Bratisl Lek Listy 2010; 111 (7)
404 – 409

REVIEW

Microbiological and therapeutical aspects of pneumococcal diseases in the Slovak Republic

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Abstract: Since 1983, multiresistant pneumococcal strains, mostly 14, 23F, 19A serotypes have been reported in Slovakia. A 15-year cooperation of specialists from various fields and the representatives of different institutions revealed that the pneumococcal infection problem in the Slovak Republic remains an important healthcare task. In the prospective multicentric microbiological and clinical analysis of otitis media acuta in children under 5 years, pneumococci were isolated in 45.9 %, where 50.8 % of strains were intermediate and fully resistant to penicillin and 47.5 % resistant to macrolid antibiotics. Invasive pneumococcal infections, mostly meningitis and bacteremias, were observed in two studies. Penicillin resistance was higher in children under 5 years (52.8 %), in comparison with other age groups. The dominant serotypes of childhood were 14, 19A and 6A, while in the age group above 65 there was a broad spectrum of serotypes confirmed.
Serotype 14 is the most frequent serotype in physiologically sterile liquids and otitis media liquor in the Slovak Republic *(Tab. 3, Fig. 5, Ref. 34).* Full Text in free PDF *www.bmj.sk.*
Key words: *Streptococcus pneumonia*, bacterial resistance, serotype distribution, Slovak Republic.

Streptococcus pnenumoniae (pneumococcus) was identified in 1881 by Pasteur a Sternberg and proved as a cause of pneumonia in 1886 by Weichselbaum. Currently it is the most frequent etiological agent of pneumonias, acute otitis in children and bacterial meningitis worldwide.

For the first 80 years the pnemococci were sensitive to penicillin and other antibiotics; penicillin was the first-option for pneumococcal infection treatment. This changed in 1967, the penicillin resistant pneumococci were revealed for the first time. Later the pneumococcal stains with a resistance not only to penicillin but also other antibiotics were revealed in healthy carriers as well as in patients with manifest infection. Today, multiresistant pneumococci (MDR) complicate a disease not only in hospitals, but also in the ambulatory practice with differences given by the local resistance status.

Pneumococci are in the centre of the worldwide interest not only as an important etiological agent of human bacterial infections, but lately also as a pathogen with an incredibly spreading antibiotic resistance with significant geographical and regional differences. Pneumococci not sensitive to penicillin are divided according to the penicillin resistance level to strains with decreased sensitivity (intermediately resistant) with penicillin MIC less than 2.0 mg/l and strains fully resistant with penicillin MIC more than 2.,0 mg/l. Clinical interpretation of penicillin resistance needs to be performed on the basis of infection location and clinical status. Antibiotic failure in infections caused by such resistant pneumococci is highly probable, these infections are treated by more expensive and sometimes more toxic antibiotics (i.e. vancomycin) and frequently require hospitalisation.

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Antibiotic resistance in the ambulatory practice in the Slovak Republic

Pneumococcal resistance in the Slovak Republic has a long history. First strains resistant to both penicillin and other antibiotic and a failure of antibiotic treatment were described in 1983 by Moravčík et al (1). But sufficient concern was not paid to this paper as well as the paper by Rakovsky et al with the epidemiology analysis of highly resistant pneumococcus incidence in the Slovak Republic (2).

In 1993 Kotulová, Trupl et al. in their multicentric international study analyzed pneumococcal carrier state in children in ambulatory practice. Pneumococci were found in 27 % of children, where 36% of revealed strains were penicillin resistant (4).

At the same time Trupl, Hupkova et al. mentioned the negative status of pneumococcal penicillin resistance in their study of *S. pneumoniae* incidence in the Slovak Republic in strains, revealed from the ambulatory practice as well as from the hospitalized patients. The authors detected significant regional differences in their resistance (5): the lowest resistance to penicillin and macrolides was in Bratislava (12.0 % ev. 10.7 %), the highest in Lučenec (67.1 % ev. 34.2 %).

Tab. 1. Otitis media acuta in the Slovak Republic in 1999 and 2006.

	1999	2006
Number of children (n)	171	133
S. pneumoniae (%)	42.1	45.9
H. influenzae (%)	17.5	24.1
M. catarrhalis (%)	1.2	1.5
S. pyogenes	4.7	12.0

Tab. 2. Isolated pneumococcus resistancy in otitis media acuta in 1999 and 2006.

