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Measuring Antibiotic Use and Resistance at various healthcare levels

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ABSTRACT

The evolution of antibiotic resistance is a global public health crisis building over decades. In this build-up antibiotic use has been the main driver for antibiotic resistance. To develop context-specific interventions, effective surveillance of antibiotic use and resistance are needed in countries like India, which have witnessed a rapid rise in resistance recently and where the need for effective antibiotics is high.

Keywords: antibiotic, resistance, health, prescribing.

INTRODUCTION

Public health care in India has 28 states and 7 union territories. States have their own elected governments. India has adopted a universal health care system, which is run by the states and union territories of India (WHO SEARO 2012).

India's primary health care system is based on the primary health center (PHC) and its sub centers. Each PHC (manned by a physician and health workers and auxiliary nurse midwifes) caters to a population of about 30,000 in the plain areas and for a population of 20,000 in hilly, tribal and backward areas. Each sub-center provides health care to every5000 population in general and for every 3000 in hilly, tribal and backward areas (WHOSEARO 2012). Drug discovery and development is a deep, prolonged and an inter disciplinary venture. Drug discovery is chiefly described as a unidirectional, successive procedure which begins with objective and show the way to innovation, tracked by lead optimization and pre-clinical learn to decide if these complexes gratify a numeral of criterion for beginning clinical growth. The procedure of drug discovery starts with the consideration of getting better humans what's more by therapeutic, justifying, recuperating a syndrome state. It rivets years of nonstop study hard work to expand a pills to do something on novel aim within the individual body, or with a newer instrument of medicine deed.

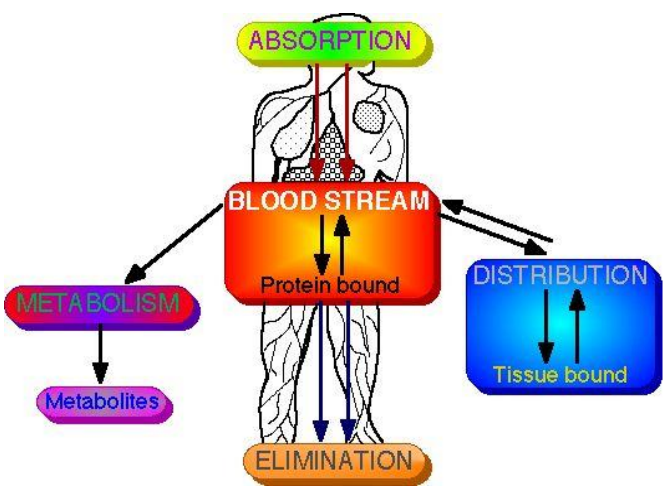

Fig.1: Various ADME processes during drug sojourn in human body

Urban health services

Most Indian urban areas have secondary and tertiary facilities provided by the government. Most of the health care facilities in the government hospitals are either free or highly subsidized (WHO SEARO 2012).

Inadequacies of public health services in India the performance of the primary public health care has been poor. Main reasons for poor performance have been pointed out in a world bank report (Radwan, 2005) and include: lack of flexibility of public-health structure and administration- resulting ineffective response to the needs of a specific geographical area, lack of accountability resulting in absentee doctors and staff, limited staff salaries, informal payments to obtain admission to a hospital, to obtain a bed or to obtain or deliver a drug, inability to fill vacancies, lack of public health management capacity among administrators or doctors, political interference with allocation of resources, poor infrastructure of the health centers and the hospitals and little or no community participation.

Private health care in India has one of the most highly privatized health care systems in the world in terms offance and delivery (Sengupta and Nundy 2005). In the year 2005 it was estimated that private health care facilities accounted for 82% of outpatient visits, 58% of inpatient expenditure, and 40% of births in institutions (Sengupta and Nundy 2005). India ranks among the top 20 of the world's countries in its private spending, at 4.2% of GDP (GOI2002). According to World Bank estimates in year 2008, 74.3% of the health care expenditure was out-of-pocket. As a result, more than 40% of all patients admitted to hospital have to borrow money or sell assets to cover expenses, and 25% of farmers are driven below the poverty line by the costs of their medical care (GOI 2002).

MEASURING ANTIBIOTIC USE

The antibiotic use data can be gathered at various healthcare levels or in the community using different sources and methods (WHO 2012a). For health care, data could be gathered at primary care or hospital level and results presented as total use for the hospital using the purchased, prescribed, dispensed or administered data on antibiotics. Antibiotic use data could also be gathered at ward level or for outpatient clinics and admitted patients separately.

