherence to antibiotic regimens in respiratory infections decreased with an increase in the number of daily doses (178).

Treatment strategies

Different treatment strategies can be applicable in order to delay the evolution of drug resistance such as follows: combination therapy, periodic withdrawal or rotating between different drugs.

Use of Narrow-Spectrum Antibiotics

Several investigations suggest that infections such as community-acquired pneumonia can usually be successfully treated with narrow-spectrum antibiotics, especially if the infections are not life-threatening (179, 180). Similarly, the avoidance of broad-spectrum antibiotics (e.g., cephalosporins) and the reintroduction of narrow-spectrum agents (e.g., trimethoprim, and gentamicin) along with infection control practices have been successful in reducing the occurrence of infections with *Clostridium difficile* (181). However, when patients have already received antibiotic treatment and are most likely infected with an antibiotic-resistant pathogen (182), initial empirical treatment with broad-spectrum agents is often necessary to avoid inappropriate treatment until culture results become available (183, 184).

Combination Therapy

The use of combination therapy that include drugs with different targets were first used in the treatment of TB and have now become routine practice in the treatment of cancer and HIV/AIDS (6). Combinations of artemisinin and its derivatives with other antimalarials, notably mefloquine, have accelerated recoveries, increased cure rates, and reduced transmissibility (6).

Several recent meta-analyses recommend the use of monotherapy with a β-lactam antibiotic for the definitive treatment of neutropenic fever and severe sepsis, once antibiotic susceptibilities are known (185, 186). However, there is no definitive evidence that the emergence of resistance to antibiotics is reduced by the use of combination antibiotic therapy (187).

Shorter Courses of Antibiotic Treatment

Prolonged administration of antibiotics to patients has been shown to be an important risk factor for the emergence of colonization and infection with antibiotic-resistant bacteria (188, 189). Therefore, recent attempts have been made to reduce the duration of antibiotic treatment for specific bacterial infections (187). Several clinical trials have found that antibiotic treatment for 7–8 days is acceptable for most patients with ventilator-associated pneumonia who do not have bacteremia (189-191), patients with pyelonephritis (192), and patients with community-acquired pneumonia (193).

Antibiotic Cycling

Antibiotic class cycling has been suggested as a potential strategy for reducing the emergence of antibiotic resistance (194). Withdrawal of a class of antibiotics or a specific antibiotic drug from use for a defined period and reintroducing at a later point is occasionally accompanied by the replacement of resistant strains with sensitive ones (6), resulting in more-effective treatment of nosocomial infections. Antibiotic cycling is one method of achieving antibiotic heterogeneity, a practice whereby multiple antibiotic classes are used to reduce the emergence of resistance that might occur as a result of using a single or limited number of antibiotic classes (187). Other methods include mixing of antibiotic classes and scheduled changes of antibiotic classes (187).

The way forward will be a combination of many different interventions—better infection control, more appropriate use of antibiotics; research and development of new antibiotics, vaccines, and inexpensive point-of-care diagnostics; less environmental contamination with antibiotics; and stronger surveillance and containment of resistant strains (5).

As AMR of some pathogens has been first registered in developing countries, there is a rationale to correlate the increase of AMR and uncontrolled use of antimicrobials. Non-prescribed dispense of antibiotics, inappropriate use and lack of knowledge towards antibiotics are related factors of formation and spread of AMR. In this regard, there is a need to conduct pharmacoepidemiology research in those countries, that would provide us with data on antibiotic use by population, the level and conditions of self-medication with antibiotics, and knowledge, practice and awareness towards antibiotics use. These targets were being pursued in our research conducted in some developing countries: Russia, Uzbekistan, Saudi Arabia and Yemen.

4 Experimental part

4.1 *Antibiotic use and knowledge in Yemen, Saudi Arabia and Uzbekistan*

4.1.1 *Aims*

To examine knowledge, attitudes, and practices of antibiotic use in a sample of educated adults in Western and Central Asian countries- Yemen, Saudi Arabia and Uzbekistan.

4.1.2 *Methodology*

Study design

A national population-based cross-sectional survey involving 1 200 teachers of secondary's schools was conducted in November 2012 in Ibb (Yemen), Najran (Saudi Arabia) and Tashkent (Uzbekistan).

Inclusion criteria

- general education teachers
- willingness to provide the required and basic personal information for the purpose of this study
- verbal informed consent

Explanation about the purposes of the research and assurance of anonymity was provided to participants and verbal informed consent was obtained.

Observational part of study

Countries grouping was based on similarities in demographic and socioeconomic developments and a region was selected presenting the population of each country in terms of age and gender. Education teachers were selected from the cities based on systematic random sampling. These involved randomly selecting educational institutions within each city, from which teachers were randomly selected.

Data were collected using the questionnaire, developed in English by the project group of Charles University in Prague, Czech Republic, that was translated into national languages and then back-translated into English to validate the translation. The questionnaire was pilot-tested in each country on 15 teachers.

Explanation about the purposes of the research and assurance of anonymity was provided to participants.

The questionnaire was applied to the respondents using face to face interview technique by 6 public health research assistants and consisted of three parts:

Part 1 was designed to evaluate the recent use of antibiotic in the past 3 months, source of the prescription, intent to use antibiotic without consulting a physician, reason for taking the antibiotic and duration of use.

Part 2 of the questionnaire assessed knowledge and attitudes towards antibiotics and inventory at home.

Part 3 included the demographic characteristics of the respondents soliciting information about sex, age and highest degree obtained (BS, MS or other).

Statistical part of study

Data were analyzed using PASW Statistics Version 18.

Descriptive results for the quantitative variables were evaluated according to mean ± standard deviation. Results regarding binary variables (sex, questions with answers Yes-No) were applied with frequencies into percentages. To investigate association between ordinal variables Kendall's correlation was used.

The difference between countries in response to questions about the respondent's knowledge and attitude towards antibiotics was verified using contingency tables and frequency comparison. Generalized linear model - Bernoulli distribution with logistic link function was used for more complex dependence of issues on the summary of socio-demographic factors (gender, age, country of respondent) and their interactions. The level of statistical significance was set at $p<0.05$.

4.1.3 Results

Four hundred residents in each state were approached for participation. All of them provided complete information giving 100% response rate of countries. The demographic characteristics of the respondents are presented in Table 3. Most participants were females.

Table 3 **Demographic characteristics of respondents**

Characteristics	Yemen	Saudi Arabia	Uzbekistan	Total
	No. (%)	No. (%)	No. (%)	No. (%)
Gender	(N=400)	(N=400)	(N=400)	(N=1200)
Male	161 (40.3)	64 (16.0)	186 (46.5)	411 (34.3)
Female	239 (59.8)	336 (84.0)	214 (53.5)	789 (65.8)
Age				
< 20	73 (18.3)	42 (10.5)	58 (14.5)	173 (14.4)
20-30	190 (47.5)	110 (27.5)	102 (25.5)	402 (33.5)
31-40	114 (28.5)	202 (50.5)	87 (21.8)	403 (33.6)
41-60	21 (5.3)	44 (11.0)	89 (22.3)	154 (12.8)
> 60	2 (0.5)	2 (0.5)	64 (16.0)	68 (5.7)
Education				
Master's/ Ph.D.	15 (3.8)	42 (10.5)	169 (42.3)	226 (18.8)
Bachelor's degree	263 (65.8)	189 (47.3)	117 (29.3)	569 (47.4)
Secondary	122 (30.5)	169 (42.3)	114 (28.5)	405 (33.8)

The prevalence rates of prescribed and non-prescribed use of antibiotics are presented separately for countries (Table 4).

Table 4 **The prevalence rates of prescribed and non-prescribed use of antibiotics**

Source	Yemen	Saudi Arabia	Uzbekistan	Total
	No. (%)	No. (%)	No. (%)	No. (%)
Prescribed	(N=367)	(N=353)	(N=369)	(N=1089)
Always	80 (21.8)	182 (51.6)	80 (21.7)	342 (31.4)
Sometimes	271 (73.8)	155 (43.9)	263 (71.3)	689 (63.3)
Never	16 (4.4)	16 (4.5)	26 (7.0)	58 (5.3)
	No. (%)	No. (%)	No. (%)	No. (%)
Non-prescribed	(N=287)	(N=171)	(N=289)	(N=747)
Pharmacist's advice	158 (55.1)	37 (21.6)	130 (45.0)	325 (43.5)
Friend's advice	21 (7.3)	33 (19.3)	53 (18.3)	107 (14.3)
Themselves	49 (17.1)	54 (31.6)	93 (32.2)	196 (26.2)
Old prescription	59 (20.6)	47 (27.5)	13 (4.5)	119 (15.9)

Among the respondents ever treated with antibiotics 31% reported using prescribed antibiotics, while 69% reported non-prescribed use following recommendation of pharmacist, friend, their own initiative or using left-over prescription. The prevalence rates for taking antibiotics without prescription were the highest in Yemen and Uzbekistan and lower in Saudi Arabia, where half of respondents preferred to use prescribed antibiotics. The main source of non-prescribed antibiotics in Yemen and Uzbekistan was pharmacies followed by the high rate of using previous prescription and administering alone in Saudi Arabia.

About 81% of respondents used antibiotics in the previous 3 months. Cough, influenza and gynecological inflammations were the most frequent reasons followed by gastrointestinal infections and respiratory inflammations (Table 5). Treatment with antibiotics for cough symptom and influenza tended to be the highest in Saudi Arabia and Yemen. In Uzbekistan respiratory inflammations were reported as the main indications for antibiotics use.

Table 5 Clinical indications for antibiotics use in the past 3 months

Reasons	Yemen	Saudi Arabia	Uzbekistan	Total
	No. (%)	No. (%)	No. (%)	No. (%)
	(N=304)	(N=334)	(N=239)	(N=877)
Cough	125 (41.1)	175 (52.4)	53 (22.2)	353 (40.3)
Influenza	98 (32.2)	136 (40.7)	62 (25.9)	296 (33.8)
Respiratory inflammations	16 (5.3)	19 (5.7)	90 (37.7)	125 (14.3)
After Surgery	14 (4.6)	3 (0.9)	14 (5.9)	31 (3.5)
Gastrointestinal	81 (26.6)	18 (5.4)	27 (11.3)	126 (14.4)
Gynecological inflammations	86 (28.3)	181 (54.2)	12 (5.0)	279 (31.8)
Orthopedist inflammations	21 (6.9)	10 (3.0)	17 (7.1)	48 (5.5)
Urinary inflammations	15 (4.9)	6 (1.8)	20 (8.4)	41 (4.7)
Ear infection	25 (8.2)	2 (0.6)	18 (7.5)	45 (5.1)
Others	-	1 (0.3)	23 (9.6)	24 (2.7)

Nearly 44% of respondents prescribed antibiotic completed the course, however, half reported that they did not finish their last antibiotic course as prescribed because they felt better. Seven per cent changed the antibiotic if did not feel better (Table 6).

The results of the relationship between individual's socio-demographic characteristics and storage of antibiotics, attitudes toward and knowledge of the adverse effects of antibiotic use are shown in Table 7.

Table 6 Principles of antibiotic use

Statement	Yemen	Saudi Arabia	Uzbekistan	Total
	No. (%)	No. (%)	No. (%)	No. (%)
	(N=367)	(N=353)	(N=369)	(N=1089)
Stop taking the antibiotic when feel better	163 (44.4)	137 (38.8)	236 (64.0)	536 (49.2)
Change the antibiotic if do not feel better immediately	14 (3.8)	46 (13.0)	15 (4.1)	75 (6.9)
Take antibiotics as prescribed by physician/pharmacist	190 (51.8)	170 (48.2)	118 (32.0)	478 (43.9)

Table 7 Association of demographic characteristics with knowledge and behaviour statements

Statement	Yemen	Saudi Arabia	Uzbekistan	*p* value			
	No. (%)	No. (%)	No. (%)	Country	Gender	Age	Education
	(N=367)	(N=353)	(N=400)				
Inventory of antibiotics at home							
Yes	164 (44.7)	233 (66.0)	116 (29.0)	**<0.001**	0.074	**0.022**	**0.025**
No	203 (55.3)	120 (34.0)	284 (71.0)				
Knowledge of antibiotic resistant bacteria							
Yes	173 (47.1)	199 (56.4)	117 (29.3)	**0.048**	0.812	**0.031**	**0.003**
No	194 (52.9)	154 (43.6)	283 (70.8)				
Importance to complete antibiotics course							
Yes	195 (53.1)	187 (53.0)	137 (34.3)	0.844	0.066	**<0.001**	0.655
No	172 (46.9)	166 (47.0)	263 (65.8)				
Awareness of allergies/adverse reactions							
Yes	185 (50.4)	172 (48.7)	278 (69.5)	**<0.001**	0.411	<0.094	**0.001**
No	158 (43.1)	120 (34.0)	110 (27.5)				
I don't know	24 (6.5)	61 (17.3)	12 (3.0)				
Awareness that antibiotics kill off normal flora							
Yes	130 (35.4)	159 (45.0)	166 (41.5)	0.311	0.093	**0.033**	**<0.001**
No	200 (54.5)	119 (33.7)	108 (27.0)				
I don't know	37 (10.1)	75 (21.2)	126 (31.5)				

Significant values when p<0.05 are shown in bold

Gender had no significant effect on each of the statements as most of respondents were females. Country, age and education were significantly associated with storage, attitudes and knowledge of antibiotic use. We also found significant interactions between knowledge/attitudes and country and age, as well as interactions between country and education. Respondents from Yemen and Saudi Arabia that more likely to self-medicate with antibiotics were younger women ($p=0.010$), and those with a lower level of education ($p=0.017$), whereas in Uzbekistan age and education did not affect self-medication.

Almost 46% of respondents with higher preponderance in Saudi Arabia reported that they retain antibiotics at home regardless the source of obtaining. A significant relationship was found between storage and country and age ($p<0.001$). Being younger and less educated in Yemen and Saudi Arabia were associated with keeping inventory at home. In contrast, older respondents in Uzbekistan reported storing of antibiotics.

We assessed the respondent's knowledge of antibiotic bacteria resistance and did find that typically knowledge increased with age in all the studied countries ($p=0.031$). Paradoxically, however, in Yemen more educated respondents were less knowledgeable about bacteria resistance. Similar results were obtained regarding the statement of "awareness that antibiotics kill off the normal flora'' (country vs. education- $p<0.001$). Respondents in Yemen with lower qualification more frequently responded affirmatively than respondents with a degree level of education. Respondents were less knowledgeable about the principles of prudent use of antibiotic, as 54% believed that it did not matter if course of antibiotics was not completed. Poor level of knowledge was found in younger generation of Yemen and Saudi Arabia and among all age brackets in Uzbekistan ($p=0.006$) with primary or lower educational level ($p=0.033$).

However, it is important to note that knowledge about allergies/adverse reactions associated with taking antibiotics were the highest when compared with other statements of knowledge. In fact, 57% of respondents expected of adverse reactions. Strong knowledge was mostly found among respondents of older well-educated age group in all the studied countries ($p=0.001$, $p<0.001$ for country/age and country/education respectively). Participants aware of adverse reactions associated with antibiotic use were more likely to have obtained antibiotics according to physician's prescription ($p<0.001$, $\tau=0.110$).

4.1.4 Discussion

The high prevalence of self-medication and inappropriate use of antibiotics among well-educated population of Yemen, Saudi Arabia and Uzbekistan was found out. Up to 70% of respondents administered non-prescribed antibiotics and more than half of these non-prescribed medications were inappropriate. The results contribute to the evidence of growing tendency for self-medication among the general population in both developed and developing countries. However, studies from American, Asian and European countries (195-198) indicate that prevalence rates of self-medication are higher in Asia and ranged from 3% to 60%.

The causes leading to self-administration of non-prescribed antibiotics are varied. Although poor regulation of antimicrobials resulting from absent enforcement of policies is the major factor influencing self-medication, it is not the only one accounting to this behaviour (11,199). Other determinants behind antibiotic self-medication in the community of participating countries are poverty, lack of access to health care, cultural beliefs and practice of obtaining antimicrobials without prescriptions, particularly for viral respiratory infections.

Non-prescription use is frequently associated with very short courses and inappropriate drug and dose choice (200). Every second respondent in our study incompleted the course of antibiotic therapy, thereby promoting antibiotic resistance. Nonadherence was lower in Yemen and Saudi Arabia than in Uzbekistan. These findings correspond to other studies confirming that patients often are not adherent to their treatment. A patient survey in 11 countries across the world showed that 22.3% of patients who received antibiotic medication admitted not finishing the therapy (201). Adherence rates varied widely across countries. The Asian countries, China and Japan, had the highest rates and the two European countries, Italy and Netherlands, the lowest (201). Moreover, patients may store antibiotics from uncompleted courses, even beyond the expiration date, and later self-administer these drugs for self-diagnosed conditions or dispense them to family members and friends (202-204). Our results also revealed that many participants tend to keep antibiotics in case of future need.

In our study the majority of respondents, who self-medicate, identified private pharmacy as a main source of medicine and information. There is a potential for adverse events as usually pharmacy staff not questioning of patient’s allergies, not explain potential side effects, dispensing contraindicated antimicrobials like tetracyclines and fluoroquinolones or parenteral antimicrobials for home use. Other risks factors include masked diagnosis of infection disease, drug interactions and superinfection (197). Furthermore, financial concerns often govern selection of low-quality antibiotics as well as resulting in short duration of treatment (199).

The most common reasons for antibiotic use were colds and upper respiratory tract infections, where the cause is likely to be viral. Additionally, factors contributing to self-medication of these symptoms have been elucidated. Respondents considered a condition as a minor ailment depended not only upon factors relating to the current condition such as severity, but also other issues such as previous experience and knowledge (205). Lack of time was another very pressing problem among teachers to attend health facilities as well as financial concerns regarding the cost of consultations. Barriers to receiving availability of and access to health care services is surprising for the urban population and contribute to inappropriate health seeking behaviour.

The teachers who responded to this survey had less knowledge about appropriate antibiotic use than one would expect considering their high literacy rate in comparison with other groups of these developing societies. We found a consistent direct link between irrational antibiotic use and lower educational levels. Younger, less educated women were most inclined to self-medicate and lacked knowledge about the dangers associated with antibiotic use. However, there was a very robust correlation between awareness of adverse reactions and prescribing use of antibiotic. This correlation suggests that respondents who were apprehensive about antibiotic side effects did not attempt to self-medicate and consulted the physician. A possible explanation is that those respondents may have learned about the adverse impact of antibiotic use from their physician or pharmacist, from the leaflet or from their personal experience with antibiotic side effects. General education teachers should not be critical consumers of medicine research or may not have time to keep up with professional journals. However, they are primary transmitters of knowledge and until their health behavior inappropriate, it may affect on instilling health values and beliefs in children. Thus, knowledge and attitudes of this population regarding antibiotic use can be substantially improved and that improved knowledge may be important for efforts to reduce the misconceptions and misguided expectations contributing to inappropriate antibiotic use (206).

Limitations

The results of the present study should be interpreted within the context of several limitations. First, the sample was confined to nations' teachers, thereby limiting the generalizability of the results. A second significant limitation was also the possibility of sample bias. The respondents were all from the urban areas with higher socioeconomic status and may not be representative of the rest of the countries. Third, the results are based on self-reported behaviour, which may be not actual behaviour. Furthermore, some of the questions may have been doubtful resulting in potential for recall bias. For example, one item «Have you ever treat yourself or family member with antibiotics?» was meant to be an underreport of actual behaviour because some respondents can't be really sure about never use antibiotics. Finally, the high male-to-female ratio found in this study is not a truly representative value for actual gender distribution in the population but rather reflect the gender of female at the period of time.

