INCREASED MACROLIDE RESISTANCE IN *STREPTOCOCCUS PNEUMONIAE* IN SLOVAKIA MAY BE LINKED TO INCREASED MACROLIDE CONSUMPTION

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SUMMARY

Objectives: Given the widespread use of macrolide antibiotics and growing concerns over antimicrobial resistance, this study aimed to investigate recent trends in macrolide consumption in Slovakia and to determine the corresponding changes in *Streptococcus pneumoniae* resistance in a paediatric cohort.

Methods: We conducted a retrospective analysis of 1,083 nasal swab cultures from children with recurrent respiratory infections and atopy, comparing two distinct 5-year periods: 2008–2012 and 2019–2023. Consumption data was based on the European Centre for Disease Prevention and Control reports.

Results: National data confirmed that Slovakia has one of the highest consumption rates of macrolides, lincosamides, and streptogramins (ATC group J01F) in Europe. The comparative analysis of patient samples revealed a statistically significant 11% increase in erythromycin-resistant *S. pneumoniae* ($p < 0.001$) and a 5% increase in clindamycin-resistant strains ($p < 0.001$) between the two study periods.

Conclusions: The concurrent rise in macrolide consumption and *S. pneumoniae* resistance in Slovakia highlights a significant public health threat. These findings underscore the urgent need for robust antibiotic stewardship programmes and the promotion of rational prescribing practices to preserve the efficacy of macrolides.

Key words: macrolide antibiotics, antibiotic resistance, *Streptococcus pneumoniae*, macrolide consumption, antibiotic stewardship, Slovakia

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INTRODUCTION

Macrolides are a group of antibiotics (ATB) that have a macrocyclic lactone ring structure. Macrolides are effective against a wide range of bacteria, including gram-positive and gram-negative organisms. Unlike penicillins, which disrupt the bacterial wall, macrolide ATB block bacterial protein synthesis. They are widely used in clinical practice to treat a variety of respiratory and gastrointestinal infections, as well as skin, soft tissue, and genital tract infections.

The first macrolide, erythromycin, was discovered in the 1950s through the isolation of erythromycin from a soil bacterium, *Streptomyces erythraeus* (1). During the 1970s and the 1980s, researchers developed semi-synthetic derivatives of erythromycin, including clarithromycin, with enhanced oral bioavailability. A seminal advancement in the field of macrolide ATB was the identification of azithromycin in Croatia, the first 15-membered azalide incorporating a fundamental nitrogen atom within its macrocyclic structure. This innovative compound has rapidly gained popularity and has become one of the most widely prescribed antibiotics worldwide (2). Macrolide antibiotics, such as azithromycin and clarithromycin, are known for their ease of administration, rapid and efficient absorption from the gastrointestinal tract, relatively low toxicity profile (e.g., risk of QT prolongation and significant drug interactions), and ability to penetrate most tissues except the central nervous system.

These favourable characteristics have made them a popular choice for treating upper respiratory tract infections in children and adults, often prescribed in various dosage forms, without specific pathogen identification. However, despite their widespread use, many limitations of macrolides have become apparent since their introduction into clinical practice (3). The widespread and indiscriminate use of macrolides in both medical and agricultural settings over the past several decades has significantly contributed to the development of antibiotic resistance.

Resistance in *S. pneumoniae* is a particularly pressing concern, as it threatens the utility of a key therapeutic class for treating common infections like otitis media and community-acquired pneumonia (4). The prevalence of macrolide-resistant *S. pneumoniae* varies substantially by geographic region, often correlating with local ATB consumption patterns (5–7). Therefore, this study aimed to analyse the time-dependent dynamics of

macrolide resistance in *S. pneumoniae* isolates from a cohort of Slovak children and to contextualize these findings with national consumption data.

Antibiotic Consumption in Slovakia – Focus on Macrolides

Excess and irrational prescription of ATB is well known to increase not only microbial resistance but also nosocomial infections, dysbiosis, intestinal infections (such as *Clostridium difficile*), an increased risk of allergic diseases, mortality, and financial costs. The alarming rise in microbial resistance has the most significant impact from a medical perspective. The positive trend of decreasing ATB use in Slovakia following the end of the COVID-19 pandemic has reversed in recent years, despite a slight decrease recorded in the previous year (Fig. 1).