Disease or symptom specific data could be more granular in identifying rationale antibiotic use, analyzing adherence or compliance with standard treatment guidelines and to inform and evaluate resistance containment interventions.

The various methods that can be used for antibiotic surveillance are: review of prescriptions, review of pharmacy sale or dispensing data, and drug purchase or procurement data in places where the health system is weak, and there is no previously established surveillance system, WHO recommends measuring the following parameters: percentage of patients receiving antibiotics, pneumonia cases treated with recommended antibiotics, cases of upper respiratory tract infections for receiving antibiotics, and percentage of patients receiving antibiotics without prescriptions (WHO 2012a).

The antibiotic use can be reported as total use in grams, number of antibiotics constituting the 90% of the total drug utilized, financial cost for the patient or health care facility or total days of therapy, or by using prescribing indicators. The standardized measure of reporting antibiotic use information is by using the WHO Collaborating Centre for Drug Statistics Methodology, Anatomical Therapeutic Chemical (ATC) classification with Defined Daily Dose (DDD). By definition, the DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (WHO Collaborating Centre for Drug Statistics Methodology 2010).

The DDD is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose. The DDD reflects the global dosage irrespective of individual and population level genetic variations of drug metabolism. The DDD provides a fixed unit of measurement independent of drug cost, package size, and patient-specific dose ordered. To estimate antibiotic use, the total number of grams of each antibiotic used (purchased, dispensed, or administered) are summed during the period of interest and divided by the WHO-assigned DDD (WHO Collaborating Centre for Drug Statistics Methodology 2010). Expressing antibiotic use by DDDs, for example using the DDD per 1000 patient days, allows the researcher to compare the antibiotic use of one hospital with other hospitals', regardless of differences in formulary composition and antibiotic potency. The main advantage of the DDD methodology is that a researcher is able to assess trends in drug consumption and also to perform comparisons between populations groups (WHO Collaborating Centre for Drug Statistics Methodology 2010).

The other advantages are, the DDD methodology has a direct link to a widely accepted and used the rapeutic classification system i.e. ATC/DDD classification system and the hierarchical structure of the ATC/DDD system that enables the aggregation of data at various healthcare levels. The WHO ATC/DDD system is also freely available. The ATC codes are alpha numerical and categorical and are thus easy to use. The main disadvantages are that the methodology is not suitable for children and patients with impaired renal function. Also, in computation the alpha numerical nature of ATC codes is sometimes a complication.

Relationship between antibiotic use and resistance Antibiotics have unfortunately been used excessively and inappropriately since the time of their discovery. The extent of antibiotic use is linked to resistance at an ecological level and more recently links between antibiotic prescribing and resistance at individual patient level have been shown. While antibiotics are the central element in selecting resistant bacteria they are not the only driving force for persistence of resistance.

Once bacteria acquire the elements responsible for resistance and stabilize them, resistance can be then transmitted horizontally within and between species. Thus, the need for surveillance of antibiotic prescribing to monitor and identify areas for improvement cannot be over emphasized.

Surveillance networks of antibiotic use and resistance at national, regional and global level Surveillance involves systematic collection and analysis of health-related data to inform the health-care providers, administration and policy makers. An effective surveillance of antibiotic use should describe the pattern of antibiotic prescribing and "how" they are used.

Both by the patients and prescribers the goal of antibiotic use surveillance is to provide the information, insights and tools needed to guide policy at local, national and global level.

At the national level Sweden is one of the most active and successful countries in the fight against antimicrobial resistance. In Sweden, Strama (the Swedish Strategic Programs against Antibiotic Resistance) works for effective use of antibiotics. Other networks include, the Norwegian Surveillance for Antibiotic Drug Resistance(NORM), Surveillance of Antibiotic use and Resistance in Intensive Care (SARI) or Medical Antibiotic Use Surveillance and Evaluation (MABUSE) in Germany, European Surveillance of Antimicrobial Consumption (ECDC, 2010) in Europe and Intensive Care Antimicrobial Resistance Epidemiology (ICARE) in the United States.