	1999	2006
Penicillin sensitive (%)	60.7	49.2
Decreased penicillin sensitivity (%)	14.6	37.7
Penicillin resistant (%)	21.3	13.1
Macrolid sensitive (%)	35.9	52.5
Macrolid resistant	64.1	47.5

Tab. 3. Isolated pneumococcus stem serotypes representation in otitis media in 1999 and 2006.

	1999	2006
Number of stems	72	61
Vaccine serotypes *1999-9V.14.18C.19F.23F 2006-4.6B.9V.14.18C.19F.23F	33	54
Related serotypes* 1999- 6A.9A.19A 2006- 0	14	0
Non-vaccine serotypes* 1999- 3.8.11A.15A.15C.17 2006- 3. 11C	23	4
Non-typing	2	3
Representation in conjugated vaccine*	65.8 %	88.5 %

*Serotype representation in currently available pneumococcal conjugated vaccine (Prevenar)

Hupkova et al. confirmed the penicillin and multi-resistant pneumococcus incidence in clinically relevant materials that were analyzed within the international study Alexander Project (6). This large prospective study of the main bacterial pathogens prevalence in pneumonias, isolated from sputum in the ambulatory practice, confirmed that the Slovak Republic belongs to the countries with a higher pneumococcal resistance not only to penicillin but also to other antibiotics. During a 4-year study (1996-1999), the incidence of stems with decreased resistance and stems fully penicillin resistantant was quite equal (26.8 %, 26.7 %, 47.7 % ev. 31.1 %).

Many authors analyzed the resistance trends of *S. pneumoniae* in the ambulatory practice. Langšádl et al. described the pneumococcus resistance trends to penicillin in 1995– 2002. They point out the dynamics of penicillin resistant strains incidence, that raised from 2,6 % in 1995 to 22,7 % in 2002 and highlighted the fact that pneumococcal resistance not only to penicillin but also to other betalactam and macrolid antibiotics becomes a serious problem of medical practice (7).

Within the educational centre Mediforum, many important specialists from various professions prepared "The Principles of Rational Antibiotic Treatment of Respiratory Infections in Ambulatory Practice", which include also a longitudinal monitoring of main bacterial pathogens resistance to antibiotics since 2000 (8). In a 2006 study, the pneumococcal penicillin resistance was observed in 24 % stems (in 2000 – 21. 3 % stems) and macrolid resistance in 26 % stems (in 2000 – 11.6 % stems).

Since 2000, the group of Slovak microbiologists from various workplaces of microbiology have participated on the Alaska Project. During the first years of this prospective study the trends of pneumococcal penicillin resistance were compared to phenotypic differences of macrolid resistance in the consecutive revealed pneumococcal strains. Regional differences were confirmed in local resistance reviews and a high pneumococcal resistance was observed in Prešov and Zvolen (9). Since 2003, the S-MedDial Project has analyzed the trends of bacterial pathogens antibiotic resistance in ambulatory paediatric practice and compared the resistance level with the use of antibiotics. As the macrolid antibiotic resistance has recently become a serious problem, the project analyzes the correlation of such antibiotic usage and *S. pyogenes* a *S. pneumoniae* resistance in more details. Pneumococcal resistance to macrolides was 14 % in 2002, in 2006 increased to 21 %, and the number of macrolides DDD on 1000 inhabitants increased from 3.2 in 2002 to 5.0 in 2006 (10).

Otitis media acuta

Otitis media acuta belong to the most frequent diseases in children under 5 years. This infection has a specific position in the group of pneumococcal infections. It could proceed almost asymptomatically or with moderate symptoms only, but also as a severe, life treating infections with possible serious complications. In 1993–1995 the first study of isolated bacterial pathogens characteristics in otitis media acuta was performed for the purpose of data collection about bacterial pathogens incidence in this disease and on pneumococcus resistance status description of pneumococci, isolated in children in ambulatory practice of otorhynolaryngologist. In 74 examined children of the age from 10 months to 9 years 43 pneumococci were isolated from the exudate of otitis media during the intake after paracentesis tympani. In 1993, 2 strains out of 20 isolated pneumococci had decreased penicillin sensitivity. Two years later, in 1995, 5 out of 23 strains had a decreased and 1 strain had a high penicillin resistance (11). In the prospective multicentric microbiological and clinical analysis of otitis media acuta in children under 5 years from 10 microbiological and 15 ORL centres in the Slovak Republic (25) the representation of bacterial pathogens was evaluated and the quantitative analysis of isolated bacterial pathogens resistance was performed. Pneumococci were isolated in 72 children (42.1 %), where 35.9 % strains were intermediate and fully resistant to penicillin and 64.1 % to macrolid antibiotics (Tabs 1

