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Antibiotic Overuse by Jamaican Clinicians in the Treatment of Pharyngitis in Children

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SUMMARY

Background

Overuse of antibiotics in pharyngitis management is an important global and local problem contributing to increased antibiotic resistance. We aimed to assess clinician attitudes towards the management of Group A Streptococcus (GAS) pharyngitis against objective diagnostic and prescribing practices.

Methods

A national cross-sectional survey was conducted among Jamaican public and private health clinicians. Their approach to patients with pharyngitis features was assessed and compared to medical records in the 0-15 year old age group from January 1 to December 31, 2018. Antibiotic prescribing rates were calculated for unlikely vs likely GAS pharyngitis (Centor <4 vs ≥4).

Findings

337 practitioners from 19 specialties were recruited. 308 (91·3%) reported managing presumed GAS pharyngitis (pharyngeal erythema, tonsillar erythema, tonsillar hypertrophy +/- exudates, anterior cervical lymphadenopathy, soft or hard palate petechiae). 301 (97·7%) reported inconclusive clinical features, while 45 (7·6%) reported no diagnostic challenge. Although 244 (72·4%) reported having a standard approach for using antibiotics, 99·1% expressed desire for local protocols for antibiotic use in pharyngitis.373 of 7,142 pharyngitis cases in 2018 were reviewed. 321 (86·1%) had sufficient documentation. Antibiotics were prescribed in 292 (91%) cases, including 213 (93·8%) of 227 where antibiotics were avoidable.

Interpretation

The clinical and social consequences of missing diagnoses may cause practitioners to prescribe antibiotics, even in cases of likely viral infections. High case rates of pharyngitis with concurrent antibiotic use pose a serious threat to antibiotic safety and susceptibility. However, clinical decision rules (CDRs) can reduce resistance risks, costs, adverse effects and promote confident management.

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INTRODUCTION

Antibiotic overuse is a challenge worldwide and has a variety of undesirable consequences including individual events (medication side effects, opportunistic infections), population events (e.g. antimicrobial resistance, stock outs), and environmental events.[1,2,3,4,5] Overuse seems like a logical non-sequitur, however, stewardship campaigns, development of use guidelines and disseminated information on the short term and long-term effects of injudicious use have yielded little change in the use of antibiotics in unwarranted conditions, including in cases where a sore throat is due to a viral infection.[6]

Antibiotic resistance has emerged as a significant global problem and is often linked to antibiotic misuse, in the form of inappropriate prescriptions with more multidrug resistant organisms (MDROs) emerging in the past two decades than in any other period before.[7,8] Antibiotics are prescribed mainly for respiratory tract infections (RTIs). These are most likely to be viral, however 75% of antibiotic prescriptions are for RTIs. Pharyngitis cases fall within the category of RTIs and in approximately 85% of cases the pathogen is a virus.[9]

Based on data from the US Centers for Disease Control and Prevention (CDC), Barnett et al 2013 published that despite advocating the use of clinical decision rules (CDRs) for antibiotic application, clinicians continue to prescribe antibiotics in 60-70% of pharyngitis cases, as they have done since the 1980's.[10] Independent studies have demonstrated that 9-30% of patients presenting with pharyngitis actually have Streptococcus pyogenes (Group A Streptococcus; GAS), 15% of which have Centor scores of 0 to 3, where GAS is still possible in less overt pharyngitis.[11,12] The challenge is that potentially serious complications such as sepsis or immunologic sequelae like Rheumatic Fever (RF) can develop in these cases, and diagnostic accuracy can be complicated to the absence of point of care Rapid Antigen Detection Tests (RADTs) in many settings.

There is therefore a need to focus on pharyngitis and further evaluate prescribing habits with the goal of possibly finding solutions to stem the rising tide of antimicrobial misuse. In this study we considered RF patients in a resource limited setting, dedicating a component of the research to how physicians approach the diagnosis and management of suspected GAS pharyngitis. Advocacy for judicious use of antibiotics, with or without a CDR, will likely be met by resistance as we try to change what practitioners already consider correct.

Since antibiotics may reduce severity of symptoms even in viral conditions, due to immunomodulatory activity yet to be understood, clinicians can argue the clinical benefit in syndromic management.[13,14] Furthermore, as recorded internationally,[15] in the local context, Jamaican patients largely expect the use of antibiotics for any infection, regardless of viral vs bacterial cause.