At the European level the surveillance of antimicrobial resistance was conducted previously by the European Antimicrobial Resistance Surveillance System (EARSS), and is currently done by the European Antimicrobial Resistance Surveillance Network (EARSNet).The network has played an important role to provide good quality data. The dissemination of EARS-Net data has increased the awareness of the problem of antimicrobial resistance not only in the scientific community but also at the public and the political level (ECDC 2010). The 2009 situation analysis report by EARS-Net contains data from 28 countries and analyses trends of assistance in many pathogenic bacteria (ECDC 2010). Data from Europe confirm a consistent rise in multidrug resistance and reveal a steady and significant decline of antimicrobial susceptibility in Escherichia coli.

On the other hand a steady fall in the hospital prevalence of methicillin resistant Staphylococcus aureus (MRSA) has been reported (ECDC 2010). This fall has been achieved by active surveillance of carriers and patients in the hospitals and massive hand hygiene campaigns.

Need for antibiotic resistance surveillance systems in low and middle income countries Surveillance of antibiotic resistance is one of the most important components of anantibiotic stewardship program. Antibiotic stewardship is commonly described as a program that provides guidance for selection, dosing, route of administration and duration of antibiotic therapy and involves pharmacists, physicians and other healthcare providers. Antibiotic stewardship is an obligation in European Union States and the United Kingdom but is a relatively new concept for Indian hospitals.

WHO recognizes laboratory-based surveillance of antibiotic resistance as a "fundamental priority" for the development of strategies to contain antibiotic resistance and to assess the impact of interventions especially in low and middle-income countries (WHO 2011). Action has been taken in response to the mounting crisis of antibiotic resistance, but most of the efforts have remained confined to resource-rich countries. Many of the existing surveillance networks continue to provide useful information. There is however, no formal framework for collaboration among surveillance Programs worldwide. This lack of a global framework for collaborative surveillance of antibiotic resistance hinders rational discussions on antibiotic resistance patterns and also limits systematic comparison and evaluation of various intervention Programs. A standardized system for reporting antibiotic resistance needs to be established; such a system should rely on both public and private sector laboratories. In addition, Health and Demographic Surveillance Sites (HDSS) have been suggested to obtain information from communities in resource limited settings at household level.

PROBLEM OF ANTIMICROBIAL RESISTANCE IN INDIA

Rapid evolution of bacterial resistance in India (Kumarasamy et al. 2010) might be the result of a complex interaction of several factors. These include: higher burden of infectious disease, treatment uncertainty, lack of treatment guidelines, inadequate access to standard laboratory facilities, self-medication, prescription based on availability, government support to pharmaceutical industries, market forces, qualification of the prescriber, lax law enforcement, fragmented public health system, poor population-wide health coverage, inadequate adherence to universal hygiene and infection control measures, and low population-wide education level. We will mainly discuss antibiotic prescribing with respect to clinical practice in this paper.

The following are examples of the pressures and constraints under which physicians prescribe drugs:-

- Physicians are most often motivated to give the best possible treatment often disregarding cost or spectrum of activity of the chosen antibiotic.
- Lack of access to diagnostics especially near-patient diagnostics and lack of treatment guidelines forces physicians to choose empirical antibiotic therapy based on experience.
- The marketing pressures of the pharmaceutical industry and other financial incentives for prescribing can influence the choice of antibiotics prescribed.
- “The fear of failure” of empirical antibiotic therapy is often quoted as a reason, which is further fuelled by the pharmaceutical industry through their blased presentation of drug information.
- “The newer the better” is another myth in prescribing that increases patient costs and resistance.
- “The more the better” is a myth that arises from a mistaken belief that if the effective dose of a particular drug is rather small, then a larger dose and prolonged treatment should definitely be better. The pharmacokinetics and pharmacody namics of most antibiotics are complex and require extra effort on the part of physicians to understand them.
- Shorter patient consultation time and busy practice is associated with Greater antibiotic prescribing.
- There are often limited opportunities for continuing professional development for physicians, especially in low and middle-income countries.
- Empiric spiralism, as explained earlier.
- Lack of innovation by the pharmaceutical industry in approach to treatment of infections in general and development of new antibiotics in particular has resulted in an empty pipeline of antibiotics against multi-drug resistant bacteria.