According to data from the European Centre for Disease Prevention and Control (ECDC) in 2022, penicillins (ATC group J01C) are the antibiotics most commonly consumed in the community in most countries. However, Slovakia is an exception, with macrolides, lincosamides, and streptogramins (ATC group J01F) being the most consumed. The consumption of other antibacterial agents varied significantly between countries. For example, the consumption of tetracyclines (ATC group J01A) ranged from 3% in Italy to 26% in Iceland. Similarly, cephalosporins and other beta-lactams (ATC group J01D) ranged from 0% to 26%; macrolides, lincosamides, and streptogramins (ATC group J01F) ranged from 4% in Finland to 32% in Slovakia; and quinolones (ATC group J01M) ranged from 2% to 13% (Fig. 2). Compared with the Czech Republic, antibiotic consumption in Slovakia was 39% higher. This difference was particularly pronounced for azithromycin (group ATC J01F), with Slovakia consuming 6.48 DDD/1,000/day compared to the Czech Republic's 3.96 DDD/1,000/day (Fig. 3).

The World Health Organization (WHO) AWaRe antibiotic classification, introduced in 2017, is a powerful tool designed to optimize global ATB stewardship (10). This classification system categorizes antibiotics into three distinct groups: Access, Watch and Reserve. ATB in the first group, considered the most prudent

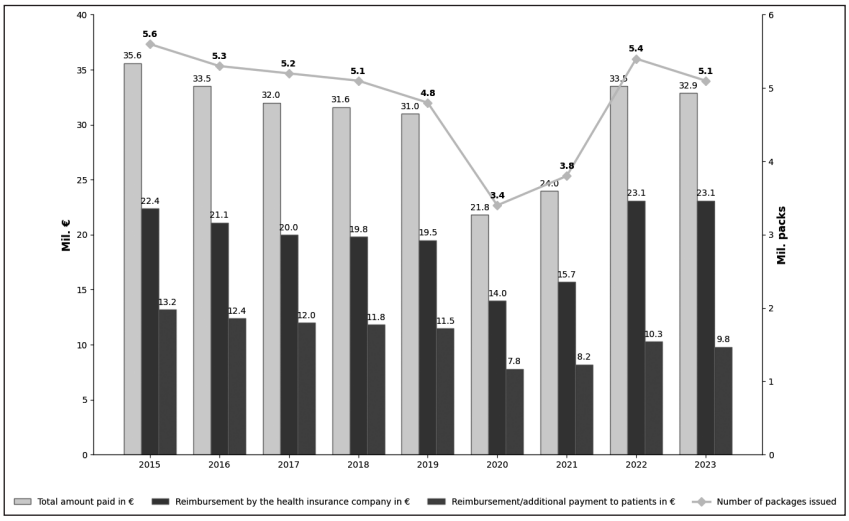

Fig. 1. *Trend in antibiotic consumption in Slovakia.*

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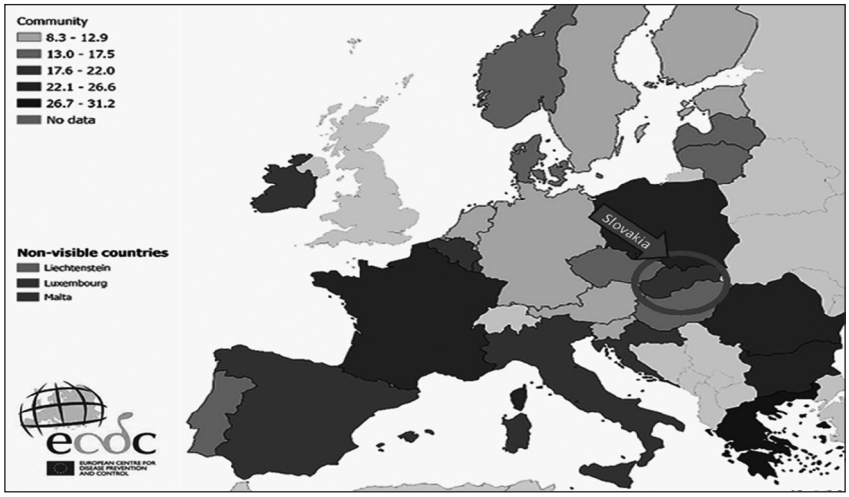