4.1.5 Conclusion

Access to nonprescription antimicrobial medicines results in inappropriate self-medication in the community of Yemen, Saudi Arabia and Uzbekistan. There is great concern surrounding the development and spread of resistance resulting from poor knowledge about the dangers of self-medication and antimicrobial misuse. Socioeconomic, demographic and cultural factors contribute to antibiotic misuse. There is a need to take decisive policy action to reduce non-prescribed antimicrobials use. Effective public information campaign to encourage appropriate use of antibiotics and to raise awareness about the problem of antibiotic resistance should be implemented.

4.2 Delay in the diagnosis and treatment of tuberculosis in Uzbekistan

4.2.1 Aims

This study aimed to evaluate the extent of delay in diagnosis and treatment of TB in Uzbekistan and identify risk factors for patient and health system delay.

4.2.2 Methodology

Setting and study design

A cross-sectional study among newly diagnosed pulmonary TB patients in two cities of Uzbekistan was conducted between August, 2013 and January, 2014. In Tashkent, the study was conducted at the Republican Specialized Scientific and Practical Medical Center for Phthisiology and Pulmonology providing treatment to patients from across the country. In Nukus, the main city of Autonomous Republic of Karakalpakstan, two hospitals and one dispensary were chosen as study settings.

Study Population

TB Electronic Surveillance Case-based Management System (ESCM) database of all cases of culture-confirmed pulmonary TB registered in the selected facilities from January 2013 through January 2014 was reviewed. Then a paper-based inpatient and outpatient medical cards from adult patients (age, ≥15 years) were checked and all patients with newly diagnosed pulmonary TB were included in the study. Patients with a recurrent TB were excluded.

The patients were interviewed by trained doctors and health workers using an adapted and slightly modified version of the WHO questionnaire developed for the assessment of TB diagnostic and treatment delay (207). All interviews were performed in either Uzbek, Karakalpak or Russian language.

Verbal informed consent was obtained from patients prior to inclusion in the survey, and the study was approved by the Ethical Committee of the Charles University in Prague, the Ministry of Health of the Republic of Karakalpakstan, and the Ethical Committee of the Republican Specialized Scientific and Practical Medical Center for Phthisiology and Pulmonology.

Definitions

Clinical, pathological and radiological findings confirmed bacteriologically and histologically were the main criteria to consider patients to have pulmonary TB.

The time between the onset of respiratory symptoms and initiation of anti-TB treatment was assessed and delays were divided into three delay types.

Patient delay was measured in days from the first onset of any TB symptom (e.g., cough, fever, weight loss, night sweats) until first presentation to the health care system (not necessarily a TB facility).

Health care delay was measured by the number of days from first presentation to the health care system until the start of TB treatment.

Total delay was computed as patient delay plus health care delay.

A medical comorbidity was defined as underlying cardiovascular, gastrointestinal, pulmonary, immunologic or malignant disease.

Self-medication was defined as use of any medication not prescribed by a health care professional. Antibiotics and other medications are available at pharmacies in Uzbekistan over-the-counter and without a prescription.

Laboratory techniques

Analysis of sputum samples for smear microscopy, culture, drug susceptibility testing (DST) and real time polymerase chain reaction (PCR) (Xpert MTB system) were conducted as per international guidelines (208, 209) at the National Reference laboratory in Tashkent and at the mycobacterial laboratory in Nukus.

Preliminary confirmations of acid-fast bacilli (AFB) were performed using Ziehl-Neelsen staining while culturing was done using Lowenstein-Jensen media. AFB strains were classified according to the WHO/International Union against Tuberculosis and Lung Disease scale: 1+ (10-99 AFB per 100 fields), 2+ (1-10 AFB per individual field), 3+ (10-100 AFB per individual field), and 4+ (more than 100 AFB per individual field) (210).

MDR-TB and HIV associated TB sputum samples were analysed using real time PCR Xpert MTB assay.

Data collection and analysis

The questionnaire included socio-demographic characteristics, risk factors of TB, comorbidities, TB knowledge and attitudes. Follow-up data included history of TB treatment, such as detailed description of diagnostic investigation process, first symptoms perceived by the patient and health seeking actions. The patients were also asked to complete a number of questions measuring psychosocial aspects, e.g. feel ashamed about having TB, fear of social isolation and stigma.

A date of diagnosis, date of treatment initiation, and laboratory results were retrieved from the patient medical cards.

Univariable and multivariable logistic regression analysis was used to evaluate risk factors for patient, health care and total delays. Median delays were used as a cut-off to define delay vs. non-delay.

Variables included in the multivariable model were based on behavioral and biological plausibility as well as statistical ($P \leq 0.2$) criteria. The regression outcome was given by the estimated (adjusted) odds ratios and the corresponding 95% confidence intervals. Hypothesis tests for regression coefficients (Wald-tests) were performed and expressed with P values at the significance level $\alpha = 0.05$. PASW statistical software was used for all analyses (IBM Corporation, Armonk, NY, USA, version 18.0).

Knowledge and stigma were measured using scoring systems. For stigma, the responses to the corresponding questions were marked on a five-point scale (1– Strongly agree, 2 – Agree, 3 – No opinion, 4 – Disagree, 5 – Strongly disagree), with a low score corresponding to a high degree of stigma (except for question “Do you feel you can talk to others about your TB” where the score was first reversed before addition to its domain). The mean percentage score for stigma was calculated as hundred times the sum of scores obtained divided by the maximum scores that could be obtained. This resulted in a Cronbach α – value of 0.655 in case where all 10 stigma questions were answered (unmarried/single patients) and in a Cronbach α – value of 0.621 in case where the last stigma question was unanswered. Knowledge was computed in a less straightforward way to reflect the different degrees of difficulty for the individual questions. For questions about knowledge, contagiosity and curability of TB, the wrong answer resulted in score 0 and the right answer in score 1, except for question if TB contagious where it was rewarded with score 2. The right answer in question about way of transmission resulted in score 3, all other answers in score 1. For question about common symptoms of pulmonary TB, the score was defined as the number of marked symptoms divided by six (the total number of displayed symptoms). This gave a Cronbach α – value of 0.545 for the 5 knowledge-related items.

4.2.3 Results

A total of 600 newly diagnosed pulmonary TB cases confirmed bacteriologically were assessed. Of these, 50 had a recurrence of a previous TB, and 12 have refused to participate due to poor clinical condition. The final sample comprised of 538 patients, 243 from Karakalpakstan, 179 from Tashkent city and 116 representing all 12 provinces of Uzbekistan. The characteristics of these patients are summarized in table 8.

Table 8 Characteristics of pulmonary tuberculosis patients in Uzbekistan

Patient characteristics	MDR-TB	NON-MDR-TB
	No. (%)	No. (%)
Gender	(N=243)	(N=295)
Male	124 (51.0)	174 (59.0)
Female	119 (49.0)	121 (41.0)
M/F ratio	1.04	1.44
Age		
≤ 15-35	120 (49.4)	106 (35.9)
> 35	123 (50.6)	189 (64.1)
Education		
Illiterate	13 (5.3)	9 (3.1)
Primary-Secondary	206 (84.8)	237 (80.3)
University/higher	24 (9.9)	49 (16.6)
Occupation		
Employed	50 (20.6)	80 (27.1)
Healthcare worker	5 (2.1)	3 (1.0)
Unemployed	124 (51.0)	122 (41.4)
Student	7 (2.9)	9 (3.1)
Housewife	10 (4.1)	42 (14.2)
Retired	47 (19.3)	39 (13.2)
Labour migrant	27 (11.1)	27 (9.2)
Residence		
Urban	132 (54.3)	225 (76.3)
Suburban	12 (5.0)	41 (13.9)
Rural	99 (40.7)	29 (9.8)

Patient characteristics	MDR-TB	NON-MDR-TB
Smoking		
Never	171 (70.4)	145 (49.2)
Current	-	-
Ex-smoking	72 (29.6)	126 (42.7)
Alcohol use		
Never	163 (67.1)	165 (55.9)
Past history	69 (28.4)	84 (28.5)
Moderate/ Excessive	11 (4.5)	46 (15.6)
Injection drug use		
Yes	1 (0.4)	20 (6.8)
No	242 (99.6)	275 (93.2)
Comorbidities		
Diabetes mellitus	12 (4.9)	40 (13.6)
HIV positive	-	32 (10.8)
COPD/emphysema/bronchitis	42 (17.3)	27 (9.1)
Symptoms		
Cough	226 (93.0)	253 (85.8)
Fever	123 (50.6)	131 (44.4)
Loss of weight	191 (78.6)	191 (64.7)
Sputum smear-for acid-fast bacilli		
Positive	117 (48.1)	166 (56.3)
Negative	126 (51.9)	129 (43.7)
Health facility first consulted		
Pharmacy	131 (53.9)	100 (33.9)
Private clinic	4 (1.6)	23 (7.8)
Primary health center/polyclinic	42 (17.3)	91 (30.8)
TB facility	52 (21.4)	48 (16.3)
Traditional remedy	2 (0.8)	2 (0.7)
Ambulance	7 (2.9)	9 (3.1)
Other (AIDS Centre, Public hospital)	5 (2.1)	22 (7.4)
Treatment before TB diagnosis		
Self-medicated	131 (53.9)	100 (33.9)
- Self-medicated with antibiotics	90 (69.0)	34 (34.0)
Prescribed antibiotics	55 (22.6)	114 (38.6)
Time taken to reach a TB health facility		
<1/2 hour	108 (44.4)	46 (15.6)
1/2-1 hour	58 (23.9)	111 (37.6)
≥ 1 hour	77 (31.7)	138 (46.8)

HIV - human immunodeficiency virus; TB- tuberculosis

MDR-TB - multi-drug resistant tuberculosis

The mean age was 40 years and there were no significant gender differences in notified TB cases. The number of cases were, however, slightly higher in males than in females. The prevalence rate was highest in males aged 25-35. Of the 538 patients, 231 (42.9%) practiced self-medication or consulted pharmacists with the onset of respiratory symptoms and of them 124 patients (54.0%) self-treated with antibiotics.

The proportion of MDR-TB among new TB cases was 41% and occurred predominantly in Karakalpakstan region. No cases of XDR-TB were observed among patients.

The median patient delay for all patients included in the study was 27 days (interquartile range, 6-62 days). Delay was significantly longer in patients who abused alcohol, were HIV positive and had specific TB symptoms of persistent cough and loss of weight (Table 9). Additionally, patients with positive sputum smear results and those who self-medicated, ordinarily with antibiotics, had longer diagnostic delay. First-visited health facilities (health centres, private or district outpatient clinics) and time to reach the nearest health care facility or facility providing TB treatment were significantly associated with longer delay.

Table 9 **Risk factors for three delay stages of pulmonary tuberculosis patients in Uzbekistan**

Predictors	No.	Patient delay (median 27 days)		Health system delay (median 7 days)		Total delay (median 50 days)	
		Median	*p* value	Median	*p* value	Median	*p* value
Gender							
Male	298	30	0.08	6.5	0.56	49	0.8
Female	240	23.5	1	8	1	50.5	1
Age							
≤ 15-35	226	25	0.3	5	0.01*	48	0.1
> 35	312	28	0.4	9	0.1	50	0.4
Education							
Illiterate	22	31	1	3	1	38.5	1
Primary-Secondary	443	25	0.5	7	0.2	50	0.6
University/higher	73	30	0.9	9	0.1	49	0.7
Occupation							
Employed	130	21	1	10	1	57	1
Healthcare worker	8	23	0.4	4	0.01*	27.5	0.8
Unemployed	246	30	0.2	5	0.001*	48	0.3
Student	16	17	0.2	14.5	0.9	36.5	0.4
Housewife	52	25	0.8	9	0.3	50	0.8

Predictors	No.	Patient delay (median 27 days)		Health system delay (median 7 days)		Total delay (median 50 days)	
		Median	*p* value	Median	*p* value	Median	*p* value
Retired	86	28	0.3	9	0.2	54	0.6
Labour migrant	54	34	0.9	7	0.02*	60.5	0.5
Residence							
Urban	357	25	1	7	1	49	1
Suburban	53	25	0.8	18	0.01*	56	0.2
Rural	128	30	0.1	4	0.1	50.5	0.9
Smoking							
Never	316	25	1	6	1	50	1
Current	24	42	0.2	8	0.2	48.5	0.9
Ex-smoking	198	29	0.3	8	0.2	49.5	0.7
Alcohol use							
Never	328	24	1	6	1	47	1
Past history	153	34	0.03*	7	0.1	54	0.1
Moderate/ Excessive	57	21	0.03*	10	0.1	50	0.1
Injection drug use							
Yes	21	24	0.5	11	0.3	48	0.9
No	517	27	1	7	1	50	1
Comorbidities							
Diabetes mellitus	52	23	0.9	10	0.6	51.5	0.9
HIV positive	32	14.5	0.03*	19.5	0.02*	46.5	0.6
COPD/emphysema/bronchitis	69	31	0.5	4	0.9	46	0.2
Symptoms							
Cough	479	29	0.008*	7	0.4	53	0.0001*
Fever	254	29	0.3	7	0.8	53	0.2
Loss of weight	382	35	0.0001*	7	0.7	57	0.0001*
Sputum smear-for acid-fast bacilli							
Positive	283	31	0.008*	8	0.3	54	0.006*
Negative	255	21	1	6	1	44	1
Health facility first consulted							
Pharmacy	231	41	0.0001*	6	0.0001*	56	0.0001*
Private clinic	27	14	0.02*	36	0.004*	88	0.01*
Primary health center/polyclinic	133	12	0.0001*	16	0.0001*	41	0.004*
TB facility	100	25	1	3	1	33.5	1

Predictors	No.	Patient delay (median 27 days)		Health system delay (median 7 days)		Total delay (median 50 days)	
		Median	*p* value	Median	*p* value	Median	*p* value
Traditional remedy	4	14	0.1	5	0.4	28	0.03
Ambulance	16	16	0.006*	5.5	0.4	25.5	0.05
Other (AIDS Centre, Public hospital)	27	30	0.6	6	0.4	45	0.2
Treatment before TB diagnosis							
Self-medicated	231	41	1	6	1	56	1
- Self-medicated with antibiotics	124	54.5	0.0001*	4	0.03*	62.5	0.0001*
Prescribed antibiotics	169	15	0.09	25	0.0001*	58	0.02*
Time taken to reach a TB health facility							
<1/2 hour	154	24	0.5	6	0.2	39	0.3
1/2-1 hour	169	26	0.4	8	0.4	55	0.4
≥ 1 hour	215	29	0.04*	7	0.6	51	0.04*

HIV - human immunodeficiency virus; TB- tuberculosis; AIDS - Acquired Immune Deficiency Syndrome

* $p < 0.05$.

The median health system delay of 7 days (interquartile range, 1-32 days) seemed to be insignificant (Table 9). Longer than median health system delay was common in younger patients, those unemployed or being labour migrants, who had recently worked abroad (p=0.001 and p=0.002, respectively). Being a health care worker was a strong risk factor (p=0.01) for health system delay, but could not be fully assessed since there were only 8 (1.5%) health care workers and all of them had delayed diagnosis. Furthermore, patients who had longer health system delay also were HIV-positive, stigmatized by TB disease and self-medicated with antimicrobials.

The median total delay was nearly 2 months (50 days, interquartile range, 22-92 days), and 228 of 538 patients (42%) experienced a delay of 3 months or longer. Patients with cough, loss of weight, who self-medicated, were prescribed anti-TB medications by non-TB physician, from distant location to health care facility or facility providing TB treatment experienced longer delays in the diagnosis and treatment of TB.

Further multivariate analysis revealed that self-medication and private facility predicted long patient delay, while administration of antimicrobial therapy as well as seeking care at private clinic were risk factors for health system delay (Table 10). Cough, self-medication, private and primary health care facility were associated with long total delay.

Because untreated MDR-TB is highly contagious, we defined the extent of delay and evaluated risk factors among patients with MDR-TB and with non-MDR-TB. Among MDR-TB patients, there was slightly longer median patient delay of 36 days, health care delay was 8 days and the total delay was 47 days. There were no differences between the 2 groups in the predictors of diagnostic delay. However, high social stigma prevailed in patients with MDR-TB (OR 1.39, 95% CI 0.74- 2.62).

Table 10 Multiple logistic regression analysis of risk factors for three delay stages of pulmonary tuberculosis patients in Uzbekistan

Predictors	Patient delay; OR (95%CI)	Health system delay; OR (95%CI)	Total delay; OR (95%CI)
Cough	0.72 (0.38 to 1.39)	1.02 (0.53 to 1.96)	4.67 (1.23 to 17.1)*
Loss of weight	0.25 (0.16 to 0.4)*	1.04 (0.65 to 1.67)	0.42 (0.27 to 0.65)*
Sputum positive	0.60 (0.40 to 0.89)*	1.12 (0.73 to 1.69)	0.77 (0.52 to 1.13)
Self-medication	1.53 (1.01 to 2.33)*	0.91 (0.53 to 1.53)	1.58 (1.12 to 2.23)*
Self-medication with antibiotics	0.73 (0.40 to 1.31)	1.31 (0.69 to 2.45)	0.94 (0.53 to 1.68)
Prescribed antibiotics	N/A	2.19 (1.18 to 4.09)*	0.5 (0.31 to 0.81)
Primary health center/ Polyclinic	1.68 (0.49 to 5.63)	3.09 (0.61 to 15.74)	5.53 (1.29 to 23.72)*
Private clinic	2.96 (1.49 to 5.88)*	2.87 (1.83 to 4.54)*	4.67 (1.27 to 17.11)*

OR= odds ratio, CI= confidence interval, N/A= not applicable

* p <0.05.

4.2.4 Discussion

Our findings showed that the median total delay time from the onset of symptoms until diagnosis and initiation of anti-TB treatment was 50 days and was mainly contributed by the patient delay of 27 days. Healthcare system delay 7 days was significantly shorter than patient delay.

Out of 228 cases 79 cases with more than two months of total delay were MDR-TB cases, when early and accurate diagnosis is critical to timely initiation of effective treatment.

Self-medication, private and primary health facility and cough were the main factors associated with the total delay in a cohort of TB patients.

Almost half of the patients used non-prescribed antimicrobials before the diagnosis and treatment of TB. As widely known self-medication with antibiotics can delay and mask the correct diagnosis of infectious disease (211). Several studies reported that antibiotic exposure, in particular fluoroquinolones, can delay the diagnosis of TB and initiation of anti-TB treatment (212-214), but the contribution of the class of antibiotics has not been examined in our research.

Considering the fact that both first- and second-line anti-TB drugs are available without a prescription encouraging self-treatment and the uncontrolled use and contributing to higher levels of resistance with a consequent deleterious impact on the treatment success (215). Wherein self-treatment only temporarily relieved the symptoms resulted in exhaustion and weakness and the necessity of transportation by ambulance.

A care seeking from primary health center/polyclinic was associated with delay in the diagnosis and might be due to failure to comply with recommended diagnostic standards. Patients managed in primary health centers were repeatedly treated with antibiotics (including fluoroquinolones) for upper respiratory infection or presumed community-acquired pneumonia. Prolonged delay in diagnosis ranging from 1 to 12 months was seen in 8% of patients first approach public polyclinics. Inadequate case detection at primary health care contributes to low treatment success rate and extended period of transmission of disease, particularly MDR-TB. Of particular concern were private physicians most often consulted first by the patients living in distant places. As per some studies from developing countries (216,217) private physicians tend to deviate from recommended TB management guidelines and rely on chest radiography rather than refer patients for sputum microscopy or monitor treatment (218).

HIV infection was found to be significantly associated with longer patient and system delay. It is possible as symptoms less specific and might be considered by the patients as symptoms connected to HIV. Despite all HIV-infected patients are routinely screened for latent and active TB infection, the interpretation of test results might be complicated by a higher incidence of false-positive results (e.g., negative tuberculin skin test, negative sputum and normal chest x-ray findings), and the lack of specificity of symptoms (219).

