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PROTEAN NATURE OF INFECTIOUS DISEASES – TRENDS IN THE TERRITORY OF THE REPUBLIC OF SERBIA

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Summary. *In infectology, more than anywhere else in medicine, we are witnessing the variability, vicissitude of pathology. The changes of the relationship of man and his microbial environment have been especially dynamic in the last decades. In order to define the nature of this process, its possible origin and regularity, we compared the reports on infectious diseases in the Republic of Serbia for 1987 (from 1983 to 1987) and 2004 (from 2000 to 2004). A statistically significant reduction of morbidity was found, caused by a reduced incidence of vaccine-preventable infections (rubella, mumps morbilli, pertussis) and infections related to basic hygiene habits and sanitation (gastrointestinal tract infections, scabies, viral hepatitis type A, gonorrhoea...). On the other hand, there were significantly more infections caused by infectious mononucleosis and morbus Lyme agents, which have a specific relationship with the immune system, as well as the diseases which are the consequence of immune deficiency, such as herpes zoster or fungal diseases. At the same time, paradoxically, changes in the immune status and increased microbial resistance are the basis of a significant increase of mortality from infectious diseases. Overall, the evolution of our relationship with microbial environment is the consequence of general social progress, as well as the progress of medicine itself, and this relationship is nowadays characterized by the prevalence of infections caused by the microbial agents conditionally compromising with their hosts.*

Key words: *Infectious disease, epidemiology, protean, Republic of Serbia*

Introduction

People and microbes have a long history of conflicts and mutual adaptation. We are now witnessing some dynamic changes in their relationship. It seems that conspicuous, traditional infectious entities are becoming more rare, and that we are commonly faced with serious infections with complex clinical presentation. Most important now are opportunistic and nosocomial infections, development of microbial drug resistance, new infectious diseases, more common infection-induced diseases and so on. Closer definition of these problems is the basis of our everyday practice, but it is also the initial principle for the prediction and possible planning of our future with microenvironment.

This paper aims at analyzing the trends of infectious diseases in the Republic of Serbia in order to verify the supposed epidemiologic changes, to determine in more detail their nature, possible origin and rules they are governed by.

Materials and Methods

We utilized in this paper the Reports on Infectious and Parasitic Diseases in the territory of the Republic of Serbia by the National Institute of Public Health Surveillance "Dr Milan Jovanović – Batut" (1,2). Taking care that there was at least 15 years between the reports, we randomly chose those for 1987 and 2004. Each report analyzed the epidemiologic situation in the previous 5-year period (from 1983 to 1987, and from 2000 to 2004), with special consideration of 1987 and 2004. With Student's *t*-test or Cochrane and Cox method, we compared the data on morbidity and mortality of infectious diseases.

Results

Comparing the reports, we established that there was a significant decrease in average yearly morbidity of infectious diseases in the period 1987-2004 (2 015 ± 110 *vs* 1 264 ± 136, $p < 0.001$) (Figure 1). In order to analyze their origin, we observed the first ten (most common) diseases, which made up over 90% of overall morbidity (Table 1). Marked decrease in morbidity was demonstrated for rubella (227 ± 204 *vs* 9.2 ± 7.3, $p<0.05$), mumps (175 ± 88 *vs* 5.2 ± 2.5, $p<0.001$), morbilli (58 ± 49 *vs* 0.25 ± 0.11, $p<0.001$) and similar was observed for pertussis (16.5 ± 7.9 *vs* 0.16 ± 0.09, $p<0.001$), the 12th most common disease in the report

for 1987 (Figure 2). A statistically significant decrease in morbidity was also registered for gastrointestinal tract infections (554 ± 71 *vs* 343 ± 30, $p<0.001$), scabies (254 ± 51 *vs* 73 ± 12, $p<0.001$), acute viral hepatitis A (89 ± 32 *vs* 14.4 ± 8.3, $p<0.01$), scarlatina (69 ± 22 *vs* 37 ± 6.3, $p<0.05$) and gonorrhoea (43 ± 16 *vs* 2.23 ± 0.71, $p<0.001$) (Figure 3).