Adverse effects of antibiotics include mild to moderate gastrointestinal upset, hypersensitivity reactions, severe anaphylaxis, and opportunistic infections of varying severities, from candida vaginitis to pseudomembranous colitis and even fatal anaphylaxis.[1,2] The management of adverse events include medical and non-medical management, with financial and quality of life costs rivalling the impact of failing to use antibiotics,. Adverse reactions account for 0·9-5% of hospital admissions in Europe and 15% in the US, with an estimated cost of US$18 billion annually.[16]

Drug induced fatal anaphylaxis accounted for 59% of anaphylactic fatalities in the USA,[17] and beta-lactam drugs have been demonstrated to account for 42·6% of drug-induced anaphylactic deaths.[18] In the hospital setting 17-20% of antibiotic courses were associated with adverse drug reactions. An estimated 15-30% of these are deemed avoidable, since 70% of outpatient and 30-50% of inpatient antibiotic prescribing is not indicated.[19] Pharyngitis is the third most common primary prescribing indication at 10%, with Amoxicillin being the most frequently implicated antibiotic at 59% of those prescribed.[20,21]

The objectives of the research were to conduct a knowledge, attitude and practice survey

concerning GAS Pharyngitis among medical practitioners in Jamaica and determine antibiotic prescribing rates for sore throat in primary care. This study is important in evaluating antibiotic overuse in Jamaica, especially in consideration of pharyngitis and acute rheumatic fever/rheumatic heart disease (ARF/RHD).

Methods

Study design

This cross-sectional study was conducted in national and subnational parts in the island of Jamaica between September 2021 and April 2022. For the national component, a sample of Medical Officers and Family Nurse Practitioners from public and private realms from all health jurisdictions were interviewed using an internally developed and pretested questionnaire to evaluate their approach to the patient with possible Strep throat. Their approach to RF diagnosis and to follow up were also assessed. For the sub-national component, medical records were required from primary care to determine pharyngitis incidence and antibiotic use. Daily sheets (a health record tool which summarises demographics and diagnoses of all clients seen per day) from all 22 primary care curative centres in Kingston and St Andrew (KSA) were used. To represent pharyngitis cases reported from private care, the two applicable health insurance companies were approached to provide depersonalised data, stratified by medical claims for pharyngitis, with and without antibiotics, for patients 0 to 15 years of for the period January to December 2018. Public secondary care was excluded as, based on the Emergency Severity Index (ESI) Triage system implemented in hospital sites in 2016, pharyngitis cases would have been referred to primary care, and inclusion of hospital reported cases would have resulted in an overestimation via duplication. Ethical approval was received from the Ethics Committee of The University of the West Indies, Mona, as well as the Southeast Regional Health Authority (SERHA) prior to data collection. There was no funding source for this study.

Participants (or patients)

Inclusion criteria

- All Medical Doctors and Family Nurse Practitioners registered under the Medical Council of Jamaica (MCJ) who have practiced in Jamaica for at least one year

Exclusion criteria

- Medical practitioners not practising, living outside of Jamaica, retired, died or otherwise removed from the local practice list

The population frame used for registered physicians was based on the Knight-Madden 2014 analysis of the MCJ where the number of locally available, practicing medical practitioners (2,567) was used.[22] The number of Family Nurse Practitioners (FNPs) currently in practice was ascertained from the Family Nurse Practitioners Association and numbered 63. Considering the small population size of the FNP group, FNP and registered physician groups were consolidated to a total population of 2,630. The sample of doctors consisted of practising medical doctors invited to complete the requisite questionnaire virtually or physically. Stratified sampling was initially pursued to capture most of the primary care and paediatric practitioners from private and public domains via the Family Nurse Practitioner Association, Medical Association of Jamaica (MAJ), Paediatric Association of Jamaica (PAJ), Caribbean College of Family Physicians (CCFP) and the Jamaica Medical Doctors Association (JMDA). However, with an unsatisfactory yield of less than 10%, a convenience sampling approach was followed, targeting all medical practitioners available from primary care, secondary care, and public health. Participants gave written consent via a printed consent form for printed questionnaires, while an electronic consent page preceding the virtual questionnaire facilitated indication of consent. In addition to the explicit form, procedures and expectations were verbally explained en mass in both physical and virtual meetings. Participants were given sufficient time and opportunity to consider before consenting/declining.