The reasoning behind the cough symptom was associated with delayed TB diagnosis is not clear. It might be that patients considered it as a transient symptom from an upper respiratory illness, hence initiating self-treatment lasting until deterioration in condition and manifestation of other specific symptoms. Further, timely referral to healthcare facility was challenging for work migrants due to limited access to health care, financial constraints, poor health literacy and fear of deportation after positive TB diagnosis.

Although awareness and knowledge of TB was higher in Karakalpakstan, the extent of total delay was similar across regions, yet patient delay was longer in Karakalpakstan, possibly due to higher stigmatization, fear and belief in the incurability of the disease. Approximately 30% of those with diagnostic delay in Karakalpakstan had relatives and friends with MDR-TB disease or even experienced the death of a family member, and the feeling of hopelessness was overpowering.

The current smoking was associated with earlier diagnosis. Never-smokers were more likely to have delays than smokers. This finding is in contrast with another study confirming smoking is a significant risk factor for delay, as smokers often do not present themselves to the health facilities in the belief that their cough is due to smoking (207). Our results can be explained in terms that smokers are more worried about their health or the physicians consider them a higher risk group.

Alcohol abuse was another risk factor for delayed TB diagnosis.

Limitations

There are several limitations to this study. First, recall bias may have influences our results, as the onset of first symptoms may have been inaccurately reported by the patients. In order to minimize patient recall bias we encouraged physicians to check patient medical cards when completing the questionnaire. Second, lack of information on class of antibiotic used for self-medication as well as prescribed by physician, meaning that fluoroquinolone use may have been associated with delay in diagnosis of TB.

Although this study investigates the risk factors associated with delayed diagnosis and treatment of TB, there are clinical consequences of late TB diagnosis. Further studies assessing morbidity, mortality, treatment success, outcome of previous antibiotic treatment, the risk of transmission and developing active TB associated with delay in initiation of treatment are required.

4.2.5 Conclusion

It is critical to reduce TB diagnostic and treatment delay to the least possible time interval. There is a need to decrease TB stigma, promote public awareness of TB curability and importance of early referral to health services. An essential step is to improve the diagnostic awareness among private and primary care practitioners. A high index of suspicion of TB should be maintained in public and private practitioners and an appropriate diagnostic work-up should be performed. Regulation prohibiting the dispensing of antibiotics, including anti-TB medicines, without prescription should be enforced to prevent further development of drug- resistance.

4.3 Knowledge and attitudes toward antibiotic use and antimicrobial resistance among Saudi population

4.3.1 Aims

To evaluate knowledge of antibiotics, race, gender and age as independent risk factors for self-medication.

4.3.2 Methodology

Study population

Between June 2014 and February 2015, a cross-sectional epidemiological study was conducted. The inclusion criteria were as follows:

- Saudi nationals and legal resident non-Saudi nationals.
- Older than 18 years
- To volunteer for participation in the survey

A unique national identification number has been provided to each participant. The identity of participants was anonymized through the process of data analysis.

Questionnaire

The questionnaire was developed in Arabic or English according to scientific literature and WHO report on antimicrobial resistence (220,221). The questionnaire included socio-demographic characteristics, antibiotics knowledge, attitudes and antibiotics usage behaviour. The survey was mainly conducted in Southwestern region of Kingdom of Saudi Arabia but also among randomly selected participants from other regions of the country. The questionnaire was distributed by random in person interview of participants in public areas, clinics, hospitals, houses, and universities.

Analysis

Data were analysed using PASW statistical software (IBM Corporation, Armonk, NY, USA, version 18.0). The dependent variable, self-prescription of a respondent, was defined as prescription by anyone else than a physician (including pharmacists, nurses, friends, etc.). The influence of independent variables on self-prescription of antibiotics was evaluated using univariate logistic regression analysis. The regression outcome of self-prescription was given by the estimated odds ratios and the corresponding 95%

confidence intervals. Hypothesis tests for regression coefficients (Wald-tests) were performed and expressed with p values at the significance level $\alpha = 0.05$. Knowledge was measured using a scoring system. There were four questions on basic knowledge, namely (1) What is an antibiotic? (2) What is a prescription? (3) Can antibiotics be used for all types of infections including viral, bacterial, and fungal origin? (4) Are antibiotics used to treat viral infections? Three other questions were more specialized, namely (1) Do you know what antimicrobial susceptibility testing is? (2) Have you heard of the term antimicrobial resistance before? (3) Do you know what AMR is? The variable total knowledge was computed in a way to reflect the different degrees of difficulty for the individual questions. For the four basic questions, the wrong answer resulted in a score of 0, the right answer in a score of 1, and answer "do not know" in a score of 1/3. Responses in the three specialized questions resulted in a score of 1 for the answer "yes", and a score of 0 for the answer "no". The value of the final variable total knowledge was defined as the sum of the scores of all seven knowledge questions. This gave a Cronbach α – value of 0.537. The association of demographic characteristics with a number of chosen variables was investigated using Pearson's Chi-square tests.

4.3.3 Results

Of the 1310 questionnaires that were distributed, 161 were returned as uncompleted and 1149 were returned as completed. The response rate was 87.7%. The socio- demographic characteristics of the study population are shown in Table 11.

The majority of respondents were female (59.0%) and Saudi nationals (90.7%). The mean age of participants was 26.8 (SD 8.8).

Further, 71% of the respondents reported that they had used an antibiotic in the last 6 months. About 63.6 % of participants reported that they had purchased antibiotics without a prescription from pharmacies; 71.1% reported they did not finish the antibiotic course as they felt better. Of those who used prescribed or non-prescribed antibiotics, 44.7% reported that they kept left-over antibiotics from the incomplete course of treatment for future need.

Interestingly, 62% of respondents who used antibiotics without prescription agreed with the statement that antibiotics should be access-controlled drugs prescribed by a physician.

Table 11 Socio-demographic characteristics of study population

Characteristics	No. (%)
	(N=1149)
Gender	
Male	471 (41.0)
Female	678 (59.0)
Age	
18-39	1006 (87.6)
> 40	143 (12.4)
Marital status	
Single	608 (52.9)
Married	526 (45.8)
Divorced	11(1.0)
Widowed	4 (0.3)
Education	
Higher education	606 (52.7)
Intermediate	428 (37.3)
Elementary	39 (3.4)
Illiterate	76 (6.6)
Nationality	
Saudi	1042 (90.7)
Other	107 (9.3)

Amoxicillin and its combination with clavulanate was the most commonly requested antibiotic and was dispensed in 29.2% of cases. It was found that 18.2% of participants self-medicated with antibiotics for respiratory diseases. About 1.0 % females reported self-medication with antibiotics during menstrual cycle and its associated symptoms such as headache, colic and vaginal pain.

Table 12 shows the result of logistic regression analysis assessing the predictors of self-medication with antibiotics. The female respondents were less likely to self-medicate than males (OR 0.635, 95% CI 0.49-0.82) and Saudi nationals were less likely to self-medicate than representatives of other nationalities (OR 1.8, 95% CI 1.2-2.69). The association between self-medication and gender was not confirmed by a confounding effect of education, despite the fact that women were less educated than men. The availability of antibiotics without prescription was positively associated with self-prescription (OR 0.238, 95% CI 0.17-0.33).

Table 12 Predictors associated with self-prescription (Logistic regression models)

Independent variable		Dependent variable (self-prescription)		
		p-value (Wald-test)	Odds ratio	95% confidence interval
Nationality	Saudi-Arabian* or not	**0.004**	1.799	1.202 - 2.693
Age	Natural numbers	0.727	1.002	0.989 - 1.016
Gender	Male* or female	**<0.001**	0.635	0.493 - 0.819
When did you last use an antibiotic?	Less than 6 months ago, between 6 and 12 months ago, more than a year ago*	For "between 6 and 12 months ago': **0.011**	0.073	0.010 - 0.555
When do you usually use the antibiotic?	19 types of diseases	For "Accute respiratory infections": **<0.001**	0.242	0.125 - 0.469
Do you agree that antibiotics are accessed without a prescription?	Yes* or no	0.946	1.011	0.741 - 1.378
Have you purchased antibiotics from the pharmacy without a prescription?	Yes* or no	**<0.001**	0.238	0.174 - 0.326
Do you accept to use an antibiotic directly from the pharmacist without physician referral?	Yes* or no	**<0.001**	0.241	0.164 - 0.352
Do you agree that antibiotics become access-controlled drugs only by physician?	Yes* or no	**<0.001**	2.125	1.612 - 2.802
Do you keep the antibiotic for future use?	Yes* or no	**<0.001**	0.412	0.309 - 0.549
Do you follow antibiotic course as prescribed?	Yes* or no	**<0.001**	1.932	1.417 - 2.636

Independent variable		Dependent variable (self-prescription)		
		p-value (Wald-test)	Odds ratio	95% confidence interval
Do you agree to administer the antibiotic when prescribed to you?	Yes* or no	0.525	1.128	0.778 - 1.636
Do you change the prescribed antibiotic by a pharmacist help?	Yes* or no	0.497	0.898	0.658 - 1.225
Before using antibiotic. were you asked to do antimicrobial susceptibility testing?	Yes* or no	**0.004**	1.455	1.125 - 1.882
Do you request antibiotic prescription change by aid of pharmacist?	Yes* or no	**0.011**	0.713	0.550 - 0.924
Source of health-related information	Professional* or non-professional	**0.001**	1.575	1.201 - 2.066
Total knowledge	Scoring system	**0.028**	0.917	0.849 - 0.991

Reference groups of the independent variable are marked with *

Significant values when p<0.05 are shown in bold

Using a non-professional source of health-related information about AMR (like internet) was positively associated with taking antibiotics without prescription (OR 1.575, 95% CI 1.2 – 2.07).

Taking antibiotics following pharmacist's advice without physician referral (OR 0.241, 95% CI 0.16 - 0.35), keeping left-overs (OR 0.412, 95% CI 0.31 - 0.55), and incomplete course of antibiotic treatment (OR 1.932, 95% CI 1.42 - 2.64) were also positively associated with self-medication. Using for the treatment of acute upper respiratory infections (OR 0.242, 95% CI 0.125 - 0.469), and total knowledge (OR 0.917, 95% CI 0.85 - 0.99) were negatively associated with self-medication:.

The results of the relationship between individual's socio-demographic characteristics and storage of antibiotics, attitudes toward and knowledge of the antibiotic use were shown in Table 13.

Table 13 Association of demographic characteristics with knowledge, attitudes and behaviour statements (Chi-square tests)

Statement	No. (%)	*p* value			
	(N=1149)	Nationality	Gender	Age	Education
Inventory of antibiotics at home	515 (44.8)	0.445	**0.03**	0.561	**0.03**
Knowledge of antibiotic resistance	550 (47.9)	0.88	**<0.001**	**0.029**	**<0.001**
Completing a course of antibiotics as prescribed	451 (39.3)	0.445	0.724	0.70	**<0.001**
Awareness that antibiotics are used to treat viral infections	553 (48.1)	0.16	0.19	0.295	**<0.001**

Significant values when $p<0.05$ are shown in bold

Considering the most of respondents were Saudis, nationality had no significant effect on each of the statements. There was no association found with marital status. Being a female, an older age and a higher education were significantly associated with knowledge of AMR. Significant interactions were found between storage, knowledge/attitudes and education. Respondents with higher education were more adherent, however, they tended to have the inventory of antibiotics at home and believed antibiotics are used to treat viral infections.

4.3.4 Discussion

A high participation rate of 87.7% is a major strength of this study. Significant interactions between storage, knowledge/attitudes and education was found. There was low overall level of awareness on the use of antibiotics and knowledge towards antibiotic resistance among respondents. Both Saudi nationals and non-Saudi residents were included into the study. However, the main target of the study were Saudi nationals to find out the cultural effect as a risk factor for the non-prescription and increased use of antibiotics.

More than half (63.6 %) reported to have purchased antibiotics from pharmacies without a prescription. Despite many policies exist to regulate antibiotic use, but enforcement, education on antibiotic use and AMR are insufficient or lacking.

It can be suggested if access to antibiotics among Saudi population is controlled, the irrational use of antibiotics will decrease resulting in reduction of the associated evolvement of AMR threat.

Internet use, as a source for antibiotics prescription, was positively associated with taking antibiotics without prescription (OR 1.575, 95% CI 1.2 – 2.07) similar to other studies where it was reported that internet is a source of medicines and antibiotic abuses (222, 223).

The majority of respondents were female (59.0%) and females tend to more likely self-medicate with antibiotics using them for their children.

Considering the misuse and overuse of antibiotics contributes to the spread of antibiotic resistance, our results suggest the increase of antibiotic resistance in Saudi Arabia and further spread of multidrug resistant bacteria.

A better implementation of antibiotic educational stewardship, legislation improvement and surveillance programmes on antimicrobial prescription and resistance in hospitals and primary care are required in Saudi Arabia. Future effective enforcement of legislations regarding antibiotic access in community in Saudi Arabia should be advocated.

Optimizing antibiotic use can also be achieved by changing patient and clinician behaviours in the community and hospitals.

4.3.5 Conclusion

Results of the present study on uncontrolled self-medication with antibiotics are alarming. The public health awareness intervention programs on the use of antibiotics and policies regulating access to antibiotics should be implemented. This will eventually reduce the increasing level of resistance and will help alleviate the ever increasing AMR crisis.

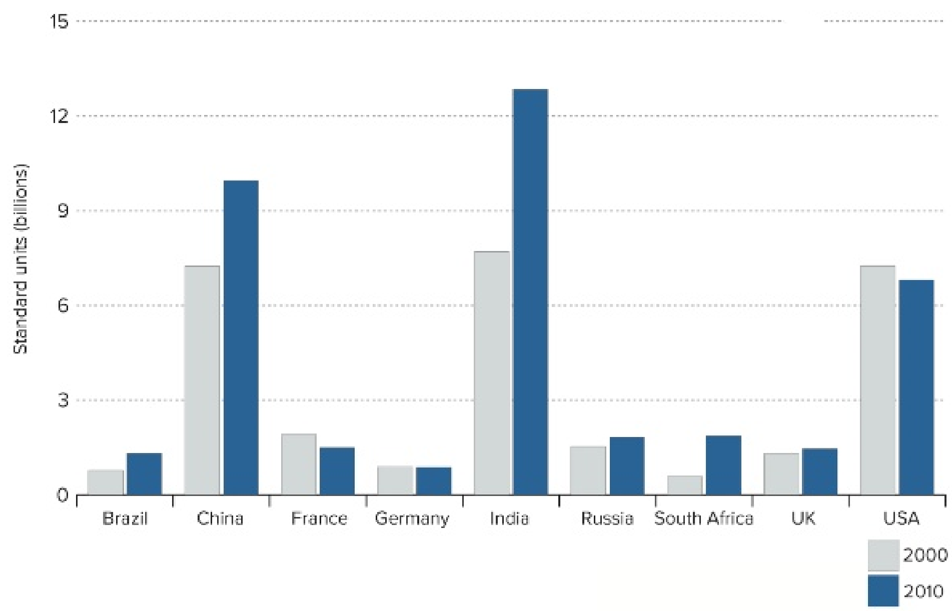
4.4 Antibiotic Use Practices of Pharmacy Staff in Saint Petersburg, the Russian Federation

4.4.1 Aims

Russia, along with Brazil, India, China, and South Africa, accounts for 76% of the overall increase in global consumption of antibiotics (Figure 2) (224). Non-prescription access to antimicrobials, leads to arbitrary attitude on antibiotics towards health professionals especially pharmacists.

Our purpose was to explore the approach of pharmacists to antibiotics treatment, including antibiotic choice and to assess their knowledge and attitudes to AMR in order to define the ways of prevention the practice of non-prescribed dispensation.

Figure 2 Antibiotic consumption in selected countries, 2000-2010



Source: Van Boeckel et al. 2014 (224)

4.4.2 Methodology

Study setting and population

The study was conducted from September-December 2015 in community pharmacies in the Saint Petersburg and Leningrad region, Russia. The sample comprised 63 pharmacies and 316 pharmacists from one of the largest pharmacy chains.

Measures

A self-administered questionnaire was adapted from a previous study conducted by our research group (221). The questionnaire included close-ended (yes/no, single choice and multiple choice) and open-ended questions (an English translation is available in Appendix A). Denoting the sixteen questions from Q1 to Q16, they can be grouped into the following categories: attitudes and behaviours towards antibiotic use and self-medication (Q1, Q2, Q3, Q7, Q11, Q12); information on the types of involved diseases, antibiotics and side effects (Q3 partially, Q4, Q9); knowledge of antibiotic use and resistance and source of antibiotic knowledge (Q5, Q6, Q8, Q10); and personal and professional information (Q13 – Q16).

Statistical analysis

The outcomes of questions Q8 (knowledge about side effects), Q10 (knowledge about influence on normal flora) and Q13 (gender) were essentially identical (up to less than one percent) for all respondents. This similarity is explained by the fact that 99,4% of the respondents were female pharmacists.

To evaluate the influence of attitudes, behaviour, knowledge and demographics on self-medication with antibiotics, univariate logistic regression analyses were performed. Self-medication occurred when the respondents indicated that they purchased antibiotics for themselves (or their children) without a physician's prescription but based on their own knowledge or on recommendations of friends (see part two of Q2). This defined the dichotomous dependent variable. The independent variables were, respectively, the outcomes of questions Q1, Q3, Q5, Q6, Q11, Q12, Q13, Q14, Q15 and Q16. We did not include variables related to information on the types of involved diseases, antibiotics and side effects (Q3, Q4, Q9), as they contained too many outcomes, and we also did not include variables with essentially only one outcome (Q8, Q10, Q13). For most of the included questions, all respondents provided answers; however, questions Q14 to Q16 had a percentage of missing values of 0.3% (1 answer) each, and Q7 was missing 3.2% (10 answers). In a few cases, multiple answers to the same question were provided; the highest score (e.g., highest education, highest age, best knowledge) was then used for the regression analysis. For question Q6, however, there were too many multiple answers to address using this approach. Therefore, Q6 was divided into three separate dichotomous variables with outcomes yes or no: Q6a, Q6b and Q6c.

The results of the regression models were presented as the estimated odds ratios and the corresponding 95% confidence intervals. Hypothesis tests for regression coefficients

(Wald tests) were performed and expressed with p values at a significance level of α = 0.05.

We also tested for associations between demographic characteristics (Q14 – Q16) and the remaining independent variables. We used Pearson chi-squared tests with p values at a significance level of α = 0.05. To avoid low expectation counts, the outcomes of Q14 – Q16 were recategorized (in clear ways) into two groups. PASW statistical software was used for all analyses (IBM Corporation, Armonk, NY, USA, version 18.0).

4.4.3 Results

Of the 410 questionnaires distributed, 316 (77.07%) were completed and collected.
The main demographic characteristics of the respondents are summarized in Table 14. The sample was predominantly female, which is rather typical for Russian pharmacies. The mean age of the respondents was 39.3 years, and almost half of them were 41-60 years.

Table 14 Personal and professional characteristics of pharmacists

Characteristics	No. (%) (N=316)
Gender	
Male	4 (1.27)
Female	312 (98.73)
Age	
< 20	1 (0.32)
20-30	100 (31.65)
31-41	65 (20.57)
41-60	143 (45.25)
>60	7 (2.21)
Education	
Higher pharmaceutical	110 (31.5)
Other higher	33 (9.5)
Vocational pharmaceutical	206 (59.0)
Years of experience in a pharmacy:	
<1	15 (4.75)
1-5	85 (26.90)
6-10	83 (26.26)
>10	133 (42.09)
Source of antibiotics:	
Prescribed	100 (31.65)
Self-medication	216 (68.35)

The vast majority of pharmacists had a baccalaureate degree, and nearly half of them had 10 years of experience of working in a pharmacy. Table 14 shows that slightly more than two-thirds of the pharmacists self-medicated.