Fig. 2. *Surveillance of antimicrobial consumption in Europe according to ECDC in 2022.*

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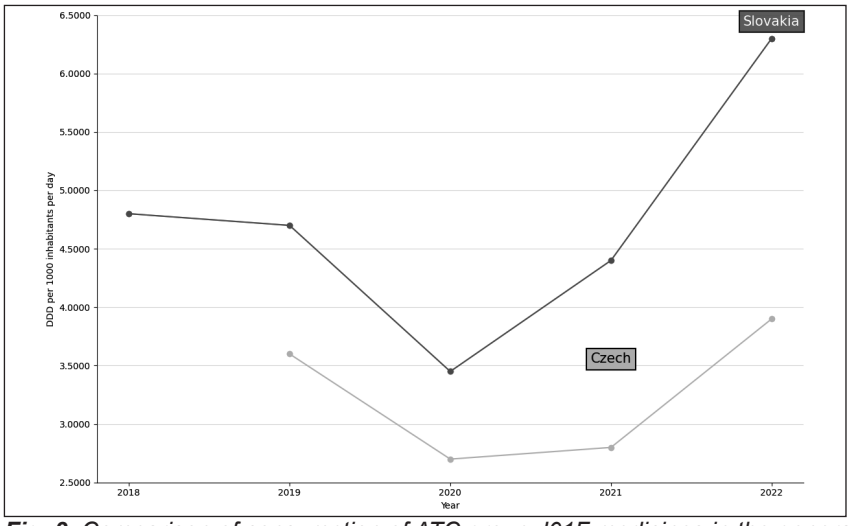

Fig. 3. *Comparison of consumption of ATC group J01F medicines in the general care segment (community and hospital) between Czechia and Slovakia.*

Source: ECDC (9)
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choice, should be prioritized over those in the other two groups. Watch ATB, while still effective, require more cautious use, and Reserve ATB are intended solely for the treatment of multidrug-resistant infections. This classification underscores the importance of rational use in the healthcare system. The disproportionately high prescription rates for azithromycin, currently classified as a Watch antibiotic, pose a significant threat to public health. As a case in point, an analysis of Croatian azithromycin distribution data from 2017 to 2020 revealed a concerning upward trend. This trend was particularly pronounced in March 2020 and during the COVID-19 pandemic, with hospital consumption increasing by a substantial 3.62 times compared to the average. In particular, non-hospital pharmacies emerged as the primary source of increased distribution during these periods (11). Regular biennial updates of the AWaRe classification are essential for maintaining the long-term efficacy of antibiotics and for protecting global health.

MATERIALS AND METHODS

Study Setting and Population

Epidemiological analyses were performed at the National Institute of Paediatric Tuberculosis and Respiratory Diseases in Slovakia. The study cohort consisted of children admitted to a pulmonary inpatient clinic for the management of chronic respiratory diseases. We evaluated nasal swabs for microbial culture of individuals with recurrent respiratory infections who met at least one of the following criteria according to de Martino and Ballotti: experiencing six or more respiratory infections per year, having at least one upper respiratory tract infection per month from September to April, or having at least three lower respiratory tract infections annually (12). Patients with an active respiratory infection at the time of sample collection were excluded from the analysis. The study included all consecutive patients meeting these eligibility criteria during the specified timeframes and was approved by the institutional Ethics Committee and adhered to the principles of the Declaration of Helsinki.

Sample and Data Collection

Nasal swabs were obtained from each participant using a sterile swab with a flocked tip. The swab was gently inserted into the nostril and rotated against the nasal mucosa to collect a sufficient sample. The swab was then carefully removed and placed in a sterile transport medium to preserve the viability of the microorganisms. Microbiological identification and antimicrobial susceptibility testing were performed according to standard laboratory protocols of the institute. All data were extracted from the institutional electronic medical records.