Procedures

Clinician responses to the pretested questionnaire were pursued solely by the principal researcher, initially between March and September 2021. The

virtual domain used to disseminate questionnaires was Google forms. The first page of the virtual form indicated the consent parameters and invited recruits to imply consent by selecting the "I consent" button to proceed to the questionnaire pages. A link to the web-based, self-applied questionnaire was distributed to general and specialist medical associations for emailed distribution to their members. To supplement the poor response rate of invitation via medical association, clinicians were actively recruited. Following permission, facilitation, and convenience scheduling by senior management for health centres, the primary researcher attended routine primary care meetings, where electronic links were shared for virtual meetings, and printed copies were shared in physical meetings. All available and willing participants from the cohort of Medical Officers were recruited. Likewise in secondary care, after permission was obtained, various departments were visited between September 2021 and April 2022. Medical Officers were given the opportunity to complete the questionnaire using printed versions, or via a link accessible through a printed Quick Response (QR) code with instructions, posted at workstations.

Statistical analysis

For component 1, using the online sample size calculator from Raosoft.com, with a population of 2630, an alpha value of 0·5, and a response rate of 50%, the sample size for this group was calculated at 336. The formula used is also given by the equation:

$n = N*X / (X + N - 1)$,

where,

$X = Z\alpha/22 -*p*(1-p) / MOE2$,

and $Z\alpha/2$ is the critical value of the Normal distribution at $\alpha/2$ (e.g., for a confidence level of 95%, α is 0·05 and the critical value is 1·96), MOE is the margin of error, p is the sample proportion, and N is the population size. Note that a Finite Population Correction was applied to the sample size formula.[23]

For component 2, to determine proportion of pharyngitis cases for which antibiotics are prescribed in public care, four health centres (Glen Vincent, Slipe Road Comprehensive, Duhaney Park and Stony Hill Health Centres) were selected as representative based on the following reasonable assumptions:Centres are staffed by family medicine and general practice primary care practitioners, best representing the diagnostic and management practices of clinicians most likely to see this type of case.There is high volume visitation, increasing the reliability of observing cases of interest. These centres span wide geopolitical and socioeconomic strata in KSA.

The population for this component consisted of all visits recoded for pharyngitis for 2018; the sample size was determined after completion of a primary care sheet review exercise. Like component 1, an online sample size calculator from Raosoft.com was used, with a population of 5,329 (public sector pharyngitis/sore throat cases in 2018), an alpha value of 0·5, and a response rate of 50%, the sample size for this group (using the formula above) was calculated at 359. Representative and inferential statistics were calculated via Microsoft Excel and Statistical Package for Social Science (SPSS) Version 21.

Results

The overall response rate was 34·6% for the 974 medical practitioners approached. Of the 337 complete questionnaire responses, 69·1% were female, with the largest age groups being 30-39 years (133, 39·6%) and 20-29 years (99, 29·5**%)**