Other characteristics of the sample that are not displayed in Table 14 are as follows.

About three-quarters of the respondents (72.8%) self-medicated when they were sick. The highest prevalence of self-medication was reported for the age group of those 41-60 years old (45.3%). Young and middle-aged respondents (31-40 years) were more responsible: 22.8% of them went to the doctor, and 20.6% self-medicated. However, the logistic regression analysis, which is addressed in more detail later, did not reveal statistically significant higher probabilities of self-medication for any of these age groups. Only 33% purchased antibiotics using a doctor's prescription. More than half (61%) of the respondents visited a doctor for an examination and received a prescription from time to time, and 6% of staff pharmacists never bought antibiotics from a prescription. The respondents who did not visit or rarely visited a doctor for prescriptions bought antibiotics based on their knowledge (81.5%) or their friends' advice (5.0%); analyses of their experiences with previous treatment (49.0%); and prescriptions provided by pharmacy customers (17.0%). Only a small number of respondents (8.0%) considered cost to a significant degree when purchasing medicine.

Antibiotics were mostly used to self-treat upper and low respiratory tract infections (53.3% and 19.3%, respectively). Other conditions addressed with self-medication were dental problems, urogenital infections and respiratory inflammation.

The most commonly used antibiotics were macrolides (33.2%). Azithromycin was predominant in this group and accounted for 81.1% of all self-prescriptions. Penicillins (30.9%) and fluoroquinolones (15.2%) were other most frequently used groups, followed by tetracyclines (7.8%), second-generation cephalosporins (5.5%), lincosamides (5.4%) and aminoglycosides (2.0%).

The main source of information regarding antibiotics was training sessions (43.2%), patient information leaflets (30.1%) and specific literature (26.7%). More than half of the respondents (66.8%) took their antibiotics according to the information on the leaflet, one-third (31%) took antibiotics in line with their physician's prescriptions, and the rest (2.2%) stopped using the antibiotic early when their symptoms decreased.

Oral dosage was the most preferred form of antibiotics.

Table 15 shows the impact of pharmacists' attitudes, behaviour and knowledge on self-medication with antibiotics.

Table 15 **Factors influencing self-medication with antibiotics based on univariate logistic regression models for individual questions. Reference groups are the outcomes not displayed between brackets after the question**

Question (evaluated outcome)	No. (N=316)	p-value (Wald-test)	Odds ratio	95% confidence interval		
When you feel ill (consult a physician)	86	**0.001***	0.405	0.232	-	0.707
Have you taken antibiotics in the past 6 months (no)	175	0.727	0.915	0.555	-	1.508
Antibiotic use:						
(stop after symptoms decreased)	8	0.727	0.759	0.162	-	3.560
(as per leaflet)	243	**0.005***	2.088	1.250	-	3.488
Source of new information about antibiotics:						
- Training sessions (no)	227	**0.014***	0.517	0.305	-	0.877
- Special literature (no)	140	**0.002***	0.441	0.260	-	0.747
- PIL** (no)	158	0.800	1.066	0.649	-	1.750
Preferable form (injections)	285	0.207	0.571	0.24	-	1.362
Use of probiotics (no)	285	0.674	0.844	0.384	-	1.856
Attitude toward antibiotic therapy:						
(against)	10	0.964	0.955	0.126	-	7.229
(extreme cases)	295	0.612	0.714	0.194	-	2.624

**PIL: Patient information leaflet; * $p < 0.05$

The following associations were found to be statistically significant. When feeling ill, those who consulted a physician had a lower probability (OR 0.41) of self-medication than those who self-medicated, which is self-evident. Concerning the way antibiotics were used, those acting according to patient leaflets had a higher chance (OR 2.09) of self-medication than those who used antibiotics as prescribed by the physician. Interestingly, pharmacists who did not obtain new information on antibiotics through educational paths or specific literature exhibited a substantially decreased probability of self-medication (OR 0.57 and OR 0.44, respectively). Although not displayed in Table 15, the logistic regression analysis indicated a strong association of self-medication with all levels of education compared to those with basic (non-pharmaceutical) vocational education, with the following odds ratios: higher pharmaceutical (OR 5.201, CI 95% 1.87-14.42), other higher education (OR 3.781, CI 95% 1.12 -12.79) and vocational pharmaceutical (OR 3.613, CI 95% 1.36-9.59).

Pearson chi-squared tests revealed no association between personal characteristics (age, education and experience) and self-medication or antibiotic use (Table 16). By contrast, variables related to the source of new information about antibiotics were shown to be significantly associated with personal characteristics.

Table 16 Association of demographic characteristics with attitudes towards antibiotic use

Statement	No. (%) (N=316)	*p* value Age	Education	Experience
Self-medicate	230	0.946	0.565	0.123
Antibiotics taken in the past 6 months	141	0.787	0.323	0.807
Stopped taking antibiotics after symptoms decreased	8	0.779	0.34	0.382
Source of new information about antibiotics:				
- Training sessions	227	0.309	0.889	**0.047***
- Special literature	140	0.318	**0.003***	0.051
- PIL**	158	**0.044***	0.465	0.195
Taking probiotics during/after treatment with antibiotics	283	0.869	0.805	0.15
Attitude toward antibiotics	298	0.683	0.622	0.633

** PIL: Patient information leaflet; * $p < 0.05$.

4.4.4 Discussion

The results of our study show that the practice of self-prescribing antimicrobials is extremely popular amongst pharmacists in Saint Petersburg. We suggest that the main contributing factor of this high prevalence is pharmacists' easy access to antibiotics, since a prescription for the dispensed antibiotics is neither required nor controlled by authorities during inspections.

Data on outpatient antibiotic use reported by the European Surveillance of Antimicrobial Consumption suggested that in 2009, Russia was the third largest outpatient consumer of antibiotics in Europe when consumption was expressed as the number of packages per 1000 inhabitants per day (225).

Another study by Stratchounski et al. also confirmed that the Russian population is inclined to stock antibiotics in home medicine cabinets for further uncontrolled and unsupervised use (204). While Russian physicians are aware of antibiotic resistance and are concerned by the over-the-counter sale of antibiotics (226), pharmacists promote an inappropriate use of medications by over-the-counter dispensation. This finding can be explained by the lack of a culture in which drugs are dispensed/purchased strictly based on prescriptions. Physicians often do not write prescriptions or they provide their recommendations, including the use of antibacterial drugs, on a regular sheet of paper that may, in the best case, have a physician's seal.

Our findings indicate that antibiotics were commonly used by pharmacists to treat upper RTIs, which raises concern regarding the potential misbelief that antibiotics can treat and eradicate infections regardless of its origin (195), as well as a lack of professional knowledge of antibiotics that largely do not act on acute cough and colds (227). Nevertheless, the results showed that educational strategies aimed at improving professional knowledge through training sessions or specific literature could have an undesired effect on pharmacists' intention to self-medicate. Some pharmacists explained this finding by saying that participating in trainings and receiving additional information about medicines, especially from medical representatives of drug companies, contributes to improving their professional skills and saves time because it removes the need to visit a doctor.

The most popular group of antibiotics used by the respondents was macrolides. In contrast, a study on the outpatient use of systemic antimicrobials in 24 different regions of Russia reported that in 23 regions (including Saint Petersburg), broad-spectrum penicillins were the most frequently used antimicrobials. It can be assumed that there is a significant difference in the outpatient consumption of systemic antimicrobials in different regions of Russia (228). In some regions, older agents with unfavourable safety profiles are widely administered, whereas in other regions, newer agents are used more frequently.

Diseases such as tuberculosis, gonorrhoea, malaria and childhood ear infections are now more difficult to treat than they were a few decades ago (229). High levels of resistance to ciprofloxacin, penicillin G, azithromycin, spectinomycin and carbapenems have been reported in Russia, as a potential result of the inappropriate use of antimicrobials (230, 50).

The widespread practice of self-medication in Russia is a result of the insufficient coverage of drug programmes and the existing problems with access to medical care. The absence of a medication reimbursement system, meaning medicines remain out-of-pocket payments, is another reason for self-medication (231), significantly affecting the prices of medicines and their availability to the public (232). In Russia, only predetermined categories of the population receive free medication within the ONLS (Population Drug

Coverage) and DLO (Extensive Drug Coverage) programmes. However, it is rather difficult for patients to obtain preferred prescriptions, as the procedure for issuing prescriptions is time-consuming and pharmacies have insufficient quantities of medicine (deficit, supply disruptions).

Limitations

This study is limited by the fact that the data were self-reported, and there is thus a possibility that the participants over-reported socially desirable behaviours or under-reported socially undesirable behaviours. There were no mechanisms that objectively assessed the honesty of the participants' answers to the survey questions. The absence of identifying data on the questionnaire sheets and the confidential nature of the study would tend to minimize this bias.

The role of pharmacists in encouraging the prudent use of antimicrobials is clearly vital. However, the practice of dispensing non-prescribed antibiotics continues to be widespread in some European countries (233-235).

4.4.5 Conclusion

Pharmacy employees must understand the rules, orders, and other relevant information on how to dispense antibiotics. However, most of these pharmacists do not follow these regulations. It is suggested that a well-planned, organized and structured educational programme for doctors and pharmacists should be implemented to improve the appropriate use of antibiotics.

5 Conclusion

The impetus for this study came from the convergence and expansion of previously conducted departmental research in Middle East countries and novel research in Eurasia region.

The first line of research analysed the practice of self-medication by the educated population of Saudi Arabia, Yemen and Uzbekistan, and with the specific focus on the pharmacists in the Russian Federation. We explored the approach of the intellectual strata of the population towards antibiotic use in the studied countries and healthcare professionals, such as pharmacists, who dispense the medicines and play an important role in providing population with the antibiotics without prescription.

The second line of research was to investigate self-medication with antibiotics as one of the possible factor associated with the delayed diagnosis and treatmen of TB in Uzbekistan, analyzing groups of patients with MDR-TB and HIV.

Both lines of research highlighted that the prevalence of self-medication with antibiotics in adult people in the studied countries is alarmingly high.

Over-the-counter availability of antibiotics plays a major role in the wide prevalence of self-medication among the population.

The general tendency is the population do not visit the physician and buy antibiotics after consulting with the pharmacist.

In the vast majority the population self-medicate for the conditions, such as viral infections, which are not required the use of antibiotics.

In many cases the course of antibiotics is not completed and antibiotics leftover from a previous treatment is kept for future use.

The overall level of awareness on antibiotics use among population of the studied countries is low.

Availability and uncontrolled use of antimicrobials such as fluoroquinolones might delay the timely diagnosis and initiation of anti- TB treatment. The study conducted in Uzbekistan confirmed that TB diagnostic and treatment delay was mainly contributed to by patient delay caused by insufficient knowledge of TB symptoms and by irrational use of antibiotics contributing to the emergence and spread of MDR TB resistant straints.

The study in Saint Petersburg, Russia confirmed that self-prescription of antibiotics is a common practice amongst pharmacists and also identified personal and professional characteristics of pharmacists strongly associated with self-medication.

We did not focus on how medicines policy applied in real live and the sensitivity of politicians to this.

We did not test knowledge and skills of the majority of healthcare workers, such as nurses, physicians and only partly pharmacists who can influence public behavior.

In order to prevent further emergence and spread of AMR the following is recommended:

Efforts should be made to minimise irrational use of antibiotics by supporting interventions to restrict over-the-counter availability of antibiotics.

Educational interventions involving health professionals and the public informing that irrational use of antibiotics leads to emergence and spread of AMR. Public health awareness intervention programs to be implemented on the use of antibiotics and can help reduce inappropriate use of antibiotics.

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Publications and presentations from this thesis

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Abstracts

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Appendix A

Supplementary material for Chapter 4.4

Questionnaire

Use of antibiotics by pharmacy employees

Dear colleague, please answer the following questions.

You can choose more than one option.

Mark your answers with an [X] or [V].

Q1.	When you're falling ill: You go to the doctor [ ] You self-medicate [ ]
Q2.	When you or one of your family members uses antibiotics, usually you buy it: 1. **According to a doctor's prescription:** Always [ ] Never [ ] Sometimes [ ] **2. Without a doctor's prescription**: According to your own knowledge [ ] According to your experiences with previous treatment [ ] According to analyses of the instructions with which customers come to the pharmacy [ ] According to a friend's advice [ ] According to the cost of the medicine [ ]
Q3.	Have you or one of you family member taken any antibiotic in the past 6 months: Yes [ ] How many times ______________________ No [ ] • If «Yes», what was the reason: Upper respiratory tract infection [ ] Lower respiratory tract infection [ ] Dental infection [ ] After surgery [ ] Gastrointestinal infection [ ] Gynaecological inflammation [ ] Bone and diarthrosis infection [ ] Skin and soft tissue infection [ ] Urogenital infection [ ] I have a chronic infectious disease [ ]

Q4.	Please name the antibiotics that you or a family member has taken in the past 6 months and **how many times:** ___________________________________
Q5.	Antibiotic use: I stop taking antibiotics when feeling better [ ] I take antibiotics as prescribed by the physician [ ] I take antibiotics as per their instructions for medical use [ ]
Q6.	You receive information about antibiotics through: Training sessions [ ] Relevant medical literature [ ] Patient information leaflet (PIL) [ ]
Q7.	You prefer: Oral form [ ] Injection form [ ]
Q8.	Are you aware of the unexpected side effects that can occur with antibiotic treatment: Yes [ ] No [ ]
Q9.	Which side effects did you experience during your antibiotic treatment: Diarrhoea [ ] Constipation [ ] Vomiting [ ] Nausea [ ] Dyspepsia [ ] Skin manifestations [ ] Myxedema [ ] Mucositis [ ] Asthenia [ ] Hyperhidrosis [ ] Tachycardia/bradycardia [ ] Blood pressure changes [ ] Other (please, name)___________________________ I did not have side effects [ ]
Q10.	Are you aware that antibiotics kill off normal microflora: Yes [ ] No [ ]
Q11.	Do you take any probiotics during/after AB treatment: Yes [ ] No [ ]
Q12.	Your attitude toward antibiotic therapy: Antibiotics are my first choice of medicine [ ] I take antibiotics only in extreme cases [ ] I am totally against antibiotics [ ]
Q13.	Gender： Male [ ] Female [ ]

Q14.	Your age: < 20 years [ ] 20-30 years [ ] 31-40 years [ ] 41-60 years [ ] > 60 years [ ]
Q15.	Your education: Higher pharmaceutical education [ ] Other higher [ ] Please state in which field ____________________ Vocational pharmaceutical degree [ ] Other vocational degree [ ] Please state in which field ____________________
Q16.	How long have you been working in the pharmacy: < 1 year [ ] 1-5 years [ ] 6-10 years [ ] > 10 years [ ]

Date ________ ___________ 20____
day month year

Place _________

Thank you for your participation!

Appendix B

Original publications

Original Article

Antibiotic use and knowledge in the community of Yemen, Saudi Arabia, and Uzbekistan

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Abstract

Introduction: Inappropriate use of antibiotics has resulted in a dramatic increase of antimicrobial resistance in developing countries. We examined knowledge, attitudes, and practices of antibiotic use in three Asian countries.
Methodology: A nationwide cross-sectional study of teachers in large cities of Yemen, Saudi Arabia, and Uzbekistan was conducted. A random sample of 1,200 teachers was selected in each country. Data were collected through a questionnaire-based survey and then analyzed using descriptive and multivariate statistical methods.
Results: The prevalence of non-prescription antibiotic use ranged from 48% in Saudi Arabia to 78% in Yemen and Uzbekistan. Pharmacies were the main source of non-prescribed antibiotics. The most common reasons for antibiotic use were cough (40%) and influenza (34%). Forty-nine percent of respondents discontinued antibiotics when they felt better. Although awareness of the dangers of antibiotic use correlated inversely with self-medication, understanding of the appropriate use of antibiotics was limited.
Conclusions: The prevalence of antibiotic self-medication in the educated adult population in the studied countries was found to be alarmingly high. Effective strategies involving regulatory enforcement prohibiting sales of antibiotics without prescription should be implemented along with educational interventions for health professionals and the public.

Key words: antibiotics; drug resistance; self–medication; developing countries

J Infect Dev Ctries 2014; 8(4):424-429. doi:10.3855/jidc.3866

(Received 11 June 2013 – Accepted 17 December 2013)

Introduction

Antimicrobial resistance is dramatically increasing worldwide in response to inappropriate antibiotic use [1]. Antimicrobial resistance to most common pathogens has reached alarming levels in developing countries, and trends show further increase. The main reasons for the increase of antimicrobial resistance include unregulated drug availability, inadequate antimicrobial drug quality assurance, inadequate surveillance, and widespread attitude to antimicrobial misuse, including self-medication [2]. It is estimated that approximately two-thirds of all oral antibiotics used worldwide are obtained without a prescription and are inappropriately used for diseases such as tuberculosis, malaria, pneumonia, and for mild childhood infections [3]. In less affluent countries, antibiotic consumption appears to be increasing steadily due to expanded population, rising incomes, and improved access to health care. In contrast with developed countries, where outpatient antimicrobials are largely restricted to prescription-only use, non-prescription access to antimicrobials is common in less affluent countries, resulting in uncontrolled use and self-medication [2,4,5].

Relatively few studies on antibiotic use in Western and Central Asian countries are available, and published data are scarce or absent. Here, we report on a study performed in Yemen, Saudi Arabia, and Uzbekistan on antibiotic use and knowledge in a sample of educated adults.

Methodology

Study design

A national population-based cross-sectional survey was designed and conducted during November 2012 in three countries of Western and Central Asia: Yemen, Saudi Arabia, and Uzbekistan. The study's participants were 400 general education teachers from each country. To perform multiple logistic regression analysis, the total sample size was determined at 1,200 study subjects, owing to the large number of studied variables. The selected cities were Ibb (Yemen), Najran (Saudi Arabia), and Tashkent (Uzbekistan). From the initial sample size of all secondary schools in each of the cities, 10 schools were selected using the probability proportional to size sampling technique. Forty teachers were then randomly selected from the list of employee names obtained from the school.

Respondents were interviewed based on the questionnaire developed in English by the project group of Charles University, Czech Republic. The questionnaire was pre-tested and translated into the local language of each country and then back-translated into English to validate the translation. An explanation of the purposes of the research and assurance of anonymity was provided to participants and verbal informed consent was obtained.

The questionnaire was administered to the respondents face-to-face by public health research assistants and consisted of three parts. Part one was designed to evaluate the recent use of antibiotics in the past three months, the source of the prescription, intent to use antibiotics without consulting a physician, reason for taking the antibiotic, and duration of use. Part two of the questionnaire assessed knowledge and attitudes towards antibiotics and storage of antibiotics at home. Part three included the demographic characteristics of the respondents such as sex, age, and highest degree obtained (BS, MS, or other).

Statistical analysis

All data were analyzed using PASW Statistics version 18. Descriptive results for the quantitative variables were evaluated according to mean ± standard deviation. Results regarding binary variables (sex, questions with yes/no answers) were applied with frequencies into percentages. Kendall's correlation was used to investigate association between ordinal variables.

Simple statistical analysis verifying the difference between countries in response to questions about the respondent's knowledge and attitude towards antibiotics was estimated using contingency tables and frequency comparison. A generalized linear model (Bernoulli distribution with logistic link function) was used for more complex dependence of issues on the summary of socio-demographic factors (gender, age, country of respondent) and their interactions. The level of statistical significance was set at $p < 0.05$.

Results

Four hundred residents in each state were approached for participation. All of them provided complete information. The demographic characteristics of the respondents are presented in Table 1. Most of the participants were females.