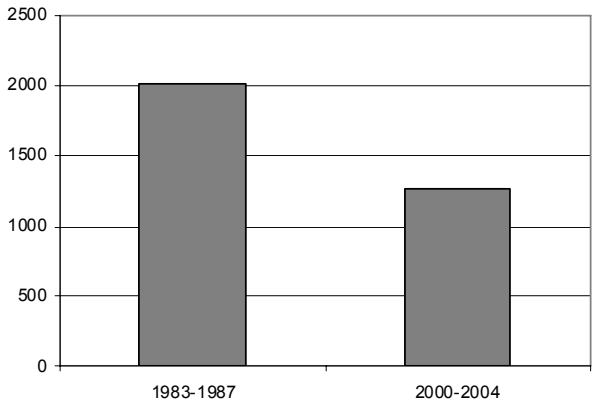

Fig. 1. Average yearly morbidity of infectious diseases

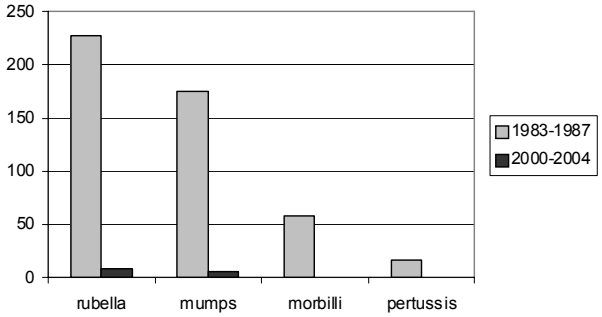

Fig. 2. Average yearly morbidity of vaccine-preventable diseases

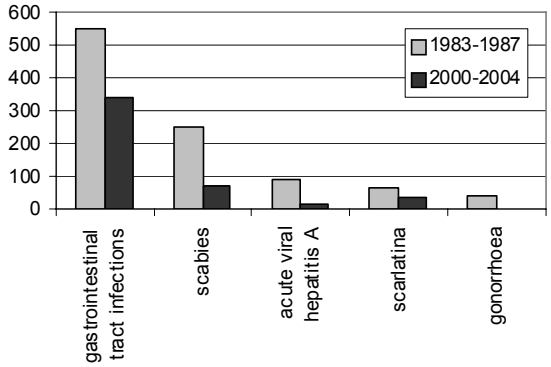

Fig. 3. Average yearly morbidity of gastrointestinal tract infections, scabies, viral hepatitis A, scarlatina and gonorrhoea

Table 1. Morbidity of ten most common diseases

Morbidity of ten most common diseases			
1983 – 1987		2000 - 2004	
Gastrointestinal tract infections	554	Varicella	571
Varicella	540	Gastrointestinal tract infections	343
Scabies	254	Scabies	73
Rubella	227	Herpes zoster	60
Mumps	175	Angina streptoccocica	50
Acute viral hepatitis A	89	Mycosis	43
Scarlatina	69	Scarlatina	37
Morbilli	58	Mononucleosis infectiva	24
Angina streptococcica	44	Acute viral hepatitis A	14
Gonorrhoea	43	Morbu Lyme	10

At the same time, altered relationships between the most common diseases were also caused by a significant rise in morbidity of herpes zoster (8.1 ± 4.5 *vs* 60.6 ± 15.5, $p<0.001$), mycoses (19.7 ± 5.2 *vs* 43.2 ± 9.1, $p<0.01$), infectious mononucleosis (8.9 ± 2.0 *vs* 24.1 ± 11.1, $p<0.05$) and Lyme borreliosis (4.5 *vs* 10.3 ± 2.7, $p<0.05$) (Figure 4).

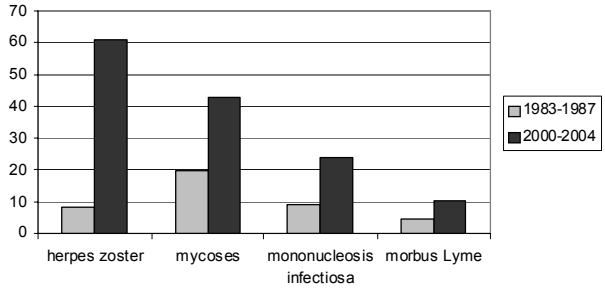

Fig. 4. Average yearly morbidity of herpes zoster, mycoses, mononucleosis infectiva and morbus Lyme

A stable incidence was observed only for varicella (540 *vs* 571) and streptococcal pharyngites (44 *vs* 50).