Study Design and Statistical Analysis

Our retrospective research design aimed to compare an identical number of nasal swab culture results (N = 1,083 samples) over two distinct 5-year periods: 2008–2012 and 2019–2023. We used descriptive statistics to characterize the study population, including their age, sex, and types of recurrent respiratory infections. To ensure the comparability of the two cohorts, an independent t-test was used to compare the mean age, and a chi-square test was used to compare the gender distribution. To analyse the quantitative dynamics of *S. pneumoniae* strains resistant to erythromycin and clindamycin, we employed inferential statistics. Specifically, we used a chi-square test to assess the significance of the observed increases in antibiotic resistance between the two time periods. A p-value < 0.001 was considered statistically significant, indicating a very low probability that the observed differences were due to chance alone. Data were analysed using Jamovi, a statistical software package (Jamovi Project, 2023, Sydney, Australia, Jamovi Version 2.3.28.0) built on the R statistical language.

To minimize selection bias, all consecutive patients who met the predefined and objective eligibility criteria within the study periods were included. By using standardized electronic medical records for data extraction, we aimed to reduce information bias. However, we acknowledge the inherent limitations of a retrospective design, where data were not originally collected for research purposes.

RESULTS

The primary focus was to analyse the quantitative dynamics of *Streptococcus pneumoniae* strains that exhibit resistance to the macrolide antibiotics erythromycin and lincosamide clindamycin. The demographic and clinical characteristics of the two cohorts were comparable. In the first period (2008–2012), the mean age was 8.8 years (±5.4 years), with 55% being male. In the second period (2019–2023), the mean age was 9.2 years (±5.8 years), with 57% being male. No statistically significant differences were found between the two cohorts in terms of age ($p=0.21$, t-test) or gender distribution ($p=0.45$, chi-square test), confirming their comparability.

Regarding the nature of recurrent respiratory infections, 56% of the participants had a history of recurrent upper respiratory tract infections, 26% experienced recurrent obstructive and non-obstructive bronchitis, 14% had bronchial asthma, and 4% had recurrent laryngitis (Fig. 4). In particular, a substantial majority of the children (86%) within the cohort exhibited confirmed atopy. A comparative analysis of an equal number of patient samples from both periods revealed a significant 11% increase in the detection of erythromycin-resistant *S. pneumoniae* (368 vs. 487 samples, $p<0.001$). In contrast, a less pronounced 5% increase was observed in the number of *S. pneumoniae* strains resistant to clindamycin (282 vs. 336 samples, $p<0.001$). The findings are shown in Figure 5.

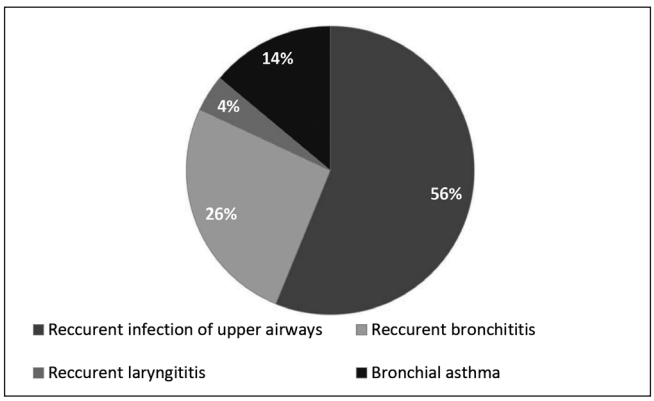

Fig. 4. *Distribution of recurrent respiratory infections among study participants.*

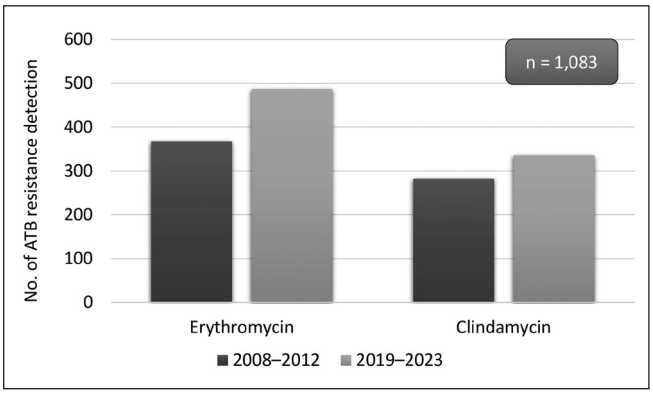

Fig. 5. *Comparison of antibiotic resistance profiles in S. pneumoniae isolates from paediatric patients with atopy between two time periods.*

DISCUSSION

S. pneumoniae, a common resident of the human nasopharynx, can cause localised infections such as otitis media and pneumonia and severe invasive infections such as septicaemia and meningitis. It is a major cause of death worldwide in children under five years of age (13). During the 1980s and the 1990s, the emergence of penicillin-resistant pneumococcus required a switch in antibiotic stewardship for presumed upper respiratory tract infections and pneumonia to macrolide antibiotics (14). The extensive use of macrolides exerts a strong selective pressure, which favours the growth of macrolide-resistant strains of *S. pneumoniae*.