The prevalence rates of prescribed and non-prescribed use of antibiotics are presented separately for each country (Table 2). Among the respondents ever treated with antibiotics, 31% reported using prescribed antibiotics, while 69% reported non-prescribed use following the recommendation of a pharmacist or friend, their own initiative, or using a leftover prescription. The prevalence rates for taking antibiotics without a prescription were the highest in Yemen and Uzbekistan and lower in Saudi Arabia, where half of respondents preferred to use prescribed antibiotics. The main source of non-prescribed antibiotics in Yemen and Uzbekistan was pharmacies, followed by a high rate of using a previous prescription and administering alone in Saudi Arabia.

About 81% of respondents had used antibiotics in the previous three months. Cough, influenza, and gynecological inflammations were the most frequent reasons, followed by gastrointestinal infections and respiratory inflammations (Table 3). Treatment with antibiotics for cough symptoms and influenza tended to be the highest in Saudi Arabia and Yemen. In Uzbekistan, respiratory inflammations were reported as the main indications for antibiotics use.

Nearly 44% of respondents prescribed an antibiotic completed the course; however, half reported that they did not finish their last antibiotic course as prescribed because they felt better. Seven percent changed the antibiotic if did not make them feel better (Table 4).

Country, age, and teacher education were significantly associated with storage, attitudes, and knowledge of antibiotic use, while gender had no significant effect. The interaction with education can be explained by different teacher education levels among the studied states, where, along with an advanced and bachelor's degree, special secondary education is eligible for a teaching certificate.

V

Table 1. Demographic characteristics of respondents

Characteristics	Yemen No. respondents (%) (N = 400)	Saudi Arabia No. respondents (%) (N = 400)	Uzbekistan No. respondents (%) (N = 400)	Total No. respondents (%) (N = 1200)
Gender				
Male	161 (40.2)	64 (16.0)	186 (46.5)	411 (34.3)
Female	239 (59.8)	336 (84.0)	214 (53.5)	789 (65.8)
Age				
< 20	73 (18.3)	42 (10.5)	58 (14.5)	173 (14.4)
20-30	190 (47.5)	110 (27.5)	102 (25.5)	402 (33.5)
31-40	114 (28.5)	202 (50.5)	87 (21.8)	403 (33.6)
41-60	21 (5.3)	44 (11.0)	89 (22.3)	154 (12.8)
> 60	2 (0.5)	2 (0.5)	64 (16.0)	68 (5.7)
Education				
Master's/Ph.D.	15 (3.8)	42 (10.5)	169 (42.3)	226 (18.8)
Bachelor's degree	263 (65.8)	189 (47.3)	117 (29.3)	569 (47.4)
Secondary	122 (30.5)	169 (42.3)	114 (28.5)	405 (33.8)

Table 2. Source of antibiotics

	Yemen	Saudi Arabia	Uzbekistan	Total
	No. (%)	No. (%)	No. (%)	No. (%)
Prescribed	(N = 367)	(N = 353)	(N = 369)	(N = 1089)
By physician	80 (21.8)	182 (51.6)	80 (21.7)	342 (31.4)
	No. (%)	No. (%)	No. (%)	No. (%)
Non-prescribed	(N = 287)	(N = 171)	(N = 289)	(N = 747)
Pharmacist's advice	158 (55.1)	37 (21.6)	130 (45.0)	325 (43.5)
Friend's advice	21 (7.3)	33 (19.3)	53 (18.3)	107 (14.3)
Self	49 (17.1)	54 (31.6)	93 (32.2)	196 (26.2)
Old prescription	59 (20.6)	47 (27.5)	13 (4.5)	119 (15.9)

Table 3. Clinical indications for antibiotic use

Reasons	Yemen No. (%) (N = 304)	Saudi Arabia No. (%) (N = 334)	Uzbekistan No. (%) (N = 239)	Total No. (%) (N = 877)
Cough	125 (41.1)	175 (52.4)	53 (22.2)	353 (40.3)
Influenza	98 (32.2)	136 (40.7)	62 (25.9)	296 (33.8)
Respiratory inflammations	16 (5.3)	19 (5.7)	90 (37.7)	125 (14.3)
After surgery	14 (4.6)	3 (0.9)	14 (5.9)	31 (3.5)
Gastrointestinal	81 (26.6)	18 (5.4)	27 (11.3)	126 (14.4)
Gynecological inflammations	86 (28.3)	181 (54.2)	12 (5.0)	279 (31.8)
Orthopedic inflammations	21 (6.9)	10 (3.0)	17 (7.1)	48 (5.5)
Urinary inflammations	15 (4.9)	6 (1.8)	20 (8.4)	41 (4.7)
Ear infection	25 (8.2)	2 (0.6)	18 (7.5)	45 (5.1)
Other	-	1 (0.3)	23 (9.6)	24 (2.7)

Table 4. Self-reported principles of antibiotic use

Statement	Yemen No. (%) (N = 367)	Saudi Arabia No. (%) (N = 353)	Uzbekistan No. (%) (N = 369)	Total No. (%) (N = 1089)
I stop taking the antibiotic when I feel better	163 (44.4)	137 (38.8)	236 (64.0)	536 (49.2)
I change the antibiotic if do not feel better immediately	14 (3.8)	46 (13.0)	15 (4.1)	75 (6.9)
I take antibiotics as prescribed by my physician/pharmacist	190 (51.8)	170 (48.2)	118 (32.0)	478 (43.9)

Respondents from Yemen and Saudi Arabia that were more likely to self-medicate with antibiotics were younger women ($p = 0.010$) and those with a lower level of education ($p = 0.017$), whereas in Uzbekistan, age and education did not affect self-medication.

Almost 46% of respondents with higher preponderance in Saudi Arabia reported that they retain antibiotics at home regardless of the source. A significant relationship was found between storage and country and age ($p < 0.001$). Being younger and less educated in Yemen and Saudi Arabia was associated with keeping inventory at home. In contrast, older respondents in Uzbekistan reported appropriate storage of antibiotics.

Respondents' knowledge of antibiotic bacteria resistance were assessed; typically, knowledge was found to increase with age in all the studied countries ($p = 0.031$). Paradoxically, however, more educated respondents were less knowledgeable about bacteria resistance in Yemen. Similar results were obtained regarding the statement "awareness that antibiotics kill off the normal flora" (country *vs*. education $p < 0.001$). Respondents in Yemen with lower qualifications more frequently responded affirmatively than respondents with a degree level of education.

Respondents were less knowledgeable about the principles of prudent use of antibiotics, as 54% believed that it did not matter if the prescribed course of antibiotics was not completed. Poor level of knowledge was found in the younger generation of Yemeni and Saudi Arabian participants and among all age brackets in Uzbekistan ($p = 0.006$) with primary or lower educational levels ($p = 0.033$).

However, it is important to note that knowledge about allergies and adverse reactions associated with taking antibiotics were the highest when compared with other statements of knowledge. In fact, 57% of respondents expected adverse reactions. Strong knowledge was mostly found among respondents of older, well-educated age groups in all the studied countries ($p = 0.001$, $p < 0.001$ for country/age and country/education, respectively). Participants aware of adverse reactions associated with antibiotic use were more likely to have obtained antibiotics according to a physician's prescription ($p < 0.001$, $\tau = 0.110$).

Discussion

The present study demonstrated the high prevalence of self-medication and inappropriate use of antibiotics among well-educated populations of Yemen, Saudi Arabia, and Uzbekistan. Up to 70% of respondents administered unprescribed antibiotics and more than half of these unprescribed medications were inappropriate. Our findings contribute to the evidence of the growing tendency for self-medication among the general population in both developed and developing countries. Nonetheless, Asian estimates [6-10] are higher compared with those from studies conducted in Europe and the United States [11-16], with prevalence rates of self-medication ranging from 3% to 60%.

The reasons for self-administration of non-prescribed antibiotics are varied. Although poor regulation of antimicrobials resulting from policies not being enforced is the major factor influencing self-medication, it is not the only one accounting for this behavior [4,17]. Poverty, lack of access to health care, cultural beliefs, and practice of obtaining antimicrobials without prescriptions, particularly for viral respiratory infections, are other driving factors behind antibiotic self-medication in the community of participating countries.

Non-prescription use is frequently associated with very short courses and inappropriate drug and dose choices [18-26]. Extrapolating from the survey results, we estimate that every second respondent did not complete the course of antibiotic therapy, thereby promoting antibiotic resistance. Non-compliance was lower in Yemen and Saudi Arabia than in Uzbekistan. These findings correspond to other studies confirming that patients often do not adhere to their treatment. A patient survey in 11 countries across the world showed that 22.3% of patients who received antibiotic medication admitted to not finishing the therapy [27]. Moreover, patients may store antibiotics from uncompleted courses, even beyond the expiration date, and later self-administer these drugs for self-diagnosed conditions or dispense them to family members and friends [28-30].

Self-medication is associated with little guidance regarding appropriate antibiotic selection for individual syndromes and safe practices to minimize adverse drug effects even when provided by a pharmacist [21,31-33]. In our study, the majority of respondents who self-medicate identified a private pharmacy as the main source of medicine and information. The potential for adverse events is known. Generally, pharmacy staff did not inquire about patient's allergies, did not explain potential side effects, and dispensed contraindicated antimicrobials such as tetracyclines and fluoroquinolones or parenteral antimicrobials for home use. Other risks factors include masked diagnosis of infection disease, drug interactions, and superinfection [12]. Furthermore, financial concerns often guide selection of low-quality antibiotics and result in short durations of treatment [17].

Several studies, [32,34,35] already provided evidence of inappropriate antimicrobial use for the treatment of bacterial infections; our results are similar. The most common reasons for antibiotic use were colds and upper respiratory tract infections, where the cause is likely to be viral. For a condition to be considered a minor ailment and self-managed depended not only upon the severity, but on previous experience and knowledge as well [36]. The teachers who responded to this survey had less knowledge about appropriate antibiotic use than one would expect, considering their high literacy rate in comparison with other groups of these developing countries. We found a consistent direct link between irrational antibiotic use and lower educational levels. Younger, less educated women were most inclined to self-medicate and lacked knowledge about the dangers associated with antibiotic use. However, there was a very robust correlation between awareness of adverse reactions and antibiotic prescription. This correlation suggests that respondents who were apprehensive about antibiotic side effects did not attempt to self-medicate and consulted their physician. A possible explanation is that those respondents may have learned about the adverse impact of antibiotic use from their physician or pharmacist or from personal experience with antibiotic side effects. General education teachers may not be critical consumers of medicine research or may not have time to keep up with professional journals. However, they are primary transmitters of knowledge, and if their health behavior is inappropriate, it may have an effect on instilling health values and beliefs in children.

Our findings should be interpreted within the context of several limitations to our study. First, the sample was confined to nations' teachers, thereby limiting the generalizability of the results. A second significant limitation was the possibility of sample bias. The respondents were all from urban areas with higher socio-economic status and may not be representative of the rest of the countries. Future studies should be undertaken to investigate antibiotic use in rural regions. Third, the results are based on self-reported behavior, which may not represent actual behavior. Finally, the high male-to-female ratio found in this study is not a truly representative value for actual gender distribution in the population.

Our study confirms that the availability of non-prescription antibiotics leads to inappropriate self-medication in the communities of Yemen, Saudi Arabia, and Uzbekistan. There is great concern surrounding the development and spread of resistance resulting from poor knowledge about the dangers of self-medication and misuse of antibiotics. This study highlights the need to take decisive policy action to reduce non-prescribed antibiotic use. Measures may include restricting the dispensing of antibiotics to prescription only, enforcing supervision by regulatory authorities, and implementing effective public information campaigns to encourage appropriate use of antibiotics.

Acknowledgements

We would like to thank Ludmila Kagakova and Safia Abdulasis Alnoeman for their help with the questionnaire.
This project was supported by the grant of Charles University in Prague (SVV 267 005).

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Conflict of interests: No conflict of interests is declared.

Belkina et al. BMC Infectious Diseases 2014, 14:624
http://www.biomedcentral.com/1471-2334/14/624

BMC Infectious Diseases

RESEARCH ARTICLE | Open Access

Delay in the diagnosis and treatment of pulmonary tuberculosis in Uzbekistan: a cross-sectional study

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Abstract

Background: Early diagnosis and prompt effective therapy are crucial for the prevention of tuberculosis (TB) transmission, particularly in regions with high levels of multi-drug resistant TB. This study aimed to evaluate the extent of delay in diagnosis and treatment of TB in Uzbekistan and identify associated risk factors.

Methods: A cross-sectional study was performed on hospital patients with newly diagnosed TB. The time between the onset of respiratory symptoms and initiation of anti-TB treatment was assessed and delays were divided into patient, health system and total delays. Univariable and multivariable logistic regression analysis was used to evaluate determinants of diagnostic and treatment delay.

Results: Among 538 patients enrolled, the median delay from onset of symptoms until treatment with anti-TB drugs was 50 days. Analysis of the factors affecting health-seeking behaviour and timely treatment showed the presence of the patient factor. Self-medication was the first health-seeking action for 231 (43%) patients and proved to be a significant predictor of delay ($p = 0.005$), as well as coughing ($p = 0.009$), loss of weight ($p = 0.001$), and visiting private and primary healthcare facilities ($p = 0.03$ and $p = 0.02$, respectively).

Conclusion: TB diagnostic and treatment delay was mainly contributed to by patient delay and should be reduced through increasing public awareness of TB symptoms and improving public health-seeking behaviour for timely initiation of anti-TB treatment. Efforts should be made to minimise irrational use of antibiotics and support interventions to restrict over-the-counter availability of antibiotics.

Background

Tuberculosis (TB) is one of the oldest human diseases, yet it still cannot be defeated and remains second only to HIV as a leading cause of death from infectious diseases worldwide. In 2012, there were an estimated 8.6 million new TB cases and 1.3 million deaths [1]. The TB epidemic has been fuelled by a surge in HIV–TB co-infection and compounded by the growing emergence of multi- and extensively drug resistant (M/XDR) TB strains, with a high prevalence in the former Soviet Union countries, especially in Central Asia [2,3]. Uzbekistan is one of the four Central Asian states among the 27 identified by the World Health Organization (WHO) with the highest burden of multi-drug resistant TB (MDR-TB).

The highest MDR-TB incidence rate exists in North-western Karakalpakstan, where the immunity of the population has been undermined by the Aral Sea ecological catastrophe. Also cotton growing regions suffer particularly because the immunity of the local people has been adversely affected by unlimited application of pesticides [4].

Substantial gains have been made in reducing TB morbidity and mortality in the past decade. New directives have been approved, TB control programmes have been implemented to prevent transmission in the community, and a good-quality directly observed therapy short-course strategy (DOTS) has been expanded throughout the country with 100% regional coverage [5].

However, the current positive trend is insufficient to ensure stable and efficient control of TB. The TB surveillance and monitoring report in Europe and Central Asia yielded an estimated 14,787 incident cases of TB in Uzbekistan in 2012 [3]. There were an estimated 2,400

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(23%) new and 1,600 (62%) retreatment MDR-TB cases among notified TB patients [6]. In 2012, 1,728 MDR-TB cases were detected among patients with reported TB [6]. This is 43.2% of all estimated cases, indicating a low detection rate of MDR-TB. Given the substantial incidence of MDR-TB in Uzbekistan, delay in diagnosis increases the risk of onward transmission through untreated patients leading to aggravation of the situation in the region.

Delay in TB diagnosis and treatment has been studied internationally and several definitions of delay have been used, but frequently applied definitions are delay due to the patient or healthcare system. To the best of our knowledge, the possible delays in diagnosis and initiation of anti-TB treatment have not been extensively researched in Central Asia, and there are limited data from the high MDR-TB-endemic countries of the former Soviet Union.

This article reviews the extent of delay in diagnosis and treatment of TB and associated risk factors that might be tackled to promote early diagnosis and improve TB prevention.

Methods

Setting and study design

Between August 2013 and January 2014, we conducted a cross-sectional study among newly diagnosed pulmonary TB patients in two cities of Uzbekistan, Tashkent and Nukus. In Tashkent, the study was conducted at the Republican Specialized Scientific and Practical Medical Centre for Phthisiology and Pulmonology providing treatment to patients from across the country. In Nukus, the main city of the Autonomous Republic of Karakalpakstan, two hospitals and one dispensary were chosen as study settings.

Study population

We reviewed the TB Electronic Surveillance Case-based Management System (ESCM) database of all cases of culture-confirmed pulmonary TB registered in the selected facilities from August 2013 to January 2014. Paper-based inpatient and outpatient medical cards from adult patients (aged ≥15 years) were reviewed and all patients with newly diagnosed pulmonary TB were included in the study. We excluded those with recurrent TB.

The patients were interviewed using an adapted and slightly modified version of the WHO questionnaire developed for the assessment of TB diagnostic and treatment delay [7]. The questionnaire was pre-tested and administered by trained doctors and health workers. All interviews were performed in the Uzbek, Karakalpak or Russian language.

Verbally informed consent was obtained from patients prior to inclusion in the survey, and the study was approved by the Ethical Committee of Charles University in Prague, the Ministry of Health of the Republic of Karakalpakstan, and the Ethical Committee of the Republican Specialized Scientific and Practical Medical Centre for Phthisiology and Pulmonology.

Definitions

Patients were considered to have pulmonary TB on the basis of clinical, pathological and radiological findings confirmed bacteriologically and histologically. The time between onset of respiratory symptoms and initiation of anti-TB treatment was assessed and delays were divided into three types. Patient delay was measured in days from the first onset of any TB symptom (e.g., cough, fever, weight loss, or night sweats) until the first presentation to the healthcare system (not necessarily a TB facility). Patient delays were allowed to be negative, indicating the situation in which regular healthcare visits detected TB infection before onset of symptoms. Healthcare delay was measured as the number of days from first presentation to the healthcare system until the start of TB treatment. Total delay was calculated as patient delay plus healthcare delay (and thus may also take negative values). Comorbidity was defined as underlying cardiovascular, gastrointestinal, pulmonary, immunologic or malignant disease. Self-medication was defined as use of any medication not prescribed by a healthcare professional. Antibiotics and other medications are available at pharmacies in Uzbekistan over-the-counter and without a prescription.

Laboratory techniques

Analysis of sputum samples for smear microscopy, culture, drug-susceptibility testing (DST) and real-time PCR (Xpert MTB system) were conducted as per international guidelines [8-10] at the National Reference laboratory in Tashkent and at the Mycobacterial Laboratory in Nukus. Preliminary confirmation of acid-fast bacilli (AFBs) was performed using Ziehl–Neelsen staining while culturing was done using Lowenstein–Jensen medium. AFB strains were classified according to the WHO/International Union against Tuberculosis and Lung Disease scale: 1+ (10–99 AFBs per 100 fields), 2+ (1–10 AFBs per individual field), 3+ (10–100 AFBs per individual field), and 4+ (>100 AFBs per individual field) [11]. The BACTEC MGIT 960 system, based on the critical concentration method, was used for determining susceptibility to first-line drugs. DST for second line drugs was performed using the agar proportion method in Lowenstein–Jensen medium. Provider-initiated HIV testing is routinely recommended for all patients presenting with symptoms and signs of TB and TB diagnosed patients [12,13]. MDR-TB and HIV-associated TB sputum samples were analysed using real-time PCR Xpert MTB assay.

Data collection and analysis

The questionnaire included sociodemographic characteristics, risk factors of TB, comorbidity, and TB knowledge and attitudes. Follow-up data included history of TB treatment, such as a detailed description of diagnostic investigation process, first symptoms perceived by the patient, and health seeking actions. The patients were also asked to complete a number of questions measuring psychosocial aspects, for example, feeling ashamed about having TB, fear of social isolation and stigma. In addition, patient medical cards were reviewed for TB diagnostic information, such as date of diagnosis, date of treatment initiation, and laboratory results.