Drug utilization studies with focus on antibiotic use from India

In India little is known about antibiotics prescribing for a given clinical diagnosis. Drug utilization studies done in India show that antibiotics are one of the most frequently prescribed drug groups, but there are surprisingly few published studies of antibiotic prescribing done in India using the WHO ATC/DDD methodology,(Sharma and Barman 2010,). The primary reason for the lack of such studies is the fact that in most health care facilities antibiotic use data is not collected at all. At pharmacy level there can be sales without prescription thus limiting the accuracy of the data. The standardised method of reporting for outpatient antibiotic use suggested by the WHO ATC/DDD methodology is DDD per 1000 inhabitants per year. This type of reporting is not possible currently as most health-care set-ups in India have no defined population to which they cater. Patients often travel to distant hospitals and purchase prescribed medications from pharmacies close to where they reside. Lack of a Computerized tracking system makes DDD per 1000 inhabitants a redundant concept for countries like India. In view of the paucity of studies and the methodological challenge two surveillance studies were planned adapting the WHO, ATC/DDD methodology to suit the local context

Adherence to treatment guidelines for diarrhea WHO and UNICEF, since 2004 recommend that all children with acute diarrhea be given zinc in some form for 10 to 14 days during and after diarrhea (10 milligrams per day for infants younger than 6 months and 20 milligrams per day for those older than 6 months) (UNICEF and WHO 2004). The Indian Academy of Pediatrics also has recommendations on ORS and zinc use since 2004 (Bhatnagar et al. 2004), which were re-endorsed in 2006 (Bhatnagar et al. 2007). Later in 2007, the Government of India recommended use of zinc for acute diarrhea. The National Rural Health Mission included ORS and zinc in the list of drugs to be made available to the sub centers (Bhatnagar et al. 2010). In spite of this only about 34% of the children with diarrhea are prescribed ORS and only about 1% children are prescribed zinc (Gitanjali and Weerasuriya 2011).

Improving the case management of diarrhea can be considered as one of the few “low hanging” fruits for reducing child mortality, as the two most important interventions, i.e. ORS and zinc use, can be scaled up using a massive public health campaign, and with minimal funding (Sabot et al. 2012). However, there has been no reported follow up on adherence to treatment guidelines in India. So, a study on prescriptions for diarrhea among children in Rohtak, Haryana, to determine factors associated with adherence to treatment guidelines by the prescribing physicians was planned.

Importance of surveillance of antibiotic resistance among commensal and pathogenic bacteria. There is a serious lack of surveillance initiatives in resource-constrained settings, where the burden of infections requiring effective antibiotics is higher. In India there is no systematic surveillance of antimicrobial resistance at national or Regional level. The National Centre for Disease Control, under the Director General of Health Services, Ministry of Health and Family Welfare, Government of India, published

The National Policy for Containment of Antimicrobial Resistance, India (The National Policy for Containment of Antimicrobial Resistance, India 2011). However, the policy lacks a solid evidence base from studies done in India. The main constraint for generation of evidence-base for policy is lack of laboratory capacity in many parts of India and many low and middle-income countries. In view of the paucity of studies from India, two surveillance studies, one on nasal carriage of commensal *S. aureus* in children below five years of age and the other on bacterial pathogens isolated from the patients with suspected infections were planned.

The procedure by which a novel drug is carried to market step consists of a figure of phases. Generally it can be procedure by which a novel medicine is brought to market place step is having a numeral of different stage. Generally it can be collection underneath two stages Preclinical and the Clinical. Preclinical engross two-steps procedure. The primary step is to recognize and mock-up the organic goal within the corpse (the protein). The instant step is to recognize a lead complex that exhibit medicine-like properties with reverence to this organic objective followed by initial showing in animals. Then, the medicine goes throughout a lot of phases of scientific development in individuals. From this small percentage, it has been estimated that less than one quarter of candidates possess all the necessary pharmacokinetic and pharmacodynamic characteristics required to successfully become marketable products. Increasing the number of NCEs progressing to the clinical trial phases then substantially increases the number of failures at this late stage. Hence, the focus of medicine development has expanded greater to include procedures aimed at identifying potential failures as well as achievements.

MEASURING ANTIBIOTIC PRESCRIBING METHODS

The prescribed antibiotic data were collected at individual patient level and were grouped according to the suspected infectious aetiology. Each prescribed antibiotic was coded according to the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology, Anatomical Therapeutic Chemical (ATC) classification with Defined Daily Dose (DDD) 2009 (Methodology 2010) as defined in the ATC fifth level inJ01 (antibacterial for systemic use). Imidazole group (P01AB) and netazoxanide (P01AX11) were also included. The DDDs were calculated per 1000 patients per diagnosis (DDD/TPD) (Study-I) and the focus-specific DDDs were calculated per hundred patient days (DDD/HPD).