A key finding of our study is the observed increasing trend in resistance of *S. pneumoniae* in a paediatric cohort in Slovakia, with an 11% rise in erythromycin resistance over the last decade. This finding aligns with the high rate of macrolide consumption in Slovakia, which in 2022 was the highest among 28 surveyed European countries (9). This suggests a direct link between prescribing habits and the development of resistance.

The dynamics of macrolide resistance in pneumococcus exhibit significant geographical variability. Our findings can be contextualized with trends in other European nations. For example, while the prevalence of resistance in Bulgaria increased to 43.9% between 2011 and 2016, Hungary experienced a decrease in resistance rates over a similar period (5, 15). In contrast, Nordic countries have maintained very low resistance rates (6). The highest prevalence of macrolide resistance has been documented in Asian regions; a study in China, for instance, revealed resistance rates as high as 89%–96% in county hospitals (7). Our data place Slovakia among the countries with a concerning upward trend in resistance.

Bacterial resistance to macrolides is primarily driven by genetic alterations, including ribosomal modifications (e.g., via erm(B) genes) and antibiotic efflux (e.g., via mef(A/E) genes) (4, 16). The introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) has complex effects on the pneumococcal population. The primary mechanism is known as serotype replacement. By effectively clearing the 13 serotypes included in the vaccine from the nasopharynx, PCV13 opens an ecological niche. This niche can then be colonized by non-vaccine serotypes (NVS) of *S. pneumoniae*. While this process successfully reduces disease from vaccine-targeted strains, it can inadvertently lead to an increase in the overall prevalence of ATB resistance if the emerging NVS are already resistant. Studies have shown that this selective pressure can favour the proliferation of NVS that carry resistance genes, such as the erm(B) gene which confers high-level macrolide resistance (17). As the vast majority of our paediatric participants (97%) had received the pneumococcal conjugate vaccine, this vaccine-driven serotype replacement may be a contributing factor to the trends we observed.

The unique design of our study involved evaluating the time-dependent dynamics of *S. pneumoniae* resistance levels in isolates obtained from two well-defined groups of children: those with recurrent respiratory infections and verified atopy, outside of acute infection periods. We posit that asymptomatic colonization of *S. pneumoniae* in these children more accurately reflects the true resistance profile of these bacteria within the paediatric community than isolates from patients with acute and severe pneumococcal infections. A significant finding of our study is the observed increasing trend in resistance to *S. pneumoniae*, highlighting a

potential future global health threat and raising concerns about the risk of crisis states, particularly in terms of mortality related to nosocomial infection.

Macrolide consumption in Europe has exhibited considerable variability among countries. In 2017, Greece emerged as the country with the highest consumption rate, whereas Sweden reported the lowest. This pattern aligns with previous years, when Greece consistently maintained a significantly higher usage level than other European nations. Slovakia ranked third in consumption during this period (18). This upward trend in macrolide consumption in Slovakia was further confirmed in 2022, where Slovakia significantly outperformed the 28 surveyed countries (19). Over the past several years, a discernible trend has emerged in the use of macrolide antibiotics in children, with a notable shift from short-acting agents, such as erythromycin, to long-acting counterparts, such as azithromycin (19). Furthermore, macrolides, lincosamides, and streptogramins (ATC group J01F) was the only ATC subgroup with a statistically significant increase in the mean community consumption rate in 2022 compared to 2019 (9). During the 2022 period, known shortages of penicillin in Europe likely contributed to the increased utilization of macrolides. This change may have occurred because of the inaccessibility of first-line penicillin treatments, despite the lack of a statistically significant difference in mean consumption between 2019 and 2022 (20). Although macrolides are effective antibiotics against certain bacterial infections, their misuse for respiratory illnesses is prevalent (21). Recent studies have demonstrated a correlation between macrolide consumption and the number of COVID-19 (22). This association suggests that macrolides are frequently prescribed for conditions that do not require ATB therapy, potentially indicating overuse or inappropriate prescription practices. According to Eurostat, Slovakia has one of the highest rates of the annual medical doctor consultations. Although the average number of doctor consultations declined in most EU countries (19/24) compared with the 2018–2020 baseline, Slovakia reversed this trend, experiencing a 3% increase in consultations (23) (Fig. 6).