Univariable and multivariable logistic regression analysis was used to evaluate risk factors for patient, healthcare and total delays, which were dichotomised into delay versus non-delay. Following studies in comparable countries (e.g. Rabin et al. [14]), median delays were used as a cut-off. Variables included in the multivariable model were chosen according to the strategy of purposeful selection [15] based on behavioural and biological plausibility as well as statistical ($p \le 0.2$) criteria. The regression outcome was given by the estimated (adjusted) odds ratios and the corresponding 95% confidence intervals. Hypothesis tests for regression coefficients (Wald tests) were performed and expressed with p values at the significance level $\alpha = 0.05$. PASW statistical software was used for all analyses (IBM Corporation, Armonk, NY, USA, version 18.0).

Knowledge and stigma were measured using scoring systems. For stigma, the responses to the corresponding questions were marked on a five-point scale (1, strongly agree; 2, agree; 3, no opinion; 4, disagree; and 5, strongly disagree), with a low score corresponding to a high degree of stigma (except for the question "Do you feel you can talk to others about your TB" where the score was first reversed before addition to its domain). The mean percentage score for stigma was calculated as 100 times the sum of scores obtained divided by the maximum scores that could be obtained. This resulted in a Cronbach α value of 0.655 in cases for which all 10 stigma questions were answered (unmarried/single patients) and 0.621 in cases for which the last stigma question was unanswered. Knowledge was computed in a less straightforward way to reflect the different degrees of difficulty for the individual questions. For questions about knowledge, contagiosity and curability of TB, the wrong answer resulted in a score of 0 and the right answer in a score of 1, except for the question of whether TB is contagious, which received a score of 2. The right answer to the question about the means of transmission resulted in a score of 3, and all other answers resulted in a score of 1. For the question about common symptoms of pulmonary TB, the score was defined as the number of marked symptoms divided by six (the total number of displayed symptoms). This gave a Cronbach α value of 0.545 for the five knowledge-related items.

Results

Baseline patient characteristics

We assessed 600 newly diagnosed pulmonary TB cases that were confirmed bacteriologically. Fifty of these showed TB recurrence, and 12 patients refused to participate due to poor clinical conditions. The final sample comprised 538 patients, 243 from Karakalpakstan, 179 from Tashkent, and 116 representing all 12 provinces of Uzbekistan. The characteristics of these patients are summarised in Table 1. The mean age was 40 years and there was no significant gender difference in notified TB cases. The number of cases was, however, slightly higher in men than in women. The prevalence rate was highest in men aged 25–35 years. Of the 538 patients, 231 (42.9%) practiced self-medication or consulted pharmacists with the onset of respiratory symptoms and 124 patients (54.0%) self-treated with antibiotics. The proportion of MDR-TB among new TB cases was 41% and occurred predominantly in Karakalpakstan. No cases of XDR-TB were observed among our patients.

Patient delay

The median patient delay for all patients included in the study was 27 days [interquartile range (IQR), 6–62 days]. Delay was significantly longer in patients who abused alcohol, were HIV positive, and had specific TB symptoms of persistent cough and loss of weight (Table 2). Additionally, patients with positive sputum smear results and those who self-medicated, ordinarily with antibiotics, had longer diagnostic delay. The first healthcare provider consulted (pharmacies, private or district outpatient clinics, ambulance services) and time to reach the nearest health care facility or facility providing TB treatment were significantly associated with longer delay.

Health system delay

The median health system delay of 7 days (IQR, 1–32 days) seemed to be insignificant (Table 2). The health system delay was associated with younger age, unemployment, or labour migration, for those who had recently worked abroad ($p = 0.001$ and $p = 0.02$, respectively). Being a health care worker was a strong risk factor ($p = 0.01$) for health system delay, but could not be fully assessed since there were only eight (1.5%) healthcare workers and all of them had delayed diagnosis. Furthermore, patients who

Table 1 Characteristics of pulmonary tuberculosis patients in Uzbekistan, 2014 (n = 538)

Patient characteristics	MDR-TB (n = 243)		NON-MDR-TB (n = 295)	
	N	(%)	N	(%)
Gender				
Male	124	51.0	174	59.0
Female	119	49.0	121	41.0
M/F ratio	1.04		1.44	
Age (years)				
≤ 15-35	120	49.4	106	35.9
> 35	123	50.6	189	64.1
Education				
Illiterate	13	5.3	9	3.1
Primary-Secondary	206	84.8	237	80.3
University/higher	24	9.9	49	16.6
Occupation				
Employed	50	20.6	80	27.1
Healthcare worker	5	2.1	3	1.0
Unemployed	124	51.0	122	41.4
Student	7	2.9	9	3.1
Housewife	10	4.1	42	14.2
Retired	47	19.3	39	13.2
Labour migrant	27	11.1	27	9.2
Residence				
Urban	132	54.3	225	76.3
Suburban	12	5.0	41	13.9
Rural	99	40.7	29	9.8
Smoking				
Never	171	70.4	145	49.2
Current	-	-	24	8.1
Ex-smoking	72	29.6	126	42.7
Alcohol use				
Never	163	67.1	165	55.9
Past history	69	28.4	84	28.5
Moderate/Excessive	11	4.5	46	15.6
Injection drug use				
Yes	1	0.4	20	6.8
No	242	99.6	275	93.2
Comorbidities				
Diabetes mellitus	12	4.9	40	13.6
HIV positive	-	-	32	10.8
COPD/emphysema/bronchitis	42	17.3	27	9.1
Symptoms				
Cough	226	93.0	253	85.8
Fever	123	50.6	131	44.4
Loss of weight	191	78.6	191	64.7

Table 1 Characteristics of pulmonary tuberculosis patients in Uzbekistan, 2014 (n = 538) *(Continued)*

Sputum smear-for acid-fast bacilli				
Positive	117	48.1	166	56.3
Negative	126	51.9	129	43.7
Health facility first consulted				
Pharmacy	131	53.9	100	33.9
Private clinic	4	1.6	23	7.8
Primary health center/polyclinic	42	17.3	91	30.8
TB facility	52	21.4	48	16.3
Traditional remedy	2	0.8	2	0.7
Ambulance	7	2.9	9	3.1
Other (AIDS Centre, Public hospital)	5	2.1	22	7.4
Treatment before TB diagnosis				
Self-medicated	131	53.9	100	33.9
- Self-medicated with antibiotics	90	69.0	34	34.0
Prescribed antibiotics	55	22.6	114	38.6
Time taken to reach a TB health facility				
<1/2 hour	108	44.4	46	15.6
1/2-1 hour	58	23.9	111	37.6
≥ 1 hour	77	31.7	138	46.8

TB = tuberculosis, MDR-TB = multidrug-resistant tuberculosis, HIV = human immunodeficiency virus, COPD = chronic obstructive pulmonary disease, AIDS = acquired immune deficiency syndrome.

had longer health system delay also were HIV-positive, stigmatised by TB disease, and prescribed antimicrobials.

Total delay

The median total delay was nearly 2 months (50 days, IQR, 22–92 days), and 228 of 538 patients (42%) experienced a delay of ≥3 months. Patients with a cough, loss of weight, who self-medicated, were prescribed anti-TB medications by non-TB physicians, from distant location to healthcare facility, or facility providing TB treatment experienced longer delays in the diagnosis and treatment of TB.

Further multivariate analysis revealed that self-medication and initial consultation with a private facility predicted long patient delay, while administration of antimicrobial therapy as well as seeking care at private clinics were risk factors for health system delay (Table 3). Cough, self-medication, and private and primary healthcare facilities were associated with long total delay.

Untreated MDR-TB is highly contagious; therefore, we defined the extent of delay and evaluated risk factors among patients with and without MDR-TB. Among MDR-TB patients, there was a slightly longer median patient delay of 36 days, healthcare delay was 8 days, and total delay was 47 days. There were no differences

Table 2 Risk factors for three delay stages of pulmonary tuberculosis patients in Uzbekistan, 2014 (n = 538)

Predictors	N	Patient delay (median 27 days)		Health system delay (median 7 days)		Total delay (median 50 days)	
		Median	P value	Median	P value	Median	P value
Gender							
Male	298	30	0.08	6.5	0.56	49	0.8
Female	240	23.5	1	8	1	50.5	1
Age (years)							
≤ 15-35	226	25	0.3	5	0.01*	48	0.1
> 35	312	28	0.4	9	0.1	50	0.4
Education							
Illiterate	22	31	1	3	1	38.5	1
Primary-Secondary	443	25	0.5	7	0.2	50	0.6
University/higher	73	30	0.9	9	0.1	49	0.7
Occupation							
Employed	130	21	1	10	1	57	1
Healthcare worker	8	23	0.4	4	0.01*	27.5	0.8
Unemployed	246	30	0.2	5	0.001*	48	0.3
Student	16	17	0.2	14.5	0.9	36.5	0.4
Housewife	52	25	0.8	9	0.3	50	0.8
Retired	86	28	0.3	9	0.2	54	0.6
Labour migrant	54	34	0.9	7	0.02*	60.5	0.5
Residence							
Urban	357	25	1	7	1	49	1
Suburban	53	25	0.8	18	0.01*	56	0.2
Rural	128	30	0.1	4	0.1	50.5	0.9
Smoking							
Never	316	25	1	6	1	50	1
Current	24	42	0.2	8	0.2	48.5	0.9
Ex-smoking	198	29	0.3	8	0.2	49.5	0.7
Alcohol use							
Never	328	24	1	6	1	47	1
Past history	153	34	0.03*	7	0.1	54	0.1
Moderate/Excessive	57	21	0.03*	10	0.1	50	0.1
Injection drug use							
Yes	21	24	0.5	11	0.3	48	0.9
No	517	27	1	7	1	50	1
Comorbidities							
Diabetes mellitus	52	23	0.9	10	0.6	51.5	0.9
HIV positive	32	14.5	0.03*	19.5	0.02*	46.5	0.6
COPD	69	31	0.5	4	0.9	46	0.2
Symptoms							
Cough	479	29	0.008*	7	0.4	53	0.0001
Fever	254	29	0.3	7	0.8	53	0.2
Loss of weight	382	35	0.0001*	7	0.7	57	0.0001

Table 2 Risk factors for three delay stages of pulmonary tuberculosis patients in Uzbekistan, 2014 (n = 538) *(Continued)*

Sputum smear-for acid-fast bacilli							
Positive	283	31	0.008*	8	0.3	54	0.006*
Negative	255	21	1	6	1	44	1
Health facility first consulted							
Pharmacy	231	41	0.0001*	6	0.0001*	56	0.0001*
Private clinic	27	14	0.02*	36	0.004*	88	0.01*
Primary health center/polyclinic	133	12	0.0001*	16	0.0001*	41	0.004*
TB facility	100	25	1	3	1	33.5	1
Traditional remedy	4	14	0.1	5	0.4	28	0.03
Ambulance	16	16	0.006*	5.5	0.4	25.5	0.05
Other (AIDS Centre, Public hospital)	27	30	0.6	6	0.4	45	0.2
Treatment before TB diagnosis							
Self-medicated	231	41	1	6	1	56	1
Self-medicated with antibiotics	124	54.5	0.0001*	4	0.03*	62.5	0.0001*
Prescribed antibiotics	169	15	0.09	25	0.0001*	58	0.02*
Time taken to reach a TB health facility							
<1/2 hour	154	24	0.5	6	0.2	39	0.3
1/2-1 hour	169	26	0.4	8	0.4	55	0.4
≥ 1 hour	215	29	0.04*	7	0.6	51	0.04*

HIV = human immunodeficiency virus, COPD = chronic obstructive pulmonary disease, AIDS = acquired immune deficiency syndrome. * p <0.05.

between the two groups for predictors of diagnostic delay. However, high social stigma prevailed in patients with MDR-TB (odds ratio 1.39, 95% confidence interval 0.74–2.62).

Discussion

We found that the median total delay time from onset of symptoms until diagnosis and initiation of anti-TB treatment was 50 days and was mainly contributed to by patient delay of 27 days. The healthcare system delay of 7 days was significantly shorter than patient delay. These data are similar to the results of recent studies from Georgia and Ukraine [14,16].

Importantly, in our study, 79 of 228 cases with >2 months total delay had MDR-TB, for which early and accurate diagnosis is critical to timely initiation of effective treatment.

The main factors associated with total delay in a cohort of TB patients after adjusted multivariate analysis were self-medication, seeking initial care from a primary health facility or the private sector, and cough.

Almost half of the patients used unprescribed antimicrobials before diagnosis and treatment of TB. It is known that self-medication with antibiotics can delay and mask the correct diagnosis of infectious disease [17]. Several studies have reported that antibiotic exposure, in

Table 3 Multiple logistic regression analysis of risk factors for three delay stages of pulmonary tuberculosis patients in Uzbekistan, 2014 (n = 538)

Predictors	Patient delay; OR (95%CI)	Health system delay; OR (95%CI)	Total delay; OR (95%CI)
Cough	0.72 (0.38 to 1.39)	1.02 (0.53 to 1.96)	4.67 (1.23 to 17.1)*
Loss of weight	0.25 (0.16 to 0.4)*	1.04 (0.65 to 1.67)	0.42 (0.27 to 0.65)*
Sputum positive	0.60 (0.40 to 0.89)*	1.12 (0.73 to 1.69)	0.77 (0.52 to 1.13)
Self-medication	1.53 (1.01 to 2.33)*	0.91 (0.53 to 1.53)	1.58 (1.12 to 2.23)*
Self-medication with antibiotics	0.73 (0.40 to 1.31)	1.31 (0.69 to 2.45)	0.94 (0.53 to 1.68)
Prescribed antibiotics	N/A	2.19 (1.18 to 4.09)*	0.5 (0.31 to 0.81)
Primary health center/ Polyclinic	1.68 (0.49 to 5.63)	3.09 (0.61 to 15.74)	5.53 (1.29 to 23.72)*
Private clinic	2.96 (1.49 to 5.88)*	2.87 (1.83 to 4.54)*	4.67 (1.27 to 17.11)*

OR = odds ratio, CI = confidence interval, N/A = not applicable.
*p <0.05.

particular fluoroquinolones, can delay the diagnosis of TB and initiation of anti-TB treatment [18-20]. However, in our study, the contribution of the class of antibiotics was not investigated.

In addition, both first- and second-line anti-TB drugs are available without prescription, which encourages self-treatment and the uncontrolled use of these drugs may contribute to higher levels of resistance, with a consequent deleterious impact on treatment success [21,22]. Self-treatment only temporarily relieved the symptoms and resulted in exhaustion, weakness and the need for transportation by ambulance.

Importantly, care seeking from a primary health centre/ polyclinic was associated with a delay in diagnosis that might have been due to failure to comply with recommended diagnostic standards. Patients managed in primary health centres were repeatedly treated with antibiotics (including fluoroquinolones) for upper respiratory infection or presumed community-acquired pneumonia. Prolonged delay in diagnosis ranging from 1 to 12 months was seen in 8% of patients first approaching public polyclinics. Inadequate case detection at primary health care contributes to low treatment success rate and an extended period of disease transmission, particularly MDR-TB. Of particular concern were private physicians who were most often consulted first by patients living in distant places. As in some studies from developing countries [23,24], private physicians tend to deviate from recommended TB management guidelines and rely on chest radiography rather than referral of patients for sputum microscopy or monitoring treatment [25].

HIV infection was significantly associated with longer patient and health system delay. This was possibly because symptoms were less specific and might have been considered by the patients to be associated with HIV. Despite all HIV-infected patients being routinely screened for latent and active TB infection, the interpretation of test results might be complicated by a higher incidence of false-positive results (e.g., negative tuberculin skin test, negative sputum and normal chest x-ray findings), and lack of specificity of symptoms [26].

The reason that cough was associated with delayed TB diagnosis is not clear. It might be that patients considered it as a transient symptom from an upper respiratory illness, hence initiating self-treatment lasting until deterioration and manifestation of other specific symptoms. Furthermore, timely referral to healthcare facilities was challenging for work migrants due to limited access to health care, financial constraints, poor health literacy, and fear of deportation after positive TB diagnosis.

Although awareness and knowledge of TB were high in Karakalpakstan, the extent of total delay was similar across regions, yet patient delay was longer in Karakalpakstan, possibly due to greater stigmatisation, fear and belief in the incurability of the disease. Approximately 30% of those with diagnostic delay in Karakalpakstan had relatives and friends with MDR-TB or even experienced the death of a family member, and the feeling of hopelessness was overpowering. This is in line with the findings of Kuznetsov et al. [27], who described hopelessness as a basis for TB diagnostic delay in the Arkhangelsk region.

In agreement with previous studies on delay in TB diagnosis [28,29], we found that current smoking was associated with longer patient delay. This could be explained by the fact that some TB symptoms can be confused with other smoking-related conditions [30]. For example, chronic obstructive disease was found to be a comorbid condition in 14% of smokers diagnosed with TB and could mask the symptoms of TB, resulting in delayed TB diagnosis. Alcohol abuse was another risk factor for delayed TB diagnosis.

There were several limitations to our study. First, recall bias may have influenced our results, because the onset of first symptoms may have been inaccurately reported by the patients. In order to minimise patient recall bias, we encouraged physicians to check patient medical cards when completing the questionnaire. Second, a lack of information on the class of antibiotic used for self-medication, as well as that prescribed by the physician, meant that fluoroquinolone use may have been associated with delay in diagnosis of TB.

Although we investigated the risk factors associated with delayed diagnosis and treatment of TB, there are clinical consequences of late TB diagnosis. Further studies are required to assess morbidity, mortality, treatment success, outcome of previous antibiotic treatment, risk of transmission, and development of active TB associated with delay in initiation of treatment.

However, the significance of delay for treatment success remains unclear.

Conclusion

TB diagnostic and treatment delay should be reduced to the least possible time interval. There is a need to decrease TB stigma and promote public awareness of TB curability and the importance of early referral to health services. An essential step is to improve the diagnostic awareness among private and primary care practitioners. A high index of suspicion of TB should be maintained in public and private practitioners and an appropriate diagnostic work-up should be performed. Regulations prohibiting the dispensing of antibiotics, including anti-TB medicines, without prescription should be enforced to prevent further development of drug- resistance.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TB was a principle investigator responsible for design and conception of the study, data collection, and interpretation of data, and wrote the manuscript. DK, MT, ZT and MK participated in study design, coordination, and data collection and drafted the manuscript. JDT conducted statistical analysis and drafted the manuscript. JV participated in study design and coordination, and review of the manuscript. All the authors read and approved the final manuscript.

Acknowledgements

We are grateful to all physicians of the Republican Specialized Scientific and Practical Medical Centre for Phthisiology and Pulmonology in Tashkent and the Republican tuberculosis dispensary and tuberculosis hospitals #2,3 of the Republic of Karakalpakstan for their assistance with data collection.
We thank Richard Cameron Lewis for editing assistance.
This project was supported by the grant of Charles University in Prague (SVV 260 066).

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Received: 19 June 2014 Accepted: 10 November 2014
Published online: 25 November 2014

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doi:10.1186/s12879-014-0624-y
Cite this article as: Belkina *et al.*: **Delay in the diagnosis and treatment of pulmonary tuberculosis in Uzbekistan: a cross-sectional study.** *BMC Infectious Diseases* 2014 **14**:624.

