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ORIGINAL ARTICLES

Surveillance report

SURVEILLANCE OF ANTIMICROBIAL RESISTANCE IN BULGARIA - A SYNOPSIS FROM BULSTAR 2003

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We introduce Bulgarian Surveillance Tracking Antimicrobial Resistance (BulSTAR) and make the first report on surveillance data for 2003. This longitudinal surveillance programme monitors the isolation and antimicrobial susceptibility of all clinically significant microorganisms isolated from blood cultures, cerebrospinal fluid, upper and lower respiratory tract, urine and wound samples in the participating microbiology laboratories. Twenty eight public, 45 hospital and 6 private laboratories from all 28 counties of the Republic of Bulgaria participated in BulSTAR 2003. The total number of isolates from marked sources during the surveillance period was 98 929. Seven microorganisms represented 72% of all isolated bacteria in BulSTAR 2003: *Escherichia coli, Staphylococcus aureus*, Proteus-Providencia-Morganella group, Klebsiella spp., Pseudomonas spp, *Streptococcus pneumoniae* and *Streptococcus pyogenes*. Generally the resistance of clinically significant Gram positive and Gram negative bacteria in Bulgaria was estimated to be at a medium level when compared with many other surveillance sources worldwide. A unique 32-year experiment on the population by treating all severe infections with an ampicillin/gentamicin combination resulted in twofold higher levels of resistance to amynoglycosides compared with other countries worldwide. This is due to the extremely conservative treatment schemes used in the former socialist countries, based on national directives and cheap domestic production of gentamicin and ampicillin. The forthcoming introduction of a computer network and improvements in detecting mistakes are expected to increase the sensitivity and the significance of BulSTAR surveillance system – an indispensable tool in the combat against increasing worldwide antibiotic resistance.

Euro Surveill 2005; 10(6): 79-82 Published online June 2005

Key words: antimicrobial resistance, Bulgaria, BulSTAR, microbiology, surveillance

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Introduction

Bulgaria is a small country situated in the north part of the Balkan Peninsula, near the geographical border between Europe and Asia. With a population of 7.9 million inhabitants, the Republic of Bulgaria is divided into 28 counties that are served by approximately 100 public microbiology laboratories of the national healthcare system. An increasing number of private microbiology laboratories are being established and are becoming part of the national healthcare surveillance system. The aims of this study are to introduce Bulgarian Surveillance Tracking Antimicrobial Resistance (BulSTAR), to make a synopsis on the surveillance data and to point out particular aspects of the resistance trends of some major pathogens in Bulgaria for 2003.

Methods

We introduce the Bulgarian Surveillance Tracking Antimicrobial Resistance (BulSTAR) and report summarised national data for year 2003. The surveillance programme was initiated in 1997 by the Department of Microbiology in the National Center of Infectious and Parasitic Diseases (NCIPD) in Sofia as a voluntary system for annual reporting of the isolation and antimicrobial susceptibility of all clinically significant microorganisms in 45 public microbiology laboratories from

blood cultures, cerebrospinal fluid (CSF), upper and lower respiratory tract, urine and wound samples. In the years that followed, the programme evolved into a national system for longitudinal surveillance of antimicrobial resistance, BulSTAR, organised and conducted under the jurisdiction of the Bulgarian Ministry of Health and coordinated by the Bulgarian Association of Microbiologists (BAM) [1]. Data from previous years are available on the Internet (www.bam-bg.net). BulSTAR monitors all clinically significant microorganisms, isolated in the collaborating centres and their susceptibility to more than 30 antimicrobial agents, tested routinely in the laboratories, using nationally recognised standardised method and an element of rule-based result checking, applied before the data are accepted. At present, the surveillance system covers almost the entire population in all 28 regions of Bulgaria. Data are collected separately for in-and outpatients, and for urine samples are also divided by sex. Additional information concerning patients' clinical data, samples assessment, laboratory methods and total number of materials and positive cultures in the laboratories is also included in a separate, supplementary part of the reports. We present here the first report on cumulative data, collected during the BulSTAR surveillance period from 1 January to 31 December 2003. Seventy nine microbiology laboratories from all regions of the country including 28 public, 45 hospital and 6 private laboratories sent their annual reports for this year. All organisms were assessed according nationally recognised guidelines [2,3,4]. Participating laboratories used the disk diffusion method of the National Committee for Clinical Laboratory Standards [5] or different commercial broth microdilution systems. Extended spectrum beta-lactamase (ESBL) production among Gram negative bacteria was assessed according to the National Committee for Clinical Laboratory Standards [5]. Standard (with Group A and B agents) and extended (with Group C agents) antibiograms are consistent with the National Committee for Clinical Laboratory Standards [6]. A National External Quality Assessment Programme (EQA) was implemented in 1998 to support the surveillance system. All microbiology laboratories participating in BulSTAR also participated in the EQA.

