SURVEILLANCE OF ANTIMICROBIAL RESISTANCE - KEY POINTS

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Editorial

Man has always struggled with infectious diseases that throughout the centuries, have cost millions of lives mainly through epidemics and pandemics. Impressive discoveries at the end of 19thC and through the 20thC improved the situation resulting from a growing understanding of the aetiology and pathogenesis of infectious diseases. However, the main beneficial effect on the course of infectious diseases came from the discovery of vaccines and antibiotics. The former have given long lasting protection against many of them leading to the eradication of some such as smallpox and polio. The latter the most important weapon in the treatment of infections, decreased morbidity and mortality significantly. Unfortunately the microbes did not give up. In time, the emergence of new infectious diseases was noted and the re-emergence of old ones, thought to have been eradicated. Next came the unexpected phenomenon of rapidly emerging and growing resistance to antimicrobial agents. The latter is mainly the result of overuse and misuse of antimicrobial compounds. When penicillin, - the first antibiotic, was introduced into clinical practice in 1940s Alexander Fleming warned the medical world about the danger of the resistance emergence, especially when used inappropriately. But this important voice has been heard only comparatively recently, after our armamentarium of effective antimicrobial drugs started to shrink suddenly.

The emergence of resistance to all classes of antibiotics and chemotherapeutic agents in almost all bacterial species and their clonal spread on a global scale is of great concern from the perspective not only of the individual patient but also of public health.

In addition, the development of new antimicrobial drugs has slowed down and even some of the leading pharmaceutical companies have stopped research in this field because of great risk and low profit.

The leading public health institutions, scientific societies, study groups etc and also the European Commission and World Health Organization (WHO) responded to this new threat by establishing recommendations and legislation calling for immediate action to stop the spread of resistant bacteria (1-4). All agreed that the most important steps are: establishment of national surveillance systems, improvement in microbiological diagnostics especially by developing deoxyribonucleic acid (DNA) based methodologies, research on new drugs and vaccines, enforcement of infection control programmes and education of professionals and the public in order to decrease antibiotic consumption. In Europe a number of meetings have been held, supported by the European Commission and WHO to address the issue of antibiotic resistance.

Surveillance of resistance is one of the most important systems used in combating resistance development and spread since it allows to identify "Hot Spots" where resistance develops most quickly and thus allows for targeted interventions. It should not be limited to human infections only but it should include veterinary medicine in particular with regard to food and plant production.

Several countries in different parts of the world have introduced national programmes of antibiotic resistance surveillance. In 1999 the European Antimicrobial Resistance Surveillance System was established (EARSS) and presently almost all European countries including non-EU have been participating (http://www.earss.rivm.nl) (5). The system has been monitoring *Escherichia coli, Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus faecalis* and *Enterococcus faecium* isolated from invasive infections according to a standardized protocol. There are also other European networks restricted to very specific pathogens as e.g.Euro -Tb. Most of the surveillance studies in the USA have been organized by the Centers of Disease Control and Prevention (CDC).

Surveillance according to the definition of ESCMID Study Group for Antimicrobial Resistance Surveillance (ESGARS) presenting European recommendations for antimicrobial resistance surveillance indicate "a systematic, ongoing data collection, analysis and reporting process that quantitatively monitors temporal trends in the occurrence and distribution of susceptibility and resistance to antimicrobial agents, and provides information useful as a guide to medical practice, including therapeutics and disease control activities" (6). It should be stressed that the most important role of surveillance is that the collected data must be

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disseminated to those who need to know in order to undertake targeted actions.

There are internationally accepted standards, which every surveillance system should meet (6, 7). However, the range of collected data may vary greatly, according to the use to which it is to be put, the expertise of the laboratory and the finances available (6-9). The latter is why in some countries only industry-sponsored surveillance studies have been feasible. Of them the best known are the ALEXANDER Project, SENTRY, PROTEKT, MYSTIC. Usually, bacterial isolates locally collected in many different centres all over the world are sent to central laboratory, which perform susceptibility testing according to well standardized procedure. The shortcoming of this type of surveillance is that immediate actions are not possible and the study has mostly epidemiological value. Moreover, only limited data about patient characteristics, treatment etc are often available.

Although since antibiotic resistance has been considered as one of the major threat to public health a growing number of countries world wide have established government-supported programmes.

Good standardized methodology is a major requirement in every surveillance study. This permits a reliable comparison to be made between different centers and different countries.