Int J Clin Pharm
DOI 10.1007/s11096-016-0362-x

RESEARCH ARTICLE

Knowledge, awareness, and attitudes toward antibiotic use and antimicrobial resistance among Saudi population

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Received: 18 February 2016 / Accepted: 22 July 2016

Abstract *Background* Inappropriate use of antibiotics is a public health problem of great concern. *Objective* To evaluate knowledge of antibiotics, race, gender and age as independent risk factors for self-medication. *Setting* Residents and population from different regions of Saudi Arabia. *Methods* We conducted a cross sectional survey study among residents. Data were collected between June 2014 to May, 2015 from 1310 participants and data were recorded anonymously. The questionnaire was randomly distributed by interview of participants and included sociodemographic characteristics, antibiotics knowledge, attitudes and behavior with respect to antibiotics usage. *Main outcome measure* Population aggregate scores on questions and data were analyzed using univariate logistic regression to evaluate the influence of variables on self-prescription of antibiotics. *Results* The response rate was 87.7 %. A cumulative 63.6 % of participants reported to have purchased antibiotics without a prescription from pharmacies; 71.1 % reported that they did not finish the antibiotic course as they felt better. The availability of antibiotics without prescription was found to be positively associated with self-medication (OR 0.238, 95 % CI 0.17–0.33). Of those who used prescribed or non-prescribed antibiotics, 44.7 % reported that they kept left-over antibiotics from the incomplete course of treatment for future need. Interestingly, 62 % of respondents who used drugs without prescription agreed with the statement that antibiotics should be access-controlled prescribed by a physician. We also found significant association between storage, knowledge/attitudes and education. *Conclusions* The overall level of awareness on antibiotics use among

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Published online: 29 August 2016

residents in Saudi Arabia is low. This mandates public health awareness intervention programs to be implemented on the use of antibiotics.

Keywords Antibiotics · Awareness · Inappropriate use · Resistance · Risk factors · Saudi Arabia · Self-medication

Impacts on practice

- Residents in Saudi Arabia show low level of awareness on the use of antibiotics and antimicrobial resistance.
- There is an urgent need for public health intervention programs to increase the awareness on use and knowledge towards antimicrobial resistance in Saudi Arabia.
- It must be possible to implement strict legislatures on the dispensing of antibiotics without prescription in Saudi Arabia because Saudi patients who used an antibiotic without prescription agreed with the statement that antibiotics should be access-controlled drugs prescribed by a physician.

Introduction

Antibiotics have been potential sources of life-saving and protection against infectious diseases, but they are hampered by the propensity of bacteria to rapidly develop resistance, which often results in failure of therapy. Antimicrobial resistance represents a current and ongoing threat to human and animals [1, 2]. Both appropriate and inappropriate antibiotic use drive antimicrobial resistance [3, 4]. Inappropriate use of antimicrobial agents and the consequences of spread of antimicrobial resistance is an ever existing public health problem of great concern. In recent years, resistance to antimicrobial agents that were previously effective has emerged or re-emerged in many geographical regions causing global health threat and huge economic impacts that involve humans, livestock, and wildlife. In the United States, it is estimated that two million people become infected with antimicrobial resistant pathogens, and there are twenty thousand antimicrobial resistant related deaths annually [5].

Antimicrobial resistance is a global public health concern. Antibiotic resistance is one of the biggest threats to human health nowadays. In the latest available Saudi census [6], Saudi nationals comprised around 68.9 % of the total population (27.1 million) and the expatriate (non-Saudi) population accounted for 31.1 % of the total population of Saudi Arabia. The non-Saudi population has distinct racial, socioeconomic, and demographic characteristics; accordingly, the received healthcare, response to therapy, and clinical outcomes may differ in this population compared to the population of Saudi nationals. Furthermore, Saudi Arabia is a multi-population country involving a unique and dynamic influx of expatriate workers from numerous countries, and tourists all over the year [7, 8]. Non-prescription dispensing of antibiotics remains a public health issue in Saudi Arabian community raising an increasing concern on its contribution to the spread of antimicrobial resistant pathogens and the emergence of antimicrobial resistance [9–12].

More importantly, the country is the focus of pilgrimage for Muslims from all over the globe for the hajj practice where more than a million of pilgrims gather annually for at least one-month stay in Mecca. In addition, pilgrims visit Mecca all year round for practicing Umrah and some of them can stay up to 3 months in Mecca and may visit other key religious cities and sites. Altogether, this creates a critical public health issue due to extreme congestion of people and may facilitate the occurrence and global spread of several infectious diseases of bacterial, viral, and parasitic infections specifically if the existing infection control and healthcare systems are not well-prepared or experienced [7, 13]. These factors may drive a need to use antibiotics, often inappropriately. The only existing public health contingency plan for hajj focuses on vaccination against infectious diseases. The ongoing uncontrolled use of antibiotics together with the traffic of people through Saudi Arabia during these circumstances have the potential to contribute to national as well as global spread of resistant infectious agents.

Access to antibiotics is uncontrolled among the Saudi population and it is not prescription restricted. Antibiotic agents are available and accessible to the public and can be bought over the counter. There may be silent unreported outbreaks in Saudi hospitals and in healthcare settings. There is no national surveillance system on antimicrobial resistance and healthcare acquired infections. This free access to antibiotics changes the context for antibiotic related interventions in Saudi Arabia. Data on the awareness, among patients and the public, about antibiotic resistance revealed that antimicrobial resistance is an escalating serious concern [10]. There are few reports in literature on the use of antibiotics among the population in Saudi Arabia.

Aim of the study

The aim of this study was to assess the knowledge and behaviours of Saudi individuals towards antibiotics use and self-medication.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The research protocol of the present study was approved by the Institutional Review Board and Future Scientists Program Committee and faculty of Public Health, Jazan University, Saudi Arabia.

Methods

Study population

A cross sectional epidemiological study using survey design was carried out from June 2014 to May, 2015. The inclusion criteria were that participants had to be Saudi nationals and legal resident non-Saudi nationals. All participants had to be older than 18 years and had to have volunteered to participate in the survey. All participants were asked to give a written consent. To avoid double-counting of participants, each participant provided a unique national identification number. The identity of participants was anonymized through the process of data analysis.

Questionnaire

The questionnaire was developed according to scientific literature and the antimicrobial resistance report by the World Health Organization [14, 15] and the questionnaire was presented in written form in Arabic or English by the team. The completed questionnaires were then analyzed. The questionnaire included socio-demographic characteristics, antibiotics knowledge, attitudes and behavior as predictors for antibiotics usage. The questionnaire was conducted among the public in Southwestern region of Kingdom of Saudi Arabia as well as randomly selected participants from other regions of the kingdom. The questionnaire was distributed by random in person interview of participants in public areas, clinics, hospitals, houses, and universities.

Analysis

Data were recorded anonymously in a Microsoft excel database and transferred to PASW statistical software (IBM Corporation, Armonk, NY, USA, version 18.0), which was used for all analyses. The dependent variable, self-prescription of a respondent, was defined as prescription by anyone else than a physician (including pharmacists, nurses, friends, etc.). Univariate logistic regression analysis was used to evaluate the influence of independent variables on self-prescription of antibiotics. The regression outcome of self-prescription was given by the estimated odds ratios and the corresponding 95 % confidence intervals. Hypothesis tests for regression coefficients (Wald-tests) were performed and expressed with p values at the significance level $\alpha = 0.05$. Knowledge was measured using a scoring system. There were four questions on basic knowledge, namely (1) What is an antibiotic? (2) What is a prescription? (3) Can antibiotics be used for all types of infections including viral, bacterial, and fungal origin? (4) Are antibiotics used to treat viral infections? Three other questions were more specialized, namely (1) Do you know what antimicrobial susceptibility testing is? (2) Have you heard of the term antimicrobial resistance before? (3) Do you know what antimicrobial resistance is? The variable total knowledge was computed in a way to reflect the different degrees of difficulty for the individual questions. For the four basic questions, the wrong answer resulted in a score of 0, the right answer in a score of 1, and answer "do not know" in a score of 1/3. Responses in the three specialized questions resulted in a score of 1 for the answer "yes", and a score of 0 for the answer "no". The value of the final variable total knowledge was defined as the sum of the scores of all seven knowledge questions. This gave a Cronbach α—value of 0.537. The association of demographic characteristics with a number of chosen variables was investigated using Pearson's Chi square tests.

Results

Of the 1310 questionnaires that were distributed, 161 were returned as uncompleted and 1149 were returned as completed. The response rate was 87.7 %. The socio- demographic characteristics of the study population are shown in Table 1. Among respondents, 41 % were males, and most of respondents were educated except for 6.6 % were illiterate, and respondents represented different residents from different regions in Saudi Arabia shown in Fig. 1. The mean age of participants was 26.8 (SD 8.8). The majority of respondents were female (59.0 %) and Saudi nationals (90.7 %).

Further, 71 % of the respondents reported that they had used an antibiotic in the last 6 months. About 63.6 % of participants reported that they had purchased antibiotics without a prescription from pharmacies; 71.1 % reported they did not finish the antibiotic course as they felt better. Of those who used prescribed or non-prescribed antibiotics, 44.7 % reported that they kept left-over antibiotics from the incomplete course of treatment for future need.

Interestingly, 62 % of respondents who used antibiotics without prescription agreed with the statement that antibiotics should be access-controlled drugs prescribed by a physician.

Amoxicillin and its combination with clavulanate was the most commonly requested antibiotic and was dispensed

Table 1 Socio-demographic characteristics of study population

Characteristics	No. respondents (N = 1149)	%
Gender		
Male	471	41.0
Female	678	59.0
Age		
18–39	1006	87.6
>40	143	12.4
Marital status		
Single	608	52.9
Married	526	45.8
Divorced	11	1.0
Widowed	4	0.3
Education		
Higher education	606	52.7
Intermediate	428	37.3
Elementary	39	3.4
Illiterate	76	6.6
Nationality		
Saudi	1042	90.7
Other	107	9.3

in 29.2 % of cases. We found that 18.2 % of participants self-medicated with antibiotics for respiratory diseases (Fig. 1).

Logistic regression analysis examining the predictors of self-medication with antibiotics was conducted and presented in Table 2. We identified that female respondents were less likely to self-medicate with antibiotics than males (OR 0.635, 95 % CI 0.49–0.82) and Saudi nationals were less likely to self-medicate with antibiotics than representatives of other nationalities (OR 1.8, 95 % CI 1.2–2.69). The association between self-medication and gender was not confirmed by a confounding effect of education, despite the fact that women were less educated than men. The availability of antibiotics without prescription was positively associated with self-prescription (OR 0.238, 95 % CI 0.17–0.33). In addition, using a non-professional source of health-related information about antimicrobial resistance (like internet) was positively associated with taking antibiotics without prescription (OR 1.575, 95 % CI 1.2–2.07).

The following independent variables were also positively associated with self-medication: taking antibiotics following pharmacist's advice without physician referral (OR 0.241, 95 % CI 0.16–0.35), keeping left-overs (OR 0.412, 95 % CI 0.31–0.55), and incomplete course of antibiotic treatment (OR 1.932, 95 % CI 1.42–2.64). The following predictors were negatively associated with self-medication: using for the treatment of acute upper respiratory infections (OR 0.242, 95 % CI 0.125–0.469), and total knowledge (OR 0.917, 95 % CI 0.85–0.99).

The results of the relationship between individual's socio-demographic characteristics and storage of antibiotics, attitudes toward and knowledge of the antibiotic use were shown in Table 3.

Nationality had no significant effect on each of the statements as most of respondents were Saudis. There was no association found with marital status. Gender, age and education were significantly associated with knowledge of antimicrobial resistance. We also found significant interactions between storage, knowledge/attitudes and education.

Figure 2 shows the frequency of diseases which antibiotics were used for by the respondents. In addition, 1.04 % of female respondents in the present study reported to self-medicate with antibiotics when they experience menstrual cycle and its associated symptoms such as headache, colic and vaginal pain.

Discussion

There are many drivers for the emergence of antimicrobial resistance among pathogens. Inappropriate use of antibiotics constitutes a growing global public health concern. Increasingly, there are reports of outbreaks caused by bacterial strains that have acquired multiple mechanisms of antimicrobial drug resistance [16, 17]. The unnecessary widespread and imprudent use of antibiotics in humans and in agriculture plays an inevitable role in the increasing problem of antimicrobial resistance in both developing and developed countries [18, 19]. In the present study, a high participation rate of 87.7 % is a major strength. The present study found significant interactions between storage, knowledge/attitudes and education. A significant finding of the present study is that the overall level of awareness on the use of antibiotics and education on antibiotic resistance among residents in Saudi Arabia were found to be low. The study targeted populations including Saudi nationals as well as non-Saudi residents who come from various parts of the world. The overwhelming respondents of Saudi nationals were an objective to mainly target Saudi nationals and it is related to the cultural effects as a risk factor for the non-prescription and increased use of antibiotics.

It was found that 63.6 % of participants reported to have purchased antibiotics from pharmacies without a prescription from the physician. This may be explained by the fact that although many policies exist to regulate antibiotic use but enforcement, education on antibiotic use and antimicrobial resistance are insufficient or lacking. Results of the present study are alarming and we hypothesized that if access to antibiotics among Saudi population is controlled, it should reduce the irrational use of antibiotics and consequently will contribute to the reduction of the associated antimicrobial resistance threat.

In the present study use of internet as a nonprofessional indiscriminate drug use and source for prescription of antibiotics was positively associated with taking antibiotics without prescription (OR 1.575, 95 % CI 1.2–2.07) similar to other studies where it was reported that internet is a source of medicines and antibiotic abuses [20, 21]. In the present study, it was found that the majority of respondents were female (59.0 %) which could be attributed to that females are more likely to self-medicate with antibiotics because they might use these antibiotics to treat respiratory tract symptoms among their children as shown Fig. 2. Self-medication contributed to the excessive use of antibiotics as was previously reported [22, 23].

The findings of the present study demonstrate the community antibiotic medications overuse, which may contribute to increase antibiotic resistance. It has been previously reported that antibiotic overuse contribute to the increased antimicrobial resistance as well as emergence of resistant bacterial strains [24]. Consequently, the findings of the present study suggest that the community antibiotic medications overuse may contribute to increase antibiotic resistance in Saudi Arabia and the spread of multidrug resistant bacteria.

Our results are similar to another study performed in Saudi Arabia [15] which confirmed that 48 % of participants reported using antibiotics without consulting a physician. In addition, reports from neighboring countries including Iraq, Egypt, Jordan, Palestine, as well as other parts of the globe showed the imprudent, overuse and self-medication with antibiotics [23, 25–31].

Fig. 1 Study site locations in Saudi Arabia. Residents from different provinces including Makkah Al Mokaramah, Al Madinah Al Munawarah, Jeddah, Taif, Riyadh, Al Baha, Jazan, Bisha, Najran, Abha, Tabuk, Sakaka, Hail, Buraydah, Al Hofuf, and Dammam were included in the study. Non Saudi residents included nationals from Algeria, Bahrain, Egypt, Iraq, Jordan, Kuwait, Lebanon, Morocco, Oman, Palestine, Sudan, Syria, United Arab Emirates and Yemen. Figure was reproduced from World fact book available at https://www.cia.gov/library/publications/the-world-factbook/docs/refmaps.html

Table 2 Predictors associated with self-prescription (Logistic regression models)

Independent variable		Dependent variable (self-prescription)			
Predictor	Possible values	*p* value (Wald-test)	Odds ratio	95 % CI	
Nationality	Saudi-Arabian* or not	**0.004**	1.799	1.202	2.693
Age	Natural numbers	0.727	1.002	0.989	1.016
Gender	Male* or female	**<0.001**	0.635	0.493	0.819
When did you last use an antibiotic?	<6 months ago, between 6 and 12 months ago, more than a year ago*	For "between 6 and 12 months ago": **0.011**	0.073	0.010	0.555
When do you usually use the antibiotic?	19 types of diseases	For "Acute respiratory infections": **<0.001**	0.242	0.125	0.469
Do you agree that antibiotics are accessed without a prescription?	Yes* or no	0.946	1.011	0.741	1.378
Have you purchased antibiotics from the pharmacy without a prescription?	Yes* or no	**<0.001**	0.238	0.174	0.326
Do you accept to use an antibiotic directly from the pharmacist without physician referral?	Yes* or no	**<0.001**	0.241	0.164	0.352
Do you agree that antibiotics become access-controlled drugs only by physician?	Yes* or no	**<0.001**	2.125	1.612	2.802
Do you keep the antibiotic for future use?	Yes* or no	**<0.001**	0.412	0.309	0.549
Do you follow antibiotic course as prescribed?	Yes or no*	**<0.001**	1.932	1.417	2.636
Do you agree to administer the antibiotic when prescribed to you?	Yes* or no	0.525	1.128	0.778	1.636
Do you change the prescribed antibiotic by a pharmacist help?	Yes* or no	0.497	0.898	0.658	1.225
Before using antibiotic. were you asked to do antimicrobial susceptibility testing?	Yes* or no	**0.004**	1.455	1.125	1.882
Do you request antibiotic prescription change by aid of pharmacist?	Yes* or no	**0.011**	0.713	0.550	0.924
Source of health-related information	Professional* or non-professional	**0.001**	1.575	1.201	2.066
Total knowledge	Scoring system	**0.028**	0.917	0.849	0.991

Reference groups of the independent variable are marked with *

Significant values when $p < 0.05$ were shown in bold

Table 3 Association of demographic characteristics with knowledge, attitudes and behavior statements (Chi square tests)

Statement	No. (%) respondents (N = 1149)	*p* value			
		Nationality	Gender	Age	Education
Inventory of antibiotics at home	515 (44.8)	0.445	**0.03**	0.561	**0.03**
Knowledge of antibiotic resistance	550 (47.9)	0.88	**<0.001**	**0.029**	**<0.001**
Completing a course of antibiotics As prescribed	451 (39.3)	0.445	0.724	0.70	**<0.001**
Awareness that antibiotics are used to treat viral infections	553 (48.1)	0.16	0.19	0.295	**<0.001**

Significant values when $p < 0.05$ were shown in bold

Conclusion

The findings of the present study clearly highlight the need for better implementation of antibiotic stewardship, legislation of antibiotic use and a need for surveillance programs on antimicrobial prescription and resistance in hospitals and primary care settings in Saudi Arabia. Future effective enforcement of legislations regarding antibiotic access in community in Saudi Arabia should be advocated and will help change the driving factors for purchasers.

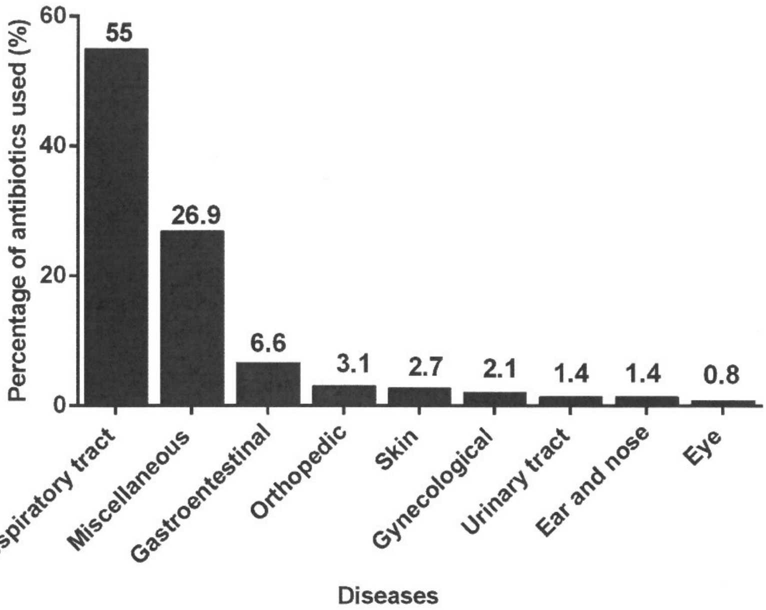

Fig. 2 Percentage of antibiotics used for different diseases among study population (n = 1149)

In addition, optimizing antibiotic use should also be achieved by changing patient and clinician behaviors in the community and hospitals. We have found unrestricted overuse of other classes of medications that require further attention including nonsteroidal anti-inflammatory drugs, acetaminophen, and antiviral agents among participants. More importantly, outpatient prescription practices in health centers, primary care settings, and hospitals require investigation to guard against the overuse of antibiotic medications among population in Saudi Arabia. Among the proposed methods that will help track antibiotic prescription in communities is an antibiotic prescription data records and network to monitor all dispensed antibiotics in pharmacies and hospitals. In conclusion, results of the present study recommend that public health awareness intervention programs on the use of antibiotics should be implemented. In addition, health care decision makers should implement policies on access, use and prescription of antibiotics and to further limit and control the access to antibiotics. This will eventually reduce the increasing level of resistance and will help alleviate the ever increasing antimicrobial resistance crisis.