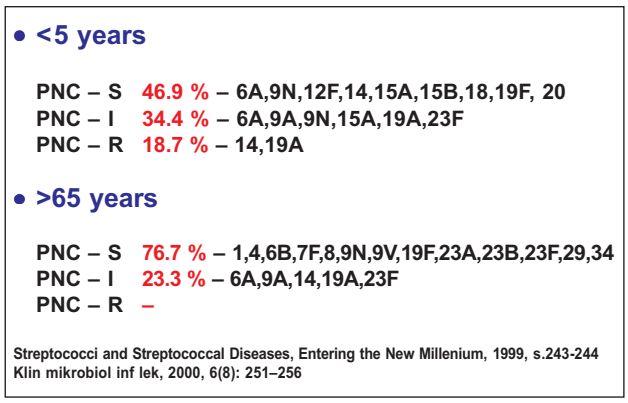

Fig. 1. 1996–1999…33 workplaces in SR invasive pneumococcal infections.

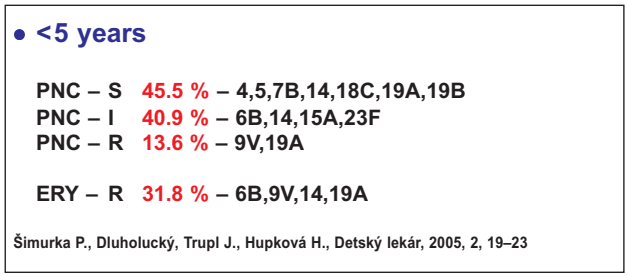

Fig. 2. 2001–2003…13 workplaces in SR invasive pneumococcal infections in children <5 years.

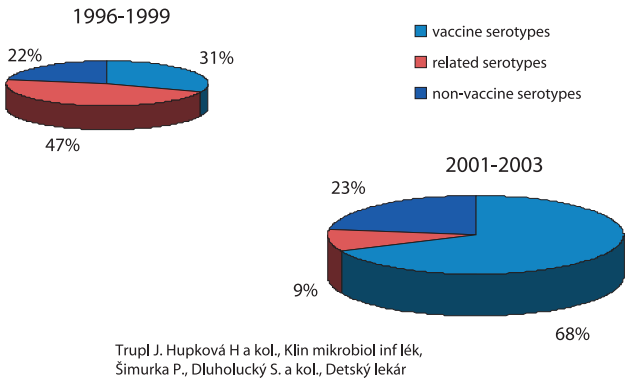

Fig. 3. Invasive pneumococcal infection of childhood, SR, study comparison: 1996–1999 and 2001–2003.

and 2). In this study the serotypes of isolated pneumococcal strains were evaluated and 65.8 %, resp. 88.5 % of strains were included in the available 7-valent conjugated pneumococcal vaccine (25). After seven years, in 2006, the study was repeated with the same settings and in the sample of 133 children younger than 5 years the pneumococci were isolated in 45.9 % of children. From the isolated pneumococcal strains, 50.8 % strains have decreased sensitivity and full resistance to penicillin, 47.5 % strains showed macrolid antibiotics resistance and 87 % strains were included in the 7-valent conjugated pneumococcal vaccine (25). Table 3 presents a comparison of serotype representation in conjugated pneumococcal vaccine in 1999 and 2006.

Invasive pneumococcal infections in the Slovak Republic

Invasive pneumococcal infections, mostly meningitis and bacteremias, were observed in two studies with a cooperation of microbiologists, paediatrists and infectologists. In 1996–1999, 153 pneumococci were isolated from sterile liquids, from which 36% strains were intermediate and fully resistant to penicillin and 30.7 % were resistant to ceftriaxon (13). Penicillin resistance was higher in children under 5 years (52.8 %), in comparison with other age groups (Fig. 1).