Results

General information - Supplementary data

Cumulated results from the supplementary part of the reports show that in 2003 the total number of clinical samples received in all participating microbiology laboratories was 1 208 234. Their numbers by sample type were as follows: 400 668 stool samples; –241 960 urines; –90 107 throat; –52 283 nasal; –62 176 sputum; –42 214 genital; 7167 punctures; 64 274 blood; 25 773 wound; 1636 CSF; 165 615 serological tests; and 54 361 others. The distribution reveals that stool samples make up a large part of the overall structure of specimens collected in the microbiology laboratories (34%), followed by urine samples (20%) and respiratory tract specimens (16%). The relatively high proportion of stool specimens observed is due to the inclusion in the supplementary part of the reports of great number of screening faecal samples received by the Hygiene Epidemiology Inspectorates for prophylactic examinations of food industry workers, military personnel and children under 3 years of age. Bacteria isolated from stool specimens and their susceptibility to antibacterial agents are monitored and analysed in a separate survey carried out by Enter-net [7].

BulSTAR 2003 analysed 485 926 samples collected from the six aforementioned sources. As explained above, stool samples are not the subject of BulSTAR. The total number of isolates from monitored sources is 98 929. This means that 20.4% of all clinical samples were positive (22.1% among community-acquired and 19.7% among nosocomial samples). According to the national guidelines based on NCCLS [6], a standard antibiogram is sensibility testing to 5-7 first line agents. The total number of antibiograms is 151 437, or approximately 1.5 antibiogram per isolate, which shows that approximately 50% of the isolates required an extended antibiogram with second and third line agents.

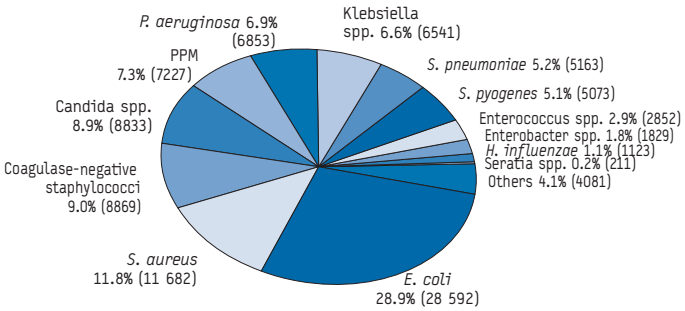
Aetiological structure

Figure 1 represents the relative proportion of all bacteria by species, isolated from six monitored sources, during the BulSTAR one year surveillance period. The most frequently isolated bacteria are: *Escherichia coli*, *Staphylococcus aureus*, Proteus-Providencia-Morganella group, Klebsiella species, Pseudomonas species, *Streptococcus pneumoniae* and *Streptococcus pyogenes*. These seven microorganisms represent 72% of all bacteria, isolated in participating laboratories in BulSTAR 2003. Candida species and coagulase-negative Staphylococci (CNS) increased to 9% each. The proportion is high, but can be explained by the lack of a strict definition of contamination, colonisation and infection.

However, despite this shortcoming, the overall structure of infections, based on the relative percent of isolated microorganisms monitored in BulSTAR 2003 is generally similar to that in most European countries [8,9].

FIGURE 1

Most common bacterial species isolated in microbiology laboratories – BulSTAR 2003

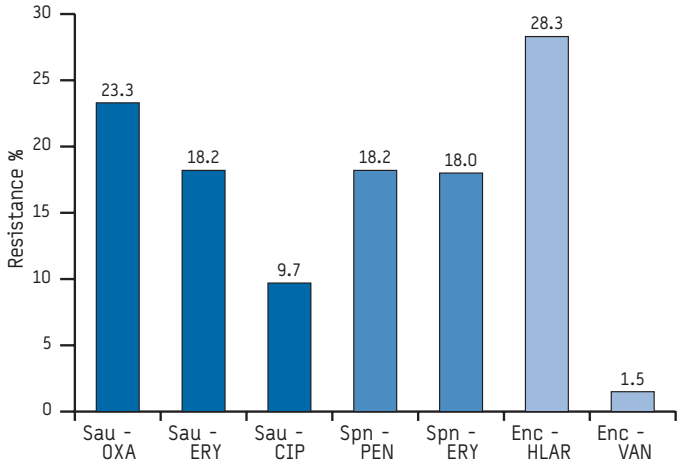


Resistance

Another aim of this study is to point out some aspects in the prevalence of resistance among the seven leading pathogens isolated in Bulgaria during the surveillance period to some indicator antibiotics. Figure 2 presents resistance rates among selected Gram positive bacteria.