Surveillance can be undertaken at both local and national levels and can also be part of international network such as eg EARSS. Its aim is to accumulate knowledge about the prevalence of resistant strains amongst bacterial pathogens.

Many of the surveillance data are derived from routine diagnostic microbiology so both inter laboratory and external laboratory quality control should be put in place. EARSS- participating laboratories perform annually an External Quality Assurance Scheme (EQAS) distributed by United Kingdom National External Quality Assessment Scheme (UKNEQAS) (10). In many countries susceptibility testing is performed by agar disc diffusion test in others minimal inhibitory concentrations (MICs) are determined by agar or broth dilution methods or Etest.

It is impossible to cover all pathogens isolated from all patients in the surveillance programme since these types of collative data would be strongly biased. The incorporation of the most clinically relevant bacterial species should therefore be the best solution. Some studies, especially those performed on a larger scale are restricted to selected sources of isolates eg blood, respiratory tract, urinary tract. Whatever the source, one isolate per patient must be included and it should constitute the most probable etiologic agent of an infection. In order to decrease bias consecutive isolates should be reported. There are also surveillance programmes which follow resistance incidence in selected pathogens derived from different sites of infection. It has to be remembered that etiologic agents of infections may differ between patients populations depending on age (neonates vs children vs adults), risk factors, underlying pathology, geographical location etc and this is why they should be reported separately for each group. For example, neonatal meningitis is most commonly caused by *S. agalactiae, L. monocytogenes*, and *E. coli* (harbouring usually K1 capsular antigen) while in an adult population the most prevalent are *N. menigitidis* and *S. pneumoniae*.

In a good surveillance systems isolates from infection should be separated from those responsible for only colonization, difficult to achieve in some samples. This is why some systems, such as EARSS rely only on isolates recovered from sterile body sites, which give more reliable results.

The data are mostly presented as prevalence, i.e. the proportion of resistant isolates per total number of isolates being analysed. They value is strongly augmented when they are linked to adequate denominators such as characteristics of patients, medical institutions, general population etc. In some studies they are enriched by molecular investigations of resistance mechanisms, their evolution and epidemiology. This type of surveillance has a very important role in pointing to major risks of resistance emergence. Recently, thanks to a wide European Project (European Surveillance of Antimicrobial Consumption - ESAC) it was elegantly shown that one of the most important factors in the development and dissemination of antibiotic resistance is the level of antimicrobial drugs consumption (11). This seems to be one of the most important driving force of this phenomenon.

In addition to European networks several surveillance studies have been conducted on a national level. In Poland the most important is the government sponsored programme OPTY/NEURON/ESAC. This is closely linked to EARSS and ESAC and reporting the resistance prevalence from the network of 60 hospitals linked to patients, hospitals, and laboratory data. In those hospitals as well as nationally antibiotic consumption is also recorded. Continuous surveillance of community-acquired central nervous system infections and meningococcal disease is linked to European network which allowed recently to reveal the important increase of *N. meningitidis* group C and the appearance of

meningococci with decreased susceptibility to penicillin (submitted for publication). In response to these data the vaccine against group C was purchased as an epidemiological reserve and vaccination has been recommended. The continuation of the international study - ALEXANDER Project has been carried out at the national level and the data on susceptibility of bacterial pathogen responsible for community acquired lower respiratory tract infections and pharyngitis have been collected (12). It serves as a base to verify and update National Guidelines for antimicrobial therapy of respiratory tract infections. Country wide studies on the susceptibility of urinary tract pathogens helped to establish current therapeutic recommendations (13).
Surveillance studies on the prevalence of resistance and its evolution in selected bacterial species of major clinical importance have been carried out in Poland for many years. Their results point at trends and reveal the most important threats of which the main are: extended spectrum ß-lactamases (ESBLs), methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin intermediate *Staphylococcus aureus* (VISA), penicillin-resistant pneumococci (PRP), vancomycin resistant enterococci (VRE), macrolide resistant *Streptococcus pyogenes* and recently carbapenemases of *Pseudomonas aeruginosa* (MBL) (14-18). Antimicrobial resistance in Poland reflects global epidemiology. Surveillance permits not only to improve antibiotic policy and infection control but also constitutes excellent base for evidence-based education. Moreover when accompanied by research it provides better insight into the biology of microorganisms and contributes to the discovery of new targets for novel agents and vaccines.