Acknowledgments We are indebted to participants for providing their time and information. Authors would like to thank Deanship for Scientific Research, Jazan University, KSA. The present project was conducted and supervised by Prof. Dr Mohamed Ezzat El Zowalaty as part of the JU Future Scientists program's II projects. This project was supported in parts by the Grant of Charles University in Prague (SVV 260,187) for statistical analysis. The sponsors of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study. MEZ conceived and designed the study; SD, MAG, FAM, NIN, RK, RS, KD, MK, SH, BM, AG, RH, JZ, AWA, AAA performed the experiments; MEZ, TB, JDT analyzed the data; JV contributed analysis tools; MEZ and AEZ statistics analysis, MEZ wrote the paper, MEZ and TB revised it at all stages of publication, HAA, SB, AK, TB, AN, AEZ, MEZ revised the manuscript.

Funding The funding sponsors had no role in the design of the study; collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

Conflicts of interest Prof Dr Mohamed Ezzat El Zowalaty is listed as a member and champion of "Antibiotic Action" an independent UK-led global initiative wholly funded by the British Society for Antimicrobial Chemotherapy (BSAC). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Belkina *et al. BMC Pharmacology and Toxicology* (2017) 18:11
DOI 10.1186/s40360-017-0116-y

BMC Pharmacology and Toxicology

RESEARCH ARTICLE Open Access

Antibiotic use practices of pharmacy staff: a cross-sectional study in Saint Petersburg, the Russian Federation

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Abstract

Background: Non-prescription access to antimicrobials is common, and self-prescribing is increasingly popular in Russian society. The aim of this study was to assess the attitudes of community pharmacists regarding antibiotic use and self-medication.

Methods: We conducted a cross-sectional study from September-December 2015 of community pharmacists in the Saint-Petersburg and Leningrad region, Russia. A self-administered questionnaire was used to assess antibiotic use and self-medication practices. The data were analysed using logistic regression and Pearson chi-squared tests.

Results: Of the 316 pharmacists (77.07%) who completed the questionnaire, 230 (72.8%) self-medicated with antibiotics. Antibiotics were mostly used to self-treat upper (53.3%) and lower respiratory tract infections (19.3%), relying on their own knowledge (81.5%), previous treatment experience (49%) and patients' prescriptions (17%). The most commonly used antibiotics were macrolides (33.2%). Characteristics such as age, education and experience were related to antibiotic use and self-medication.

Conclusions: The study confirmed that self-prescription of antibiotics is a common practice amongst pharmacists in Saint Petersburg and also identified personal and professional characteristics of pharmacists strongly associated with self-medication.

Keywords: Antibiotic use, Pharmacists, Antimicrobial resistance

Background

In the past decade, the worldwide consumption of antibiotic drugs has increased substantially. Russia, along with Brazil, India, China, and South Africa, accounts for 76% of the overall increase in the global consumption of antibiotics [1]. Non-prescription access to antimicrobials, including antituberculosis drugs, is common, and self-prescribing has become increasingly popular in Russian society [2]. Conditions that require prescriptions for the dispensation of antibiotics are not explicitly defined in the legislation of the Russian Federation. This leads to arbitrary attitudes toward antibiotics among health professionals, especially pharmacists, whose primary role in dispensing over-the-counter antibiotics offsets with imperfect enforcement. Moreover, in an environment with a relatively low level of public trust in physicians and the lack of formal need for a doctor's office visit, pharmacists have become the main alternative for patients not only in providing proper counselling but in functioning as a substitute for physicians in antibiotic selection, the administration of antibiotic regimens and the course of therapy [3].

The purpose of this article is to explore pharmacists' approach to antibiotic treatment, including antibiotic choice, and to assess their knowledge of and attitudes toward antimicrobial resistance to define ways to prevent the practice of dispensation without prescriptions.

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Methods

Study setting and population

The study was conducted from September-December 2015 in community pharmacies in the Saint Petersburg and Leningrad region, Russia. The sample comprised 63 pharmacies and 316 pharmacists from one of the largest pharmacy chains.

Measures

A self-administered questionnaire was adapted from a previous study conducted by our research group [4]. The questionnaire included close-ended (yes/no, single choice and multiple choice) and open-ended questions (an English translation is available in Additional file 1). Denoting the sixteen questions from Q1 to Q16, they can be grouped into the following categories: attitudes and behaviours towards antibiotic use and self-medication (Q1, Q2, Q3, Q7, Q11, Q12); information on the types of involved diseases, antibiotics and side effects (Q3 partially, Q4, Q9); knowledge of antibiotic use and resistance and source of antibiotic knowledge (Q5, Q6, Q8, Q10); and personal and professional information (Q13 – Q16).

Statistical analysis

To evaluate the influence of attitudes, behaviour, knowledge and demographics on self-medication with antibiotics, univariate logistic regression analyses were performed. Self-medication occurred when the respondents indicated that they purchased antibiotics for themselves (or their children) without a physician's prescription but based on their own knowledge or on recommendations of friends (see part two of Q2). This defined the dichotomous dependent variable. The independent variables were, respectively, the outcomes of questions Q1, Q3, Q5, Q6, Q11, Q12, Q13, Q14, Q15 and Q16. We did not include variables related to information on the types of involved diseases, antibiotics and side effects (Q3, Q4, Q9), as they contained too many outcomes, and we also did not include variables with essentially only one outcome (Q8, Q10, Q13). For most of the included questions, all respondents provided answers; however, questions Q14 to Q16 had a percentage of missing values of 0.3% (1 answer) each, and Q7 was missing 3.2% (10 answers). In a few cases, multiple answers to the same question were provided; the highest score (e.g., highest education, highest age, best knowledge) was then used for the regression analysis. For question Q6, however, there were too many multiple answers to address using this approach. Therefore, Q6 was divided into three separate dichotomous variables with outcomes yes or no: Q6a, Q6b and Q6c.

The results of the regression models were presented as the estimated odds ratios and the corresponding 95% confidence intervals. Hypothesis tests for regression coefficients (Wald tests) were performed and expressed with p values at a significance level of $\alpha = 0.05$.

We also tested for associations between demographic characteristics (Q14 – Q16) and the remaining independent variables. We used Pearson chi-squared tests with p values at a significance level of $\alpha = 0.05$. To avoid low expectation counts, the outcomes of Q14 – Q16 were recategorized (in clear ways) into two groups. PASW statistical software was used for all analyses (IBM Corporation, Armonk, NY, USA, version 18.0).

Results

Of the 410 questionnaires distributed, 316 (77.07%) were completed and collected.

The main demographic characteristics of the respondents are summarized in 1. The sample was predominantly female, which is rather typical for Russian pharmacies. The mean age of the respondents was 39.3 years, and almost half of them were 41-60 years. The vast majority of pharmacists had a baccalaureate degree, and nearly half of them had 10 years of experience of working in a pharmacy. Table 1 shows that slightly more than two-thirds of the pharmacists self-medicated.

Other characteristics of the sample that are not displayed in Table 1 are as follows.

About three-quarters of the respondents (72.8%) self-medicated when they were sick. The highest prevalence of self-medication was reported for the age group of those 41-60 years old (45.3%). Young and middle-aged

Table 1 Personal and professional characteristics of pharmacists, 2015 ($n = 316$)

Characteristic	No (%) ($N = 316$)
Gender:	
Male	4 (1.27)
Female	312 (98.73)
Age (years):	
<20	1 (0.32)
20–30	100 (31.65)
31–41	65 (20.57)
41–60	143 (45.25)
>60	7 (2.21)
Education:	
Higher pharmaceutical	110 (31.5)
Other higher	33 (9.5)
Vocational pharmaceutical	206 (59.0)
Years of experience in a pharmacy:	
<1	15 (4.75)
1–5	85 (26.90)
6–10	83 (26.26)
>10	133 (42.09)
Source of antibiotics:	
Prescribed	100 (31.65)
Self-medication	216 (68.35)

respondents (31-40 years) were more responsible: 22.8% of them went to the doctor, and 20.6% self-medicated. However, the logistic regression analysis, which is addressed in more detail later, did not reveal statistically significant higher probabilities of self-medication for any of these age groups. Only 33% purchased antibiotics using a doctor's prescription. More than half (61%) of the respondents visited a doctor for an examination and received a prescription from time to time, and 6% of staff pharmacists never bought antibiotics from a prescription. The respondents who did not visit or rarely visited a doctor for prescriptions bought antibiotics based on their knowledge (81.5%) or their friends' advice (5.0%); analyses of their experiences with previous treatment (49.0%); and prescriptions provided by pharmacy customers (17.0%). Only a small number of respondents (8.0%) considered cost to a significant degree when purchasing medicine.

Antibiotics were mostly used to self-treat upper and low respiratory tract infections (53.3% and 19.3%, respectively). Other conditions addressed with self-medication were dental problems, urogenital infections and respiratory inflammation.

The most commonly used antibiotics were macrolides (33.2%). Azithromycin was predominant in this group and accounted for 81.1% of all self-prescriptions. Semi-synthetic penicillins (30.9%) and fluoroquinolones (15.2%) were other most frequently used groups, followed by tetracyclines (7.8%), second-generation cephalosporins (5.5%), lincosamides (5.4%) and aminoglycosides (2.0%).

The main source of information regarding antibiotics was training sessions (43.2%), patient information leaflets (30.1%) and specific literature (26.7%). More than half of the respondents (66.8%) took their antibiotics according to the information on the leaflet, one-third (31%) took antibiotics in line with their physician's prescriptions, and the rest (2.2%) stopped using the antibiotic early when their symptoms decreased.

Oral dosage was the most preferred form of antibiotics.

Table 2 shows the impact of pharmacists' attitudes, behaviour and knowledge on self-medication with antibiotics.

The following associations were found to be statistically significant. When feeling ill, those who consulted a physician had a lower probability (OR 0.41) of self-medication than those who self-medicated, which is self-evident. Concerning the way antibiotics were used, those acting according to patient leaflets had a higher chance (OR 2.09) of self-medication than those who used antibiotics as prescribed by the physician. Interestingly, pharmacists who did not obtain new information on antibiotics through educational paths or specific literature exhibited a substantially decreased probability of self-medication (OR 0.57 and OR 0.44, respectively). Although not displayed in Table 2, the logistic regression analysis indicated a strong association of self-medication with all levels of education compared to those with basic (non-pharmaceutical) vocational education, with the following odds ratios: higher pharmaceutical (OR 5.201, CI 95% 1.87–14.42), other higher education (OR 3.781, CI 95% 1.12 -12.79) and vocational pharmaceutical (OR 3.613, CI 95% 1.36–9.59).

The outcomes of questions Q8 (knowledge about side effects), Q10 (knowledge about influence on normal

Table 2 Factors influencing self-medication with antibiotics based on univariate logistic regression models for individual questions. Reference groups are the outcomes not displayed between brackets after the question

Question (evaluated outcome)	No. ($N = 316$)	p-value (Wald-test)	Odds ratio	95% confidence interval	
When you feel ill (consult a physician)	86	0.001*	0.405	0.232	– 0.707
Have you taken antibiotics in the past 6 months (no)	175	0.727	0.915	0.555	– 1.508
Antibiotic use:					
(Stop after symptoms decreased)	8	0.727	0.759	0.162	– 3.560
(As per leaflet)	243	0.005*	2.088	1.250	– 3.488
Source of new information about antibiotics:					
- Training sessions (no)	227	0.014*	0.517	0.305	– 0.877
- Special literature (no)	140	0.002*	0.441	0.260	– 0.747
- PIL[a] (no)	158	0.800	1.066	0.649	– 1.750
Preferable form (injections)	285	0.207	0.571	0.24	– 1.362
Use of probiotics (no)	285	0.674	0.844	0.384	– 1.856
Attitude toward antibiotic therapy:					
(Against)	10	0.964	0.955	0.126	– 7.229
(Extreme cases)	295	0.612	0.714	0.194	– 2.624

*$p < 0.05$
[a]PIL Patient information leaflet

flora) and Q13 (gender) were essentially identical (up to less than one percent) for all respondents. This similarity is explained by the fact that the respondents were with a common pharmaceutical background and 98.73% of the respondents were females.

Pearson chi-squared tests revealed no association between personal characteristics (age, education and experience) and self-medication or antibiotic use (Table 3). By contrast, variables related to the source of new information about antibiotics were shown to be significantly associated with personal characteristics.

Discussion

The results of our study show that the practice of self-prescribing antimicrobials is extremely popular amongst pharmacists in Saint Petersburg. We suggest that the main contributing factor of this high prevalence is pharmacists' easy access to antibiotics, since a prescription for the dispensed antibiotics is neither required nor controlled by authorities during inspections.

Data on outpatient antibiotic use reported by the European Surveillance of Antimicrobial Consumption suggested that in 2009, Russia was the third largest outpatient consumer of antibiotics in Europe when consumption was expressed as the number of packages per 1000 inhabitants per day [5].

Another study by Stratchounski et al. also confirmed that the Russian population is inclined to stock antibiotics in home medicine cabinets for further uncontrolled and unsupervised use [6].

While Russian physicians are aware of antibiotic resistance and are concerned by the over-the-counter sale of antibiotics [7], pharmacists promote an inappropriate use of medications by over-the-counter dispensation. This finding can be explained by the lack of a culture in which drugs are dispensed/purchased strictly based on prescriptions. Physicians often do not write prescriptions or they provide their recommendations, including the use of antibacterial drugs, on a regular sheet of paper that may, in the best case, have a physician's seal.

Our findings indicate that antibiotics were commonly used by pharmacists to treat upper respiratory tract infections, which raises concern regarding the potential misbelief that antibiotics can treat and eradicate infections regardless of its origin [8], as well as a lack of professional knowledge of antibiotics that largely do not act on acute cough and colds [9]. Nevertheless, the results showed that educational strategies aimed at improving professional knowledge through training sessions or specific literature could have an undesired effect on pharmacists' intention to self-medicate. Some pharmacists explained this finding by saying that participating in trainings and receiving additional information about medicines, especially from medical representatives of drug companies, contributes to improving their professional skills and saves time because it removes the need to visit a doctor.

The most popular group of antibiotics used by the respondents was macrolides. In contrast, a study on the outpatient use of systemic antimicrobials in 24 different regions of Russia reported that in 23 regions (including Saint Petersburg), broad-spectrum penicillins were the most frequently used antimicrobials. It can be assumed that there is a significant difference in the outpatient consumption of systemic antimicrobials in different regions of Russia [10]. In some regions, older agents with unfavourable safety profiles are widely administered, whereas in other regions, newer agents are used more frequently.

Diseases such as tuberculosis, gonorrhoea, malaria and childhood ear infections are now more difficult to treat than they were a few decades ago [11]. High levels of resistance to ciprofloxacin, penicillin G, azithromycin, spectinomycin and carbapenems have been reported in Russia, as a potential result of the inappropriate use of antimicrobials [12, 13].

The widespread practice of self-medication in Russia is a result of the insufficient coverage of drug programmes and the existing problems with access to medical care. The absence of a medication reimbursement system, meaning medicines remain out-of-pocket payments, is another reason for self-medication [14], significantly affecting the prices of medicines and their availability to the public [15]. In Russia, only predetermined categories of the population receive free medication within the ONLS (Population Drug Coverage) and DLO (Extensive Drug Coverage) programmes. However, it is rather

Table 3 Association of demographic characteristics with attitudes towards antibiotic use

Statement	*p*- value			
	No. (*N* = 316)	Age	Education	Experience
Self-medicate	230	0.946	0.565	0.123
Antibiotics taken in the past 6 months	141	0.787	0.323	0.807
Stopped taking antibiotics after symptoms decreased	8	0.779	0.34	0.382
Source of new information about antibiotics:				
- Training sessions	227	0.309	0.889	0.047*
- Special literature	140	0.318	0.003*	0.051
- PIL[a]	158	0.044*	0.465	0.195
Taking probiotics during/after treatment with antibiotics	283	0.869	0.805	0.15
Attitude toward antibiotics	298	0.683	0.622	0.633

*$p < 0.05$
[a]PIL: Patient information leaflet

difficult for patients to obtain preferred prescriptions, as the procedure for issuing prescriptions is time-consuming and pharmacies have insufficient quantities of medicine (deficit, supply disruptions).

This study is limited by the fact that the data were self-reported, and there is thus a possibility that the participants over-reported socially desirable behaviours or under-reported socially undesirable behaviours. There were no mechanisms that objectively assessed the honesty of the participants' answers to the survey questions. The absence of identifying data on the questionnaire sheets and the confidential nature of the study would tend to minimize this bias.

The role of pharmacists in encouraging the prudent use of antimicrobials is clearly vital. However, the practice of dispensing non-prescribed antibiotics continues to be widespread in some European countries [16–18]. Other research should focus on finding the causes of this condition. An option is to evaluate the knowledge and attitudes of pharmacists towards the antibiotic resistance and the basic principles of antibiotic therapy. Similarly, this could be an analogy with the project conducted among the Czech pharmacists, whose attitudes towards the use of generic substitution significantly reflected the level of the knowledge on generic medications [19].

Conclusions

Pharmacy employees must understand the rules, orders, and other relevant information on how to dispense antibiotics. However, most of these pharmacists do not follow these regulations. It is suggested that a well-planned, organized and structured educational programme for doctors and pharmacists should be implemented to improve the appropriate use of antibiotics.

Additional file

Additional file 1: Questionnaire "Use of antibiotics by pharmacy employees". (DOCX 17 kb)

Acknowledgements
We warmly thank all the pharmacists who took part in this study.

Funding
This work was supported by a grant from the Charles University in Prague (SVV 260 187). The funding body had no role in the design, collection, analysis or interpretation of this study. Grant funds were used for the manuscript editing service before its submission.

Availability of data and materials
RAW data of this study are available on request from the archive of Charles University, Faculty of Pharmacy in Hradec Kralove.

Authors' contributions
TB was the principal investigator responsible for the design and conception of the study and the collection and interpretation of data and wrote the manuscript. ND participated in the study design, coordination, and data collection and drafted the manuscript. JK participated in the study design, coordination, and data collection and drafted the manuscript. JDT conducted the statistical analysis and drafted the manuscript. JV participated in the study design and coordination and the review of the manuscript. All the authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
In accordance with Russian regulations, non-interventional studies do not need the approval of the Ethics Committee at the Federal Agency on quality control, efficiency, safety of medicines. The regulations establish control on clinical trials of a medicinal product for medical use by local Ethics Committees covered by the Federal Law on Circulation of Medicines № 61-FZ of 12 April 2010, which does not contain special requirements for non-interventional studies. The National Standard of "Good Clinical Practice" (GOST R 52379-2005) primarily relates to prospective clinical trials. Our study did not imply the clinical trial of a medicinal product and did not require any special approval of the national competent authorities. The study was, however, approved by the Ethical Committee of Charles University in Prague. № Vlcek_J_12.01.15. The pharmacists were informed about the possible use of anonymous data when evaluating the results of the observational study. Oral informed consent was obtained from all pharmacists who participated in the focus group study.

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Received: 1 November 2016 Accepted: 24 January 2017
Published online: 14 February 2017

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