In 2001–2003 the prospective study evaluatted the invasive pneumococcal infections incidence in hospitalized children under 5 years. These infections were observed in 22 children, of which 17 children were younger than 2 years. Also in this study the higher penicillin resistance of isolated pneumococci was observed (9 strains with intermediate resistance to penicillin and 3 strains fully penicillin resistant). The results are showed in the Figure 2 (13). In both studies, the serotypes representation was analyzed with the aim to detect the protective impact of currently available conjugated pneumococcal vaccine, assigned for children under 5 years (Fig. 3). In 1996–1999 the dominant serotypes of childhood were 14, 19A and 6A, while in the age group above 65 there was a broad spectrum of serotypes confirmed. In the further study in 2001–2003 the most frequently confirmed serotype was a serotype 14, for both serotypes 19A and 6A, the decrease was recorded (Fig. 4).

Principles for treatment, prevention and antibiotic prescription rationalisation

Although the science led towards rapid findings of more and more effective antibiotics, the bacteria resistance towards antibiotics is still increasing and this highly negative trend is supported also by overuse and frequently useless administration of antibiotics, and in many cases also their wrong selection, dosage and length of administration.

Repeatedly the relationship between antibiotic usage and increase of resistance to various antibiotic groups was demonstrated (15, 16). In the S-MedDial Project (Fig. 5) the resistance increase of *S. pneumoniae* bacterial types was observed after the increased usage of macrolides with extended effect – claritromycine and azitromycine (10, 17).

One of the most efficient option of antibiotic usage decrease and the antibiotic resistance cut-down are the intervention programmes in the ambulatory practice mainly, where the antibiotic usage is the highest and where the resistance of respiratory infection bacterial pathogens (including pneumococci) is created (18). Intervention programmes in the Slovak Republic has been carried since 1999, firstly in a co-operation with the Czech Republic (28), later in a co-operation with the General Health Insurance Company (19) within the S-MedDial Project

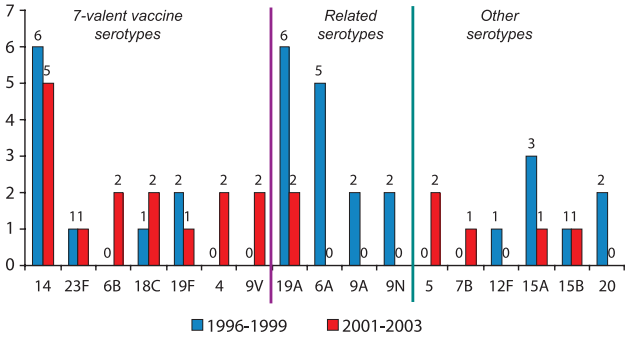

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Fig. 4. Invasive pneumococcal infection of childhood, SR, study comparison: 1996 - 1999 and 2001 - 2003.

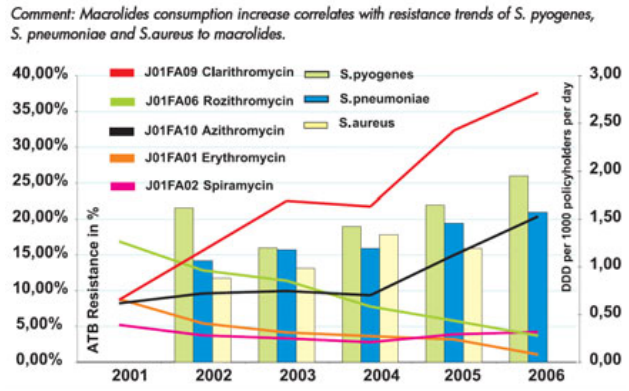

Fig. 5. Antibiotic usage in DDD in correlation with the resistance trends on macrolides in 2001–2006 in SR (S-MedDial).

and within the EU in the GRACE Project Genomics to combat Resistance against Antibiotics in Community- acquired LRTI in Europe (20). Step by step the practitioners are informed about the mistakes they make while prescribing antibiotics: antibiotic treatment of virus origin infections, insufficient antibiotic dosage, high antibiotic usage that select pneumococci penicillin resistance (i.e. cotrimoxazol, cephalosporines) or the macrolide resistance (klaritromycine, azitromycine).