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SPREMLJANJE ODPORNOSTI BAKTERIJ - KLJUČNE UGOTOVITVE

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Uvodnik

Človek se je od nekdaj boril proti infekcijskim boleznim, ki so v glavnem zaradi epidemij in pandemij skozi stoletja zahtevale na milijone življenj. Do pomembnega napredka je prišlo z odkritji ob koncu 19. stoletja in v 20. stoletju. Rezultat je bilo boljše poznavanje etiologije in patogeneze infekcijskih bolezni, s tem pa tudi izboljšanje razmer na tem področju. Najpomembneje pa je vplivalo na potek infekcijskih bolezni odkritje cepiv in antibiotikov. S cepljenjem je bila zagotovljena dolgotrajna zaščita pred številnimi najpogostejšimi infekcijskim boleznim, nekatere od njih, kot npr. črne koze in poliomielitis, so uspeli tudi izkoreniniti. Antibiotiki, ki so najmočnejše orožje v boju proti infekcijskim boleznim, so pomembno znižali obolevnost in smrtnost zaradi teh bolezni. Na žalost pa se mikrobi niso predali. S časom so se pojavile nove infekcijske bolezni, znova pa so oživele tudi tiste, za katere je veljalo, da so izkoreninjene. Temu je sledil nepričakovani pojav hitro nastajajoče in naraščajoče odpornosti bakterij proti antibiotikom, do česar je prišlo zaradi pretirane in napačne uporabe antibiotikov. Ko so v 40. letih prejšnjega stoletja uvedli v klinično prakso prvi antibiotik, penicilin, je Aleksander Fleming že opozoril medicinske kroge na nevarnost pojava odpornosti, predvsem zaradi neustrezne uporabe teh zdravil. Resnosti njegovega svarila pa so se zavedli sorazmerno pozno, ko se je število učinkovitih antibiotikov začelo nenadoma krčiti. Odpornost skoraj vseh vrst bakterij proti vsem vrstam antibiotikov in kemoterapevtikov in njeno širjenje po vsem svetu je zaskrbljujoč pojav, tako za bolnike kot za vse javno zdravstvo.

Poleg tega se je upočasnil razvoj novih antimikrobnih učinkovin. Celo nekatere vodilne farmacevtske hiše so zaradi velikega tveganja in majhnega dobička opustile raziskave na tem področju.

Vodilne javnozdravstvene ustanove, znanstvena združenja in druge raziskovalne skupine, pa tudi Evropska komisija in SZO, so odgovorile na to grožnjo s pripravo priporočil in zakonskih podlag za takojšnje ukrepanje ter zajezitev širjenja odpornih bakterij (1-4). Vsi so enotno podprli naslednje najpomembnejše ukrepe: oblikovanje nacionalnih programov za spremljanje, izboljšanje mikrobiološke diagnostike, predvsem z uvedbo metod na osnovi DNK, raziskave za izdelavo novih zdravil in cepiv, izboljšanje programov za nadzor okužb ter izobraževanje strokovnjakov in prebivalstva, ki naj bi prispevalo k zmanjšanju porabe antibiotikov. Problem odpornosti bakterij so obravnavali na številnih sestankih v Evropi, ki so potekali ob podpori Evropske komisije in SZO.

Spremljanje odpornosti je eden najpomembnejših ukrepov za zajezitev njenega razvoja in širjenja. Z nadzorom namreč prepoznamo tvegana področja, kjer se odpornost najhitreje razvija in kjer lahko ustrezno ukrepamo. Ukrepi pa niso omejeni le na medicino, temveč morajo zajeti tudi področje veterine in predvsem področje pridelave rastlin za proizvodnjo hrane.

Več držav po vsem svetu je že uvedlo nacionalne programe za spremljanje odpornosti bakterij. Leta 1999 je bil ustanovljen evropski program za spremljanje odpornosti bakterij (angl.: European Antimicrobial Resistance Surveillance System, EARSS), v katerem sodelujejo že skoraj vse evropske države, vključno z državami, ki še niso članice Evropske unije (www.earss.rivm.nl) (5). V tem programu spremljajo bakterije vrst *Escherichia coli, Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus faecalis* in *Enterococcus faecium*, ki so jih osamili po enotnem protokolu ob invazivnih okužbah. Nekatere druge evropske mreže spremljajo le specifične patogene mikrobe, npr. Euro-Tb. V ZDA so večino programov spremljanja organizirali v Centru za preprečevanje in nadzor bolezni (CDC).