On the other hand, in the period between two reports, a statistically significant increase in average yearly mortality of infectious diseases occurred (0.60 ± 0.03 *vs* 1.67 ± 0.15, $p < 0.001$) (Figure 5). The leading cause of mortality in the report of 2004 were septicaemias (morbidity 6.04; mortality 1.03), which in the 1987 report had not been registered. The increase in overall mortality is caused by an increase in lethality (from 5.96% to 10.27%) and mortality (from 0.24 to 0.51) of bacterial meningitis, with unaffected morbidity (2.66 *vs* 3.03). Additionally, the morbidity (0.17 *vs* 0.80) and mortality (0.14 *vs* 0.40) of morbus HIV increased.

Mortalities and lethalities for other infectious diseases were comparable in both reports and are sporadic as viewed within the context of the overall number of deaths.

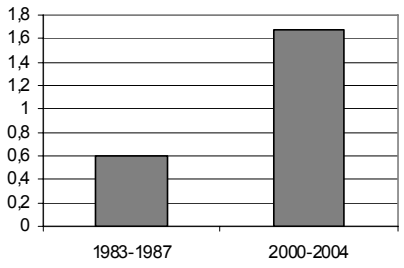

Fig. 5. Average yearly mortalty of infectious diseases

Discussion

In the period from 1987 to 2004 the overall yearly morbidity of infectious diseases dicreased, apparently, more for than a third. The incidence of vaccine-preventable diseases dicreased almost a hundred times: rubella (for which systematic vaccination was introduced in 1994), mumps (systematic vaccination was introduced in 1981), morbilli (systematic vaccination since 1971), and pertussis (systematic vaccination since 1961). There was a significant dicrease in the morbidity of gastrointestinal tract infections, scabies, viral hepatitis A and gonorrhoea, most probably caused by the introduction and adoption of hygiene habits and public health education. The reduced incidence of scarlatina, having in mind unaltered incidence of streptococcal anginas, is probably the consequence of the early antibiotic treatment.

However, changes of the list of ten most common diseases is not only the result of reduced morbidity of these diseases. Herpes zoster, the synonym for immunosuppression, for instance, demonstrated a multiple increase in morbidity and more frequent were mycoses too, which also indicated immune status changes and were associated with widespread use of antibiotics.

The increase in incidence of infectious mononucleosis was also confirmed; its possible causative agents (EBV, CMV, HIV...) have been called protean agents in the literature after Proteus, a mythological sea god, who symbolizes versatility and changeability (3,4,5). Polymorphism of the clinical presentation of these infections is determined by their specific relationship with the host immune system. Since infectious diseases are determined primarily by the relationship between virulence – V of a microbial agent (which here directly targeting the components of immune response) on the one hand, and defense – D of a macroorganism (altered in these circumstances) on the other, the possibility of expression of a disease mathematically rises to the second power: $(V:D) / (D:V) = (V/D)^2$.

In the same context, *Borrelia burgdorferi* is resistant to microbicidal mechanism of professional phagocyte, i.e. antigen presenting cells, which form the first line of defense and to a great extent determine the course of an immune reaction. Moreover, *Borrelia burgdorferi* is in fact being widely distributed by them, leading to possible affections of various tissues and organ systems. Morbus Lyme also demonstrated a significant increase in morbidity in 2004 compared to 1990, when it had been reported in the Republic of Serbia (6).

Regarding mortality trends, we may observe its almost triple elevation in the period from 1987 to 2004, in contrast to the decrease in overall morbidity of infectious diseases. In 2004 it was primarily caused by septicemias, bacterial meningitis and HIV infection.

In 1987 there were no reported cases of septicemia, while in 2004 septicemias made up around 40% of overall mortality of infectious diseases. We should bear in mind that diagnostic criteria for septicemias were established as late as 1992, and that they were widely accepted much later (7). An escalating prevalence of septicemias has been recorded throughout the world in recent decades, above all in developed countries, where they have been the principal cause of hospital morbidity and mortality in intensive care units (8). They have been called the diseases of medical development, since they predominantly occur due to the propagation of commensal flora from its native environments or hospital environment into systemic circulation, bridging the host defense mechanisms by diagnostic and therapeutic procedures. Generally, septicemias are the conditions with complex and variable clinical presentations, associated with immunosuppression problems, opportunistic infections and microbial resistance.