FIGURE 2

Prevalence of resistance among Gram-positive bacteria – BulSTAR 2003



Sau, *S. aureus*; Spn, *S. pneumoniae*; Enc, Enterococcus spp.; OXA, oxacillin; ERY, erythromycin; CIP, ciprofloxacin; PEN, penicillin; VAN, vancomycin; HLAR, higl-level aminoglycoside resistance

Among Gram negative bacteria in BulSTAR 2003 standard levels of resistance were monitored, compared with many other surveillance sources worldwide [10-15]. Just as a typical example, resistance of E. coli, the most frequent isolate, to ampicillin in Bulgaria was 53.2% [1]. According to other sources this resistance varies from 37.1% among outpatients in Russia [13,14] to 64.3% among invasive isolates in the population covered by EARSS participating Romanian laboratories in Romania [11]. Ciprofloxacin resistance was found in 13.5% of *E.coli* in Bulgaria: this proportion varied from 4.5% in Russia to 23% in Portugal [11]. According to SENTRY, the prevalence of resistance among *Pseudomonas aeruginosa* isolates was 9% to imipenem but only 16.8% to ciprofloxacin.

ESBL-producing Gram negative bacteria are of particular interest and are monitored worldwide.

ESBL production in Gram negative bacteria in Bulgaria is presented in Table 1.

ESBL production among E.coli isolates was 11.5% in Russia, 21.4% among *Klebsiella pneumoniae* isolates in Europe and 37.3% in Latin America and 21% among Enterobacter species. [14].

TABLE 1

Extended spectrum beta-lactamase production among Gram-negative bacteria – BulSTAR 2003

Bacterial species	ESBL production (percentage)
E.coli	8.0
Proteus spp.	17.8
Klebsiella spp.	23.7
Enterobacter spp.	23.3

Antibiotic consumption

In response to the Council Recommendation on the prudent use of antimicrobial agents in human medicine, [16] the Department of Microbiology in the NCIPD started to collect data for antimicrobial consumption in Bulgaria at the national level as part of BulSTAR in 2002. We introduced sales data on hospital antibiotic consumption for 2002 as the number of Defined Daily Doses (DDDs) per 100 bed-days, according to the World Health Organization's ATC/DDD methodology.

TABLE 2

Hospital antibiotic consumption in Bulgaria for 2002

Antibiotics	Number DDD per 100 bed-days
J01 - Antibacterials for systemic use (overall)	47.4
J01A - Tetracyclines	0.0
J01B - Amphenicols	0.0
J01C - Penicillins	9.6
J01D - Other beta-lactam antibacterials	16.8
J01E - Sulfonamides and trimethoprim	0.0
J01F - Macrolides, lincosamides and streptogramins	0.3
J01G - Aminoglycoside antibacterials	12.3
J01M - Quinolone antibacterials	7.6
J01X - Other antibacterials	0.7

Aminoglycosides

In Table 3 we present more detailed data concerning the resistance to agents in the aminoglycosides group, emphasising the striking difference between resistance levels in Bulgaria and those in the rest of the world.

TABLE 3

Prevalence of resistance among selected bacteria against aminoglycosides, Bulgaria

Microorganism	Gentamicin resistance (percentage)	Amikacin resistance (percentage)
S.aureus	13.8	10.0
E.coli	15.7	6.2
Klebsiella spp.	26.2	15.9
Enterobacter spp.	28.5	16.2
Pseudomonas spp.	38.7	24.9
Acinetobacter spp.	59.8	38.4

In the examples above, the levels of resistance are twofold higher than levels usually detected in European and other countries worldwide [11, 13-15]. Other sources quote resistance to gentamicin among *E.coli* –3.4% and among *K. pneumoniae* –6% (SENTRY). In Russia, *E.coli* resistance to gentamicin was 20.9%, but the resistance to amikacin was unexpectedly low: 2.2% among nosocomial isolates.

Discussion

General information – Supplementary data

The relatively high proportion of stool specimens is due to the inclusion in the Supplementary part of the reports of screening faecal samples received by Hygiene Epidemiology Inspectorates. Although they are not the subject of BulSTAR's analysis they give an overall picture of the total workload and all clinical samples received in participating Bulgarian microbiology laboratories in 2003.