V Evropskih priporočilih za spremljanje odpornosti bakterij proti antibiotikom (ESGARS) je spremljanje opredeljeno kot »sistematično, neprekinjeno zbiranje, analiziranje in posredovanje podatkov o pojavljanju in razporeditvi odpornosti bakterij in tako zagotavljanje koristnih informacij, ki usmerjajo medicinsko prakso, vključno z zdravljenjem in ukrepi za obvladovanje bolezni« (6). Poudariti je treba, da je najpomembnejša naloga spremljanja posredovanje zbranih podatkov vsem tistim, ki te informacije potrebujejo za usmerjeno ukrepanje na tem področju.

Vsak program spremljanja mora potekati skladno z mednarodno veljavnimi standardi (6, 7). Obseg zbranih podatkov je različen in je odvisen od tega, v kakšen namen so zbrani podatki ter od strokovne ravni laboratorija in finančnih sredstev, ki so na voljo (6-9).

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Zato je v nekaterih državah izpeljava programov spremljanja povsem odvisna od sponzorskih sredstev industrije. Najbolj znani programi te vrste so projekt ALEKSANDER, SENTRY, PROTEKT in MYSTIC. Bakterijske izolate običajno zbirajo v lokalnih laboratorijih po vsem svetu in jih nato pošljejo v osrednji laboratorij, kjer s standardiziranimi metodami testirajo njihovo občutljivost na antibiotike. Takšno spremljanje ima predvsem epidemiološki pomen, njegova pomanjkljivost pa je v tem, da ne omogoča takojšnjega ukrepanja. Poleg tega so podatki o značilnostih bolnika, zdravljenju itd., ki jih dobimo, pogosto precej pomanjkljivi.

Zaradi spoznanja, da je odpornost mikrobov proti antibiotikom ena največjih nevarnosti za javno zdravstvo, se vlade po vsem svetu v vedno večjem številu odločajo za financiranje programov spremljanja. Za vsak program spremljanja je bistvenega pomena dobra in standardizirana metodologija, ki omogoča zanesljive primerjave podatkov med različnimi centri in državami. Spremljanje lahko poteka na lokalni in državni ravni, pa tudi v okviru mednarodne mreže, kot je npr. EARSS. Namen programa je zbiranje podatkov o prevalenci odpornih sevov patogenih bakterij.

Ker veliko število podatkov pridobimo z rutinskimi mikrobiološkimi preiskavami, je zelo pomemben notranji in zunanji nadzor kakovosti laboratorijskega dela. Laboratoriji, ki sodelujejo v EARSS, so vključeni v redni letni nadzor (EQAS, shema za zunanji nadzor kakovosti), ki ga izvaja britanski UKNEQAS (10). V številnih državah določajo občutljivost bakterij za antibiotike z disk-difuzijsko metodo, v drugih pa določajo minimalno inhibicijsko koncentracijo (MIK) antibiotika z dilucijsko metodo na agarju ali v bujonu, ali z E-testom.

V okviru programa ni mogoče spremljati vseh izoliranih patogenih mikroorganizmov, ker bi bili podatki te vrste zelo pristranski. Najboljša rešitev je spremljanje klinično najpomembnejših vrst bakterij. Nekatere študije, predvsem obsežnejše, obravnavajo le izbrane izolate bakterij, npr. iz krvi, dihal in sečil. Ne glede na mesto odvzema pa mora biti v študijo vključen za vsakega bolnika po en izolat bakterije, ki je najverjetnejši povzročitelj okužbe. Za bolj objektivno določanje je treba obravnavati zaporedne izolate. V nekaterih programih spremljajo incidenco odpornosti izbranih patogenih mikroorganizmov, odvzetih z različnih mest okužbe. Vedeti moramo, da so povzročitelji okužb v različnih skupinah bolnikov različni; te razlike so odvisne od starosti bolnikov (novorojenčki - otroci - odrasli), od dejavnikov tveganja, od spremljajočih bolezni, od geografskega območja in od drugih dejavnikov. Zato morajo biti poročila pripravljena za vsako skupino posebej. Tako so najpogostejši bakterijski povzročitelji neonatalnega meningitisa *Streptococcus agalactiae, Listeria monocytogenes in E. coli* (ta običajno vsebuje kapsularni antigen K1), medtem ko je pri odraslih povzročitelj največkrat *Neisseria menigitidis* in *S. pneumoniae.*