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The size of the age groups was found to be significantly different (p=0·041).From the 337 practitioners, 19 different specialties were reported. General practice comprised the largest specialty group, with 97 physician (28·8%), and 15 (4·5%) Family Nurse Practitioner responses. This was followed by Paediatric, Internal Medicine and Public Health specialties respectively. Most pharyngitis cases were seen in the public secondary (139, 45·9%) and primary care (137, 45·2%) system fairly equally, with relatively few cases from the private primary (12, 4·0%), secondary (5, 1·7%) and tertiary (5, 1·7%) system. Of 331 persons who responded to this question, 308 (91·4%) reported seeing cases with features characteristic of strep throat (pharyngeal erythema, tonsillar erythema, hypertrophy of the tonsils with or without exudates, anterior cervical lymphadenopathy, and petechiae on the soft or hard palate).[24] Of these 308, 301 (97·7%) reported having cases in which the diagnosis was challenged by inconclusive clinical features often (21, 31·6%), sometimes (160, 46·8%), and rarely (96, 23·9%), while 45 (7·6%) reported never having a challenging diagnosis; 15 (2.0%) did not answer this question. Despite this, 244 (72·4%) of all respondents reported that they have a diagnostic approach (personal or literature-based) to determine in which cases antibiotics would be applicable. However, 334 (99·1%) of all respondents reported a desire to have a Jamaican protocol for determination of antibiotic use in sore throats. Evaluation of clinical features and antibiotic use was done using a sample of the public sector sore throat cases. Of the 373 sore throat cases reviewed, 52 had missing information (i.e., docket not found, incorrect docket number) while 321 were available for review. Of the 321, 13 cases had no examination recorded, and 10 recorded the word 'normal' for the throat examination. Of the 331, the mean age was 4·3 years (1·5 months to 15 years), with males constituting 72·5% of cases. Fever was recorded in 314 (97·8%) of patients, while 15 (14·7%) had lymphadenopathy recorded in the health record. Second to fever, the examination finding recorded most frequently was pharyngeal erythema alone in 166 (52·0%), followed by tonsillar swelling and pharyngeal erythema together in 79 (24·8%) of records. Tonsillar exudate was present in 43 (13·2%) cases, whether in combination with only erythema (13,14·1%), with only tonsillar enlargement (3, 0·9%), or with both erythema and enlargement (27, 8·4%), but never in isolation. Of the 321 visits evaluated, 53 (16·5%) had none of the Centor-specific clinical findings. Antibiotics were prescribed in 292 (91·0%) of the cases, of which 42 (13·1%) had a concomitant infection for which antibiotic use was indicated (e.g., bacterial lower respiratory tract infections, severe otitis media). Of the 29 (9·0%) cases which did not receive antibiotics, one (1) was referred to secondary care for urgent management, while the remaining 28 were sent home on conservative management (symptomatic relief). Overall, 93·8% of cases in which antibiotics were avoidable received antibiotics.

DISCUSSION

The challenge of differentiating bacterial from viral pharyngitis was expressed by almost 98% of clinicians and contributed to the use of antibiotics in 93·8% of cases for which Centor scoring deemed antibiotics unnecessary. Sore throat is one of the most common infectious disease presentations, with an annual 12 million cases in the US and 616 million GAS pharyngitis cases globally, 288·6 million of which occur in patients between 0 and14 years old.[25,26] We estimate that there are 33,342 annual cases in the 0-15 year-old age bracket. At such a high case rate, Jamaica too should be concerned about the short and long term effects of the excessive use of antibiotics. Antibiotic overuse is a challenge worldwide and is recognized as number 5 of WHO's top ten health threats.[27] Since advocating for CDRs has been associated with antibiotic use in 60-70% of pharyngitis cases,[10] there may be scope for improved rates in Jamaica's setting, considering the 91·0% use among all pharyngitis cases and 93·8% use among non-indicated cases in this study. McGowan et al confirmed that there is very little local data on the subject, and that there is evidence of overuse in at least in two of the largest hospitals in Jamaica.[28] Still locally, antimicrobial resistance has found itself with increasing proportions, significant and controversial outbreaks, and emergence/importation of exotic strains.[29,30] The most serious concern is the dawn of the post antibiotic era. Specialists posit that if the trend continues, developed and developing countries will encounter a time where development of antimicrobial resistance exceeds the

development of novel antibiotics to treat them, making prophylaxis and treatment akin to the pre-antibiotic era.[31] Mortality from surgical infections, diabetic complications and paediatric infections could return to the high rates of the pre-antibiotic era.[32,33] Common outpatient infections may require admission, and post-infection sequelae like post streptococcal glomerulonephritis, RF, and post-meningitis neurological deficits could overwhelm the already struggling health infrastructure.[33] All but three of the 337 clinicians indicated a desire for a national diagnostic protocol for Strep throat despite the majority of clinicians (75%) expressing confidence in their diagnostic approach. This suggests a willingness to accept locally validated clinical decision rules (CDRs) and rapid antigen diagnostic tools (RADTs), though there may be dissonance between this expressed willingness and actual acceptance. This is an area for further research, along with confirmation of local factors that influence injudicious antibiotic use and the modifiability of those factors. More local studies are needed to quantify the impact of infection control practices, and translate them into effective stewardship, both for professionals and the public. Further determination of local GAS incidence in pharyngitis should also be pursued through bacterial culture studies to refine prediction models. Lack of medical record information was by far the biggest limitation of the study. This took the form of missing records, transcription errors, illegible notes, and absence of any examination findings or needed negative and positive findings. This especially applies for cough, lymphadenopathy, and examinations described as 'normal'. Additionally, private cases were not available for detailed examination. Additional sampling exercises were conducted to make up for missing health records, with diversification of clinical sources to strengthen representativeness. In addition to poor symptom/sign documentation, the lack of RADTs decreases the applicability of Centor scores, hence a cut off score of four or more was used to represent antibiotic indication in keeping with Centor guidelines, where RADT use is optional.The poor response rate from medical practitioners also lends the study to bias since convenience sampling became necessary. To address this, clinicians were purposefully invited from a wide range of primary and secondary care departments.