Aetiological structure

Seven microorganisms represent 72% of all bacteria, isolated in participating laboratories in BulSTAR 2003 [FIGURE 1]. The relatively high proportion of Candida species and CNS (9% each) is explained by the lack of strict definition for contamination, colonisation and infection. In general the overall structure of infections, based on the relative percent of isolated microorganisms monitored in BulSTAR 2003 is similar to that in most European countries.

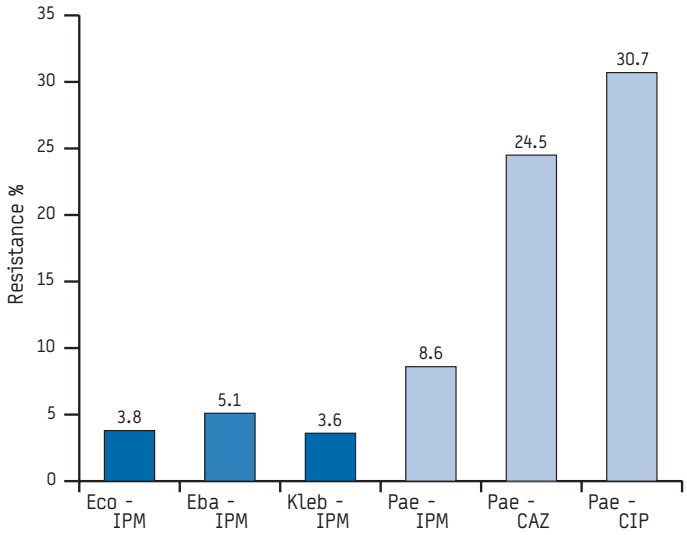
Resistance and antibiotic consumption

Resistance rates among Gram positive bacteria [FIGURE 2] in Bulgaria in 2003 were estimated to be at a medium level when compared with the levels observed in the last few years in other countries in central Europe [10,11], eastern Europe [12], Russia [13,14] and worldwide [15]. Fortunately there were no vancomycin-resistant or intermediate Staphylococcus species.

Levels of resistance in Gram negative bacteria [FIGURE 3] in BulSTAR 2003 were similar to those monitored worldwide. The ESBL production [TABLE 1] demonstrates one typical picture of resistance to the most commonly used group antibiotics in Bulgaria in the past 10 years. Table 2 demonstrates antibiotic use of major antibiotic classes as proportion of the total consumption of antimicrobials in Bulgarian hospitals, which is 47.4 DDD per 100 bed-days in Bulgarian hospitals as a proportion of a total of 47.4 DDD per 100 bed-days. Nevertheless, while it is not surprisingly that beta-lactams have the highest consumption, the significant consumption of aminoglycosides is definitely noteworthy.

FIGURE 3

Prevalence of resistance among Gram-negative bacteria – BulSTAR 2003



Eco, *E. coli*; Eba, Enterobacter spp.; Kleb, Klebsiella spp.; Pae, *P. aeruginosa*; IPM, imipenem; CAZ, ceftazidime; CIP, ciprofloxacin

Aminoglycosides

The prevalence of resistance to the two chosen agents in the aminoglycosides group [TABLE 3] is of particular interest, because Bulgaria has a unique experience in the treatment of severe infections with an ampicillin/gentamicin combination, lasting for over 32 years. This is because of the extremely conservative treatment schemes used in the former socialist countries, based on national directives and cheap domestic production of gentamicin and ampicillin.

Conclusions

Some trends in the prevalence of antimicrobial resistance are universal, while others are unique for different countries, regions and even hospitals. In Bulgaria the prevalence of resistance may be generally characterised as relatively standard for Eastern Europe, taking into account the lack of reliable methods for excluding duplicate isolates. The participating laboratories do not have strict guidelines for multiple isolate exclusion, nor do they have adequate computerisation. They also have bias results towards artificially high rates of resistance. This situation must be remedied.

The advantages of this large scale longitudinal surveillance system are the significant number of isolates, great number of microorganisms monitored, and annual data on susceptibility to more than 32 antimicrobials. Data collected and summarised in annual reports are a good basis for elaboration of local hospital strategies for containment of antimicrobial resistance. In Bulgaria, only the university hospitals currently have any experience with restrictive antibiotic policies [17,18].

The shortcomings of the system include old nationally recognised guidelines for organism assessment and lack of strict definitions for contamination, colonisation and infection. Additional disadvantages include the inclusion of multiple isolates, lack of comprehensive national strategy for combatting antimicrobial resistance and insufficient budget resources for the healthcare system in Bulgaria.

The recently introduced upgraded computer network, including the ongoing improvements in detecting mistakes, are expected to increase the sensitivity and the specificity of the surveillance of antibiotic resistance and communicable diseases in Bulgaria.

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