V dobrih programih spremljanja odpornosti morajo biti izolati, ki so povzročili okužbo, ločeni od tistih, ki le kolonizirajo površine, kar je pri nekaterih vzorcih težko izvedljivo. Zato v nekaterih programih, kot je npr. EARSS, obravnavajo le bakterije, izolirane s sterilnih področij telesa, s čimer tako dobijo bolj zanesljive rezultate. S podatki večinoma prikažejo prevalenco, tj. delež odpornih izolatov bakterij v celotnem številu analiziranih izolatov. Vrednost podatkov pa se bistveno poveča, kadar se povežejo z ustreznimi denominatorji, kot so npr. značilnosti bolnikov, zdravstvene ustanove, splošna populacija itd. V nekatere študije so vključene še molekularne raziskave mehanizmov odpornosti, razvoja mehanizmov odpornosti in njihove epidemiologije. Spremljanje te vrste ima zelo pomembno vlogo pri ugotavljanju najpomembnejših tveganj za nastanek odpornosti. S pomočjo obširnega evropskega projekta ESAC so nedavno prikazali, da je poraba antibiotikov eden najpomembnejših dejavnikov, ki vpliva na razvoj in širjenje odpornosti mikrobov na antibiotike (11). Poraba antibiotikov je tako po vsej verjetnosti najpomembnejše gibalo naraščanja odpornosti.

Poleg skupnih evropskih programov spremljanja poteka tudi več programov na nacionalni ravni. Na Poljskem je najpomembnejši program, ki ga sponzorira vlada OPTY/NEURON/ESAC. Tesno je povezan z EARSS in ESAC in poroča o prevalenci odpornosti na osnovi podatkov mreže 60 bolnišnic. Zbrani so tudi podatki o porabi antibiotikov v teh bolnišnicah in na državni ravni. Na osnovi stalnega spremljanja doma pridobljenih okužb centralnega živčevja in meningokoknih okužb, povezanega z evropsko mrežo, so nedavno ugotovili velik porast *N. meningitidis* skupine C in pojav meningokokov z zmanjšano občutljivostjo za penicilin (poročilo poslano v objavo). Posledica te ugotovitve je bila nabava cepiva proti meningokokom skupine C, kar je epidemiološka rezerva. Izdano pa je bilo tudi priporočilo za cepljenje. V nadaljevanju mednarodnega projekta ALEKSANDER, ki je potekal v nacionalnih okvirih, so zbirali podatke o občutljivosti bakterij, ki povzročijo doma pridobljene okužbe spodnjih dihal in faringitis (12). Ti podatki so osnova za preverjanje in posodabljanje nacionalnih smernic za antibiotično

zdravljenje okužb dihal. Tudi nova priporočila za zdravljenje okužb sečnih poti so pripravili s pomočjo nacionalnih študij o občutljivosti patogenih mikroorganizmov v sečnih poteh (13). Na Poljskem že več let spremljajo prevalenco odpornosti in njen razvoj pri izbranih, klinično pomembnih vrstah bakterij. Izsledki kažejo, kakšno je gibanje odpornosti in pri katerih mikrobih je nevarnost, da se pojavi odpornost, največja. Sem sodijo beta laktamaze z razširjenim spektrom (ESBL), na meticilin odporni *Staphylococcus aureus* (MRSA), *Staphylococcus aureus* z nizko stopnjo odpornosti na vankomicin (VISA), pnevmokoki, odporni na penicilin (PTP), enterokoki, odporni na vankomicin (VRE), na makrolide odporen *Streptococcus pyogenes* in v zadnjem času še *Pseudomonas aeruginosa* (MBL) (14-18). Odpornost bakterij, ugotovljena na Poljskem, odslikava svetovno epidemiološko stanje. S programi spremljanja odpornosti izpopolnjujemo smernice za uporabo antibiotikov in bolje obvladujemo okužbe, oblikujemo pa tudi izvrstno bazo podatkov za pouk, ki temelji na dokazih. Spremljanje, povezano z raziskovalnimi projekti, pa poglablja znanje o biologiji mikroorganizmov in prispeva k odkrivanju novih ciljev za nova zdravila in cepiva.

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