Role of pneumococcal vaccines in prevention

Another approach of pneumococcal infection prevention is the vaccine usage, polysaccharide for adult and older children and conjugated in childhood (21, 22). They decrease the invasive pneumococcal infections incidence, reduce vaccinal serotypes carrier state and influence the pneumococcal resistance decrease (23, 24).

In the prevention of invasive pneumococcal infections there are polyvalent and conjugated vaccines available and their usage helps to reduce severe infection complication in childhood. Serotypal studies and mainly evaluation of the epidemiological markers are very important for the appropriate prevention strategy creating as well as for the invasive diseases treatment. Usage of pneumococcal vaccines in clinical practice is a very important tool not only for pneumococcal infections morbidity and mortality reduction but it is also one of the solving tools for pneumococcal antibiotic resistance problem.

Organism protection against pneumococci is serotype specific and today more than 90 pneumococcal serotypes are described. Not all serotypes could be included into vaccine; a targeted serotype selection must be performed.

Nowadays, the worldwide described multi-resistant pneumococci appertain mostly to the serotypes 6, 9, 14, 19, 23 and 23F. There are many efforts to include these serotypes into pneumococcal vaccines for both adults and children. Today there are 2 pneumococcal vaccines available: a 23-valent polysaccharide vaccine and a 7-valent conjugated vaccine. 23-valent polysaccharide vaccine is designed for invasive pneumococcal diseases prevention of individuals older than 2 years. Resistant pneumococcal stems occurrence in children population required development of conjugated vaccines, efficient in children under 2 years, eventually younger than 5 years due to the underdeveloped or insufficient T-cell immunity. There is a great benefit of pneumococcal vaccine expected in the area of invasive pneumococcal infections in the high-risk groups and in a reduction of multiresistant pneumococcal spread risk in population.

A very important observation is an information about a high representation of *S. pneumoniae* serotypes in the studies performed in the Slovak Republic from the clinically relevant materials in conjugated pneumococcal vaccine, what support the indication of pneumococcal vaccine in the prevention of severe invasive pneumococcal infections uprise in children and also the economical costs reduction of pneumococcal disease treatment.

Trupl, Hupková et al. (11) performed a microbiological and clinical analysis of invasive pneumococcal infections, occurred in the Slovak Republic in 1996–1999 in 153 patients; highly resistant pneumococcal stems were represented by relatively small number of serotypes 19A, 23F, 14, 9V. This paper significantly supported a usage of 23-valent polysaccharide vaccine in the high-risk groups of adult population. In the prospective multicentric study of acute otitis incidence in 2006 the most frequent serotypes were 23F and 14, which showed the highest antibiotic resistance. The comparison of *S. pneumoniae* serotypes, revealed from the otitis media acuta confirmed that 88.5 % of strains are included into the 7-valent conjugated vaccine; non-vaccine strains were sensitive to penicillin (25, 26).

Discussion

A 15-year cooperation of specialists from various fields and the representatives of different institutions revealed that the pneumococcal infection problem in the Slovak Republic remains an important health-care task, which requires maximum efforts.

Resistance of *S. pneumoniae* has a dynamic character. Although the penicillin resistance is increasing in some countries,

in most countries the resistance is stabilised on the same level, eventually there was a slight decrease observed. On the other side, the pneumococcal resistance to macrolides is increasing.

The increased macrolid resistance of *S. pneumoniae* was confirmed in Spain and France, very similar situation is also in the Slovak Republic. One of the methods to influence such negative condition is an antibiotic usage analysis in ambulatory practice with the subsequent educational activities for both the practitioners and patients in such projects as S-MedDial Project.

In 2006, within the EARSS Project, that monitored antibacterial substance resistance of invasive infection etiological agents, 10 351 pneumococci were analyzed in 30 countries. Pneumococcal penicillin resistance was different in particular European countries. In the northern countries, the number of insensitive strains was about 5 %, in the southern countries of Europe the resistance was higher, more than 25 % (29, 30). The resistance status is more favourable in the countries that are the immediate neighbours of the Slovak Republic. In 2006, 18 % of strains with decreased sensitivity and fully resistant were described in Hungary and 5 % in Austria.