CONCLUSION

Despite expressed difficulty in differentiating bacterial vs viral pharyngitis, and the lack of GAS-suggestive features in most pharyngitis cases, Jamaica clinicians overwhelmingly tend to prescribe antibiotics for pharyngitis. With an expressed desire for national protocols for the diagnosis and treatment of GAS pharyngitis, even by clinicians who are confident in their current therapeutic approach, Jamaica has significant scope for antibiotic stewardship, especially through introduction of CDRs and RADTs

Abbreviations and Symbols

ARF	Acute Rheumatic Fever
BPG	Benzathine Penicillin G, benzathine benzylpenicillin
WHO-CHOICE	World Health Organization-Choosing Interventions that are Cost-Effective
FNP	Family Nurse Practitioner
GAS/ GABHS	Group A Beta-haemolytic streptococcus
HF	Heart Failure
MOHW	Ministry of Health and Wellness
RRF	Recurrent Rheumatic fever
RHD	Rheumatic Heart Disease
WHA	World Health Assembly
WHO	World Health Organization

REFERENCES

1. Dioun Broyles A. Practical Guidance for the Evaluation and. J ALLERGY CLIN IMMUNOL PRACT. 2020 Oct; 8(9S): 16-116.
2. Mayo Clinic. Mayo Clinic. [Online].; 2021. Available from: https://www.mayoclinic.org/diseases-conditions/yeast-infection/symptoms-causes/syc-20378999.
3. Jourdan A, Sangha B, Kim E, Nawaz S, Malik V, Vij R. Antibiotic Hypersensitivity and Adverse Reactions: Management and Implications in Clinical Practice. Allergy, Asthma & Clinical Immunology. 2020; 16(6).
4. Mohsen S. Update on the adverse effects of antimicrobial therapies in community practice. 2020 Sep; 66(9): 651–659.
5. University of Wisconsin Hospital and Clinics. Antimicrobial Use Guidelines. University of Wisconsin, Department of Pharmacy; 2011-2012.
6. Roos R. CIDRAP Cener for Infectious Disease Research and Policy. [Online].; 2013. Available from: https://www.cidrap.umn.edu/news-perspective/2013/10/study-antibiotic-overuse-still-rule-sore-throat-bronchitis.
7. Balkhair A, Al-Farsi YM, Al-Muharrmi Z, Al-Rashdi R, Al-Jabr M, Neilson F, et al. Epidemiology of Multi-Drug Resistant Organisms in a Teaching Hospital in Oman: A One-Year Hospital-Based Study. ScientificWorldJournal. 2014.
8. Centers for Disease Control and Prevention. cdc.gov. [Online].; 2006. Available from: https://www.cdc.gov/infectioncontrol/guidelines/mdro/epidemiology.html.
9. Krantz EM, Zier J, Stohs E, Ogimi C, Sweet A, Marquis S, et al. Antibiotic Prescribing and Respiratory Viral Testing for Acute Upper Respiratory Infections Among Adult Patients at an Ambulatory Cancer Center. 2019 May 16.
10. Barnett M, Linder JA. Antibiotic Prescribing to Adults With Sore Throat in the United States, 1997-2010. JAMA Intern Med. 2014; 174(1): 138-140.
11. Agarwal M, Raghuwanshi SK, Asati DP. Antibiotic Use in Sore Throat: Are We Judicious? Indian J Otolaryngol Head Neck Surg. 2015; 67(3): 267-270.
12. Rimoin AW, Hamza HS, Vince A, Kumar R, Walker CF. Evaluation of the WHO Clinical Decision Rule for Streptococcal Pharyngitis. Arch Dis Child. 2005 Oct; 90(10): 1066-70.
13. Abelson MB, Shapiro A, Makino A. Review of Ophthalmology. [Online].; 2008. Available from: https://www.reviewofophthalmology.com/article/the-other-side-of-antibiotics.