Microbial resistance is the principal cause of increased mortality of bacterial meningitis. Its morbidity remained unaltered, but the lethality (therefore mortality, too) increased because of the development of resistance of principal causative agents (*Streptococcus pneumoniae, Haemophylus influenzae, Neisseria meningitidis*...) (9-11).

In contrast to that, the development of novel therapeutic approaches contributed significantly to the reduced lethality of Morbus HIV in the period from 1987 to 2004. The increase in its mortality was the consequence of increased yearly morbidity, with increased total number of the diseased (from 18 cases in 1987 to 1132 cases in 2004).

Conclusion

The trends of infectious diseases are characterized by reduced morbidity and increased mortality, which is the consequence of the general social progress and development of medicine itself.

General progress removed us from some "traditional" pathogens but also from the rest of the microbial environment, with which we share the evolution and which is necessary for normal maturation of our immune system. For instance, vaccinations with *Mycobacterium vaccae*, abundantly present in the soil, are

nowadays used therapeutically in allergic, autoimmune and malignant diseases (the incidence of which is increasing) (12-14).

The introduction of vaccinations surely represents one of the first and most important steps in medicine, especially from the point of view of morbidity reduction for some infectious diseases. However, considering the issue of their general effect on the immune status, we can hardly say more than Edward Jenner himself back in 1798: "Whether a disease generated in this way has the power of affecting the constitution in any peculiar manner I cannot presume positively to determine"(15). Moreover, today we are familiar with the significant immunomodulatory action of antibiotics, and their frequent and often undiscriminating use is the reason for resistant microbial flora selection (16-20).

Altered immune status and microbial resistance undoubtedly cause polymorphic and more serious clinical presentation of infections. Our clinical practice confirms those changes in the nature of infectious diseases and their recognition, as in the myth of Proteus (21), could foretell the future predominance of infections caused by the microbial agents which have effectuated conditional compromise with the host and are characterized by the complexity of the opportunism of such a relationship.

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PROTEJSKA PRIRODA INFEKTIVNIH BOLESTI – KRETANJE ZARAZNIH BOLESTI NA TERITORIJI REPUBLIKE SRBIJE

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U infektologiji, više nego bilo gde drugde u medicini, svedoci smo promenljivosti, nestalnosti patologije. Ove izmene odnosa čoveka i njegovog mikrobnog okruženja posebno su dinamične poslednjih par decenija. U cilju definisanja prirode tog procesa, njegovog mogućeg porekla i zakonitosti, upoređivani su izveštaji o kretanju zaraznih bolesti u Republici Srbiji, za 1987. (od 1983. do 1987.) i 2004. (od 2001. do 2004.) godinu. Utvrđen je statistički značajan pad morbiditeta, uslovljen smanjenom incidencijom vakcinama preventabilnih infekcija (rubella, mumps, morbilli, pertussis) i infekcija povezanih sa osnovnim higijenskim i zdravstvenim navikama (infekcije gastointestinalnog trakta, scabies, hepatitis virosa A, gonorrhoea...). Sa druge strane, verifikovana je značajno veća učestalost infekcija uzročnicima infektivne mononukleoze i Lyme borelioze, koji su u specifičnom odnosu sa imunskim sistemom, kao i oboljenja koja su rezultat imunodeficijencije, poput herpes zostera ili gljivičnih oboljenja. Istovremeno, izmene imunskog statusa i povećana mikrobna rezistencija su osnov, naizgled paradoksalnog, značajnog povećanja mortaliteta infektivnih bolesti. Generalno gledano, evolucija našeg odnosa sa mikrookruženjem posledica je ubrzanog opšteg društvenog napretka, kao i napretka same medicine. Ovaj odnos je sada neposredniji nego ikad i karektarisan je prevladavanjem infekcija mikrobnim agensima koji su našli uslovni kompromis sa svojim domaćinom.

Ključne reči: *infektivne bolesti, epidemiologija, protejski, Republika Srbija*