The Slovak Republic was represented in the project till 2004 and in that year it belonged to the countries with the highest penicillin resistance – 29 % of strains were intermediate resistant and fully resistant.

It is generally known that the pneumococcal resistance is interconnected with some serotypes; an example could be the relation of multiresistance and a serotype 14. In history, first resistant stem of serotype 14 was isolated from the thorax punctuate and blood in Martin, the Slovak Republic in 1983 – in a child with thoracic empyema (1). Currently a serotype 14 is the most frequently occurring serotype in physiologically sterile liquids and otitis media liquor in the Slovak Republic; it is a cause of higher pneumococcal resistance to antibiotics in severe diseases mainly in childhood. In the last study that analyzed otitis media acuta in children under 5 years, the serotype 14 was present in 25.6 % of children.

Another important finding is the fact that among serotypes that cause dominantly invasive infections and almost never occurs as a carrier stems, serotypes 1, 4 and 7F belong. Clones of serotypes 14 and 6B could occur as carrier stems, but cause also invasive infections. Serotype 19F that is a typical carrier serotype with genetic variability (31).

From serotypes 1, 4 and 7F, isolated within the studies in the Slovak Republic up to date, only serotype 4 occurred, which is included in the conjugated pneumococcal vaccine. It was isolated in low numbers with slight increase. It was isolated in 2 children from sterile liquids; it was not found during otitis in the 1999 study and was found in 3 children in 2006.

Serotypes 14 and 6B that could occur as carrier strains and can cause severe invasive diseases were isolated in higher number of patients with serotype 14 dominance with the antibiotic multiresistance mentioned above. Serotypes 14 and 6B are included into conjugated pneumococcal vaccine.

In 1986 Dr Henrichsen from Copenhagen suggested that the pneumococcal stems of serotypes 14 isolated in Topoľčany had a very high penicillin resistance, not found anywhere else. Multiresistant pneumococci from Topoľčany were included into the stem collection CDC Atlanta and became a study subject of resistance mechanisms and later in 1991 had initiated an epidemiological study in Topoľčany district (32). One of the conclusions was the finding of higher antibiotic usage in ambulatory practice.

Similar situation occurred in 2000, when Nagai, Appelbaum et al confirmed a new mechanism of pneumococcal resistance to macrolides with the confirmation of L4 mutation in *S. pneumoniae* stem isolated in a child with otitis media acuta. The strain was sensitive to penicillin and erythromycin, but resistant to azitromycin. The strain with L4 mutation was described in Bulgaria and Lithuania at the same time (32). Even though an atypical azitromycin resistance in clinical isolates sensitive to erythromycin could occur only with restricted clinical impact so far, it is necessary to monitor and analyze the clinical isolates to obtain the early information about resistance evolution.

Conclusion

Analysis of infections caused by resistant pneumococcal strains support the hypothesis that the dominant factor in resistant pneumococcal spreading is the strain spread from person to person. The resistant clones spreading in pneumococcal population are supported by the stay in collective institutions, nursery schools for children, and institutions for long-term health care. Significant proportion of both children and adults could be colonized by resistant pneumococcal stems without any symptoms of disease. Another supporting factor for resistant pneumococci spread is the selective pressure of antibiotics applied uselessly and without a reason especially in respiratory infections in ambulatory practice. Most of the respiratory infections have the virus etiology and the indication of wide spectrum of antibiotics is unsubstantial for these diseases very frequently. A pneumococcal vaccine usage in the clinical practice is an important prevention measure for reduction of severe pneumococcal infections and an important tool for pneumococcal antibiotic resistance solving.

The education of not only healthcare providers but also a public is the fundamental condition of increased antibiotic resistance influencing. Consistent and conceptual approach (target group selection, methods, program efficiency monitoring) assumes the co-operation of technical institutions, state institutions as well as non-profit organisation and insurance companies with independent work groups with such a scope of employment. It is possible to influence the risk of further antibiotic resistance spreading not only in bacterial type of *Streptococcus pneumoniae* – the proofs are available in many countries (Iceland, Germany). Maintenance of recommended therapeutic practice, antibiotic use reduction, correct indication of individual antibiotic groups and also reduction of an enormous selection pressure of antibiotics, especially in the children population could be dominant.

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Received February 2, 2010.
Accepted March 31, 2010.