14. Melhus, A. Effects of Amoxicillin on the Expression of Cytokines During Experimental Acute Otitis Media Caused by Non-typeable Haemophilus influenzae. Journal of Antimicrobial Chemotherapy. 2001; 48(3): 397-402.
15. Vanden Eng J, Marcus R, Hadler JL, Imhoff B. Consumer Attitudes and Use of Antibiotics. Emerg Infect Dis. 2003 Sep; 9(9): 1128–1135.
16. Horodnycha O, Zimenkovsky A. Antibiotic Allergy as a Cause of Hospitalization in Adults: A Hospital-based Study in Ukraine. Pharm Pract (Granada). 2021; 19(1): 2055.
17. Regateiro FS, Marques ML, Gomes ER. Drug-Induced Anaphylaxis: An Update on Epidemiology and Risk Factors. Int Arch Allergy Immunol. 2020;: 481-487.
18. Gao Y, Han Y, Zhang X, Qi Y, Fei Q, Qi R, et al. Penicillin Causes Non-allergic Anaphylaxis by Activating the Contact System. Sci Rep. 2020;(10): 14160.
19. KE FD, AL H, DJ S. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010–2011. JAMA. 2016; 315(17).
20. Beck JN, Suppes SL, Smith CR, Lee BL, Leeder JS, VanDoren M, et al. Cost and Potential Avoidability of Antibiotic-Associated Adverse Drug Reactions in Children. J Pediatric Infect Dis Soc. 2019; 8(1): 66-68.
21. Silva TM, Gomes ER, Ribeiro-Vaz I, Roque F, Herdeiro MT. Prevalence and Significance of Antibiotic-Associated Adverse Reactions. In New Insights into the Future of Pharmacoepidemiology and Drug Safety.; 2021.
22. Knight-Madden J, Gray R. The Accuracy of the Jamaican National Physician Register: A Study of the Status of Physicians Registered and Their Countries of Training. BMC Health Services Research. 2008: p. 253.
23. Select Statistical Services. https://select-statistics.co.uk/. [Online].; 2022. Available from: https://select-statistics.co.uk/calculators/sample-size-calculator-population-proportion/.
24. Vincent MT, Calestin N. Pharyngitis. Am Fam Physician. 2004 Mar 15; 69(6): 1465-70.
25. Ashurst JV, Edgerley-Gibb L. Streptococcal Pharyngitis. In StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
26. Miller KM, Carapetis JR, Van BCA. The Global Burden of Sore Throat and Group A Streptococcus Pharyngitis: A Systematic Review and Meta-analysis. eClinicalMedicine. 2022; 48: 101458.
27. World Health Organization. World Health Organization. [Online].; 2019 [cited 2024. Available from: https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019.
28. Nelson JL. Jamaica Infromation Service. [Online].; 2024. Available from: https://jis.gov.jm/stewardship-programmes-a-potential-gamechanger-for-hospital-antibiotic-use/.
29. Lindsay D, Thoms-Rodriguez C, Maragh S, Nicholson AM. Multidrug Resistant Organisms in the Intensive Care Unit of a Tertiary Care Hospital in Jamaica. West Indian Med J. 2019.
30. Thoms-Rodriguez CA, Mazzulli T, Christian N. New Delhi metallo-β-lactamase in Jamaica. Journal of Infection in Developing Countries. 2016 Feb; 10(2).
31. Reardon S. Nature.com. [Online].; 2014 [cited 2022 Jun. Available from: https://www.nature.com/articles/nature.2014.15135.
32. Barriere LS. Clinical, Economic and Societal Impact of Antibiotic Resistance. Expert Opinion on Pharmacotherapy. 2014; 16(2): 151-153.
33. Erdem H, Tetik A, Arun O, Besirbellioglu BA, Coskun O, Eyigun EP. War and infection in the pre-antibiotic era: the Third Ottoman Army in 1915. Scand J Infect Dis. 2011; 43(9): 690-5.