Macrolides, with their immunomodulatory, anti-inflammatory and mucoregulatory properties, are used in long-term therapeutic regimens for selected chronic respiratory conditions including chronic bronchitis, bronchiectasis, and cystic fibrosis (24). However, the potential risks associated with prolonged macrolide therapy must be carefully weighed against anticipated benefits. An important concern is its impact on the gut microbiome. Long-term macrolide treatment can disrupt the microbial ecosystem, impair carbohydrate metabolism, and reduce short-chain fatty acid production. These alterations can lead to systemic changes in immune and metabolic biomarkers, which can affect the host physiology (25). Although macrolides offer significant therapeutic benefits, their widespread use presents another potential public health concern. For example, high levels of macrolide consumption have been associated with increased rates of childhood obesity (26).

CONCLUSIONS

In conclusion, excessive use of macrolides has led to an increase in ATB resistance, particularly among *S. pneumoniae.* Our study highlights the increasing prevalence of macrolide-resistant *S. pneumoniae* in the paediatric population with recurrent respiratory infections and atopy. The high consumption of macrolides, particularly azithromycin, in Slovakia poses a significant threat to public health. To mitigate this issue, it is imperative to implement stricter ATB stewardship programmes, promote rational antibiotic prescription practices, and prioritize the development of novel antibiotics.

Conflicts of Interest
None declared

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Adherence to Ethical Standards
The study was approved by the Ethics Committee of the National Institute of Paediatric Tuberculosis and Respiratory Diseases in Dolný Smokovec, Slovakia, and conducted as a retrospective longitudinal cohort study. All investigations involving human participants adhered to the ethical principles established in the Declaration of Helsinki (1975, revised 2013).

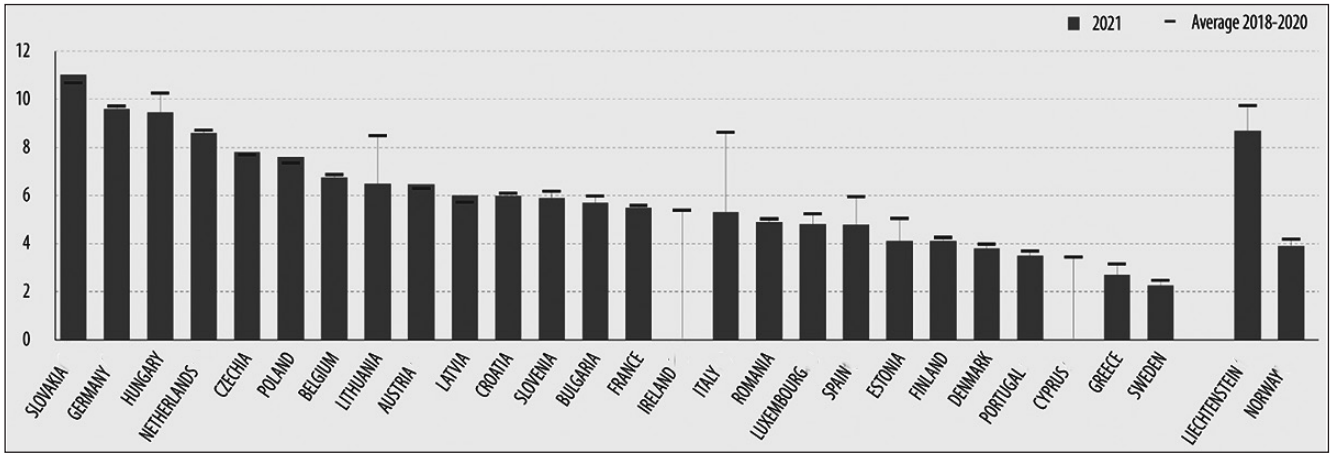

Fig. 6. *Consultation of a medical doctor in 2021.*

Source: Eurostat (23)
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