Laboratory methods

Antibiotic susceptibility testing Swabs from anterior nares were cultured within four hours of receipt in the microbiology laboratory on 5% sheep blood agar plates, incubated at 35 ± 1°C and examined for growth after 24-48 hours. The clinical samples were plated on blood agar and (or) Mac Conkey’s agar medium (HiMedia Laboratories Pvt. Ltd, Mumbai, India) within four hours of receipt in the laboratory.

The bacteria were identified by their typical colony morphology, results of Gram’s staining and conventional microbiological methods (Murray PR 1999).

Antibiotic susceptibility testing (AST) was performed by Kirby-Bauer disk-diffusion method on Muller Hinton agar plates. The disk strengths (antibiotic concentrations) were as recommended by the Clinical and Laboratory Standards Institute (CLSI) at the time of the study (CLSI 2006). CLSI interpretive criteria for susceptibility and resistance were followed (CLSI 2006). AST quality control was performed using the following reference strains: Escherichia coli ATCC (American Type Culture Collection) 25922, Klebsiellapneumoniae ATCC 70063, Pseudomonas aeruginosa ATCC 27853, Enterococcus faecalis ATCC 29212 and Stapylococcus aureus ATCC 29213. For Gram-negative bacteria, the intermediate susceptible isolates were counted as resistant in calculations. Extended-spectrum beta lactamase (ESBL) production was detected using the double-disksynergy test. According to the CLSI criteria for ESBL detection, each isolate with an inhibition zone diameter of ≤22 mm for ceftazidime or ≤27 mm for cefotaxime was considered to be a potential ESBL producer or screen positive. A zone diameter increase of≥5 mm for either antimicrobial agent when tested in combination with clavulanic acid versus when tested alone was considered as an ESBL-producing organism. K. pneumonia ATCC 700603 (positive control) and E. coli ATCC 25922 (negative control) were used for quality control in the ESBL tests (Jarlier et al. 1988).

Data Analysis

The data about all studies were entered and checked. The outcome was antibiotic prescribing calculated as DDD per TPD among patients with suspected infections attending outpatient clinics. Antibiotic prescribing among admitted patients calculated, as DDD per HPD was also the outcome. The primary outcome was ORS prescribing rate. The secondary Outcomes were (a) prescribing of "ORS together with zinc" and (b) antibiotics". For other paper the outcome was prevalence of nasal carriage of S. aureus in children below five years of age and prevalence of antibiotic resistance among isolates of S. aureus. For another paper the outcome was prevalence of antibiotic resistance among pathogens cultured from admitted patients with suspected patients.

Descriptive statistics were presented as mean, median and (or) proportion. Two-by-two tables were made to calculate crude odds ratio (OR) using Chi square test. The P-value smaller than 0.05 were taken to define statistical significance. The test of significance was two-sided. Odds ratios and their 95% confidence intervals (CI) were also computed all the variables were adjusted for age and sex. A complete case series analysis was used. A post-hoc power calculation was done for the study in study-III and was found to be 0.98. In study-II two multivariate stepwise logistic regression models, one for each secondary outcome variable, were computed. The outcome variables were controlled for design effect due to intra cluster correlation.

Ethical Considerations

There was no need for ethical committee approval as no intervention was done by the researcher and all medicines was prescribed by qualified doctors as per guidelines duly approved by ethical committee. Though an consent was taken from the patients to use their information for research purpose.

CONCLUSION

In this Study, an overall antibiotic prescribing rate of 66% was documented in the out patient diagnosis-prescribing study. In a study in Delhi using the exit interview methodology it was found that 39% of the patients attending public clinics and 43% of the patients attending private health-care facilities were prescribed antibiotics. However, that study was done among all patients attending outpatients and not specifically among patients suspected to have an infectious aetiology as in our study. Therefore, the proportion of patients receiving antibiotics is not strictly comparable. In another study done in secondary level hospitals in Maharashtra in outpatient attendees using the WHO core prescribing indicators, 35% of the prescriptions contained an antibiotic and 25% of the prescriptions contained an injection.

In our outpatient clinics inject able antibiotics were prescribed to 1.2% of the patients. This low rate could be due to the fact that our study involved only antibiotics and not all drugs in a prescription. Also, our study was done with only the specialist practitioners and not all practitioners. A study done among the Paediatric outpatient clinics of a tertiary care set-up found a rate of 29% for antibiotic prescribing among all children attending outpatients.

In contrast a study done in primary and secondary health-care facilities in Uttar Pradesh, India found a high prescribing rate (81.8%) of antibiotics. That study also noted differences in antibiotic prescribing between health care facilities at different levels. Lower prescribing rates were found in government hospitals compared to the private hospitals. Practitioners doing specialty practice prescribed fewer antibiotics compared to general practitioners. Facility level differences in the antibiotic prescribing were found, with less in the teaching hospital as compared to the non-teaching hospital.

REFERENCES

[1]. "Antimicrobial resistance: global report on surveillance" (PDF). The World Health Organization.
[2]. "GAO-11-801, Antibiotic Resistance: Agencies Have Made Limited Progress Addressing Antibiotic Use in Animals".
[3]. "General Background: Antibiotic Agents". Alliance for the Prudent Use of Antibiotics. Retrieved 21 December 2014.
[4]. "Pharmaceuticals Sold In Sweden Cause Serious Environmental Harm In India, Research Shows". ScienceDaily. ScienceDaily, LLC. 7 February 2009. Retrieved 29 January 2015. We estimated that the[water] treatment plant released 45 kilograms of the antibiotic ciprofloxacin in one day, which is equivalent to five times the daily consumption of Sweden,"
[5]. "Superbugs could kill more people than cancer, report warns". CBS News. 19 May 2016. Retrieved 12 June 2016.
[6]. "UK study warns of threat of antibiotics overuse, lack of new drugs". CCTV America.
[7]. Abdel-moein, K. A. and Samir, A. (2011) 'Isolation of entero toxigenic Staphylococcus aureus from pet dogs and cats: a public health implication.
[8]. Abell, S., Chapman, S., Nadin, L. and Warren, R. (1999) 'Seasonal variation in fluoroquinolone prescribing.
[9]. Abreu, Ana Cristina; McBain, Andrew J.; Simões, Manuel (1 September 2012). "Plants as sources of new antimicrobials and resistance-modifying agents". Natural Product Reports.
[10]. Adkoli, B. V., Gupta, V., Sood, R. and Pandav, C. S. (2009) 'From reorientation of medical education to development of medical educators', Indian J Public Health.
[11]. Adriaenssens, N., Coenen, S., Versporten, A., Muller, A., Minalu, G., Faes, C., Vankerckhoven, V., Aerts, M., Hens, N., Molenberghs, G. and Goossens, H. (2011) 'European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe.
[12]. Alekshun, M. N. and Levy, S. B. (2006) 'Commensals upon us', Biochem Pharmacol.
[13]. Al-Habib A; Al-Saleh, E (2010). "Bactericidal effect of grape seed extract on methicillin-resistant Staphylococcus aureus (MRSA)". Journal of Toxicology Science.
[14]. Alita A. Miller; Paul F. Miller (2011). "Current Strategies for Antibacterial Vaccine development". Emerging Trends in Antibacterial Discovery: Answering the Call to Arms. Horizon Scientific Press..
[15]. Allison E. Aiello; Elaine L. Larson; Stuart B. Levy (2007). "Consumer Antibacterial Soaps: Effective or Just Risky?". Clinical Infectious Diseases. 45.
[16]. Allison KR, Brynildsen MP, Collins JJ (2011). "Metabolite-enabled eradication of bacterial persisters by aminoglycosides". Nature.
[17]. Alvan, G., Edlund, C. and Heddini, A. (2011) 'The global need for effective antibiotics-a summary of plenary presentations', Drug Resist Updat.
[18]. Amadeo, B., Zarb, P., Muller, A., Drapier, N., Vankerckhoven, V., Rogues, A. M., Davey, P. and Goossens, H. (2010) 'European Surveillance of Antibiotic Consumption (ESAC) point prevalence survey 2008: paediatric antimicrobial prescribing in 32 hospitals of 21 European countries', J Antimicrob Chemother.
[19]. Anderson, M. R., Klink, K. and Cohrssen, A. (2004) 'Evaluation of vaginal complaints', JAMA.