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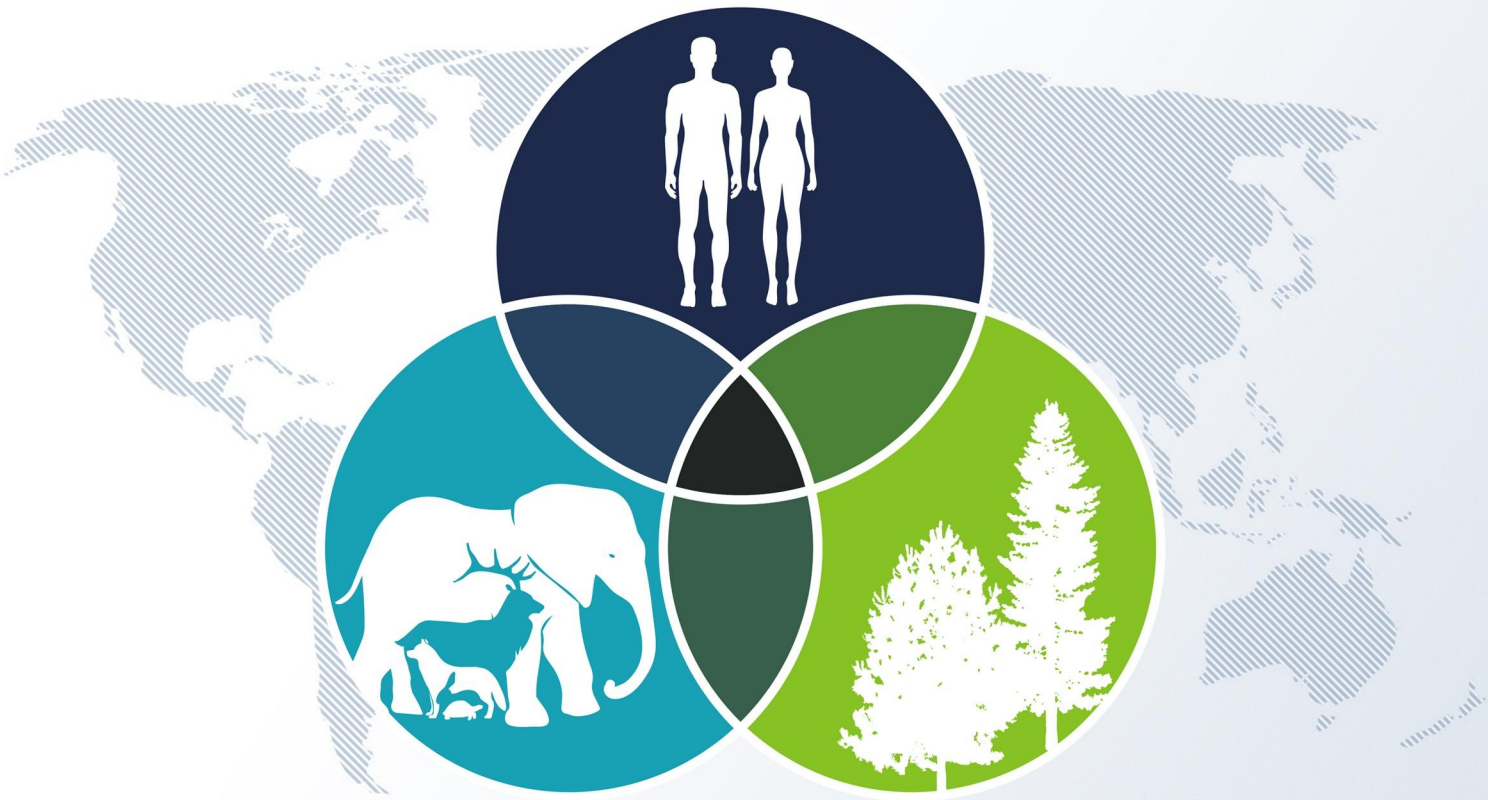

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The Moldovan Association for Biosafety and Biosecurity (MDBBA) is a scientific and practical, instructive and educational, non-governmental, apolitical and non-profit professional organization, created in 2017.

The main objective of the association is the development of good practices and culture in the field of biosafety and biosecurity and the promotion of knowledge within professional and research-innovation groups.

Biosafety – includes security principles, technologies and rules to be followed to prevent unintended exposure to pathogens and toxins or their accidental release/leakage.

"Protection of personnel, population from unintended exposure to pathogens/biohazardous material".

Biosecurity - includes a wide spectrum of measures (biosecurity policies, regulatory regime, scientific and technical measures) applied in an organized framework, necessary to minimize risks (prevention of actions, terrorist attacks by the intentional release of pathogens or toxins as well as loss, their theft or misuse).

"Protection and prevention of theft, intentional misuse of pathologies/biohazardous material".

Risk management – is a decision-making process in which the results of risk assessment (the process of estimating workplace hazards) are integrated with economic, technical, social and political principles to generate strategies for risk reduction.

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Driving global health transformation: The power of the *One Health* Approach

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In an increasingly interconnected world, the complexity of global health, environmental, and societal challenges continue to grow. Addressing these multifaceted issues requires integrated, multidisciplinary solutions that prioritize collaboration and innovation. The One Health & Risk Management journal stands at the forefront of this movement, promoting collaboration and innovation to tackle the most urgent issues of our time.

The One Health approach emphasizes the interconnectedness of human, animal, and environmental health. The journal focuses on the One Health approach, a framework that recognizes the interconnectedness of human, animal, and environmental health. By exploring the full spectrum of risks emerging from the intersections of these domains, the journal addresses a broad range of global concerns. From emerging infectious diseases to environmental degradation and antimicrobial resistance, the One Health approach provides a comprehensive lens through which to understand, prevent, and manage global risks that affect all species and ecosystems.

Established in 2019 by the Moldavian Biosafety and Biosecurity Association (MDBBA), the One Health & Risk Management journal marks a significant milestone in promoting interdisciplinary research and cooperation. It serves as a crucial platform for researchers, policymakers, and practitioners to exchange ideas, share knowledge, and drive the collective action needed to find effective solutions. Aligned with the global standards set by organizations such as the World Health Organization (WHO), the World Organization for Animal Health (WOAH), the Food and Agriculture Organization (FAO), and United Nations Environment Programme (UNEP), the journal offers invaluable insights into the interconnected nature of health and risk management.

As we face increasingly complex global health challenges, the One Health approach is essential - not only for safeguarding public health but also for achieving broader goals of sustainable development and environmental protection. The One Health & Risk Management journal plays a pivotal role in advancing this integrated approach, contributing to global efforts for a healthier, more resilient world.

Looking forward, this journal will continue to be a driving force in interdisciplinary research, fostering international collaboration, and supporting the development of innovative, effective, and scalable solutions to the challenges we face now and in the future.

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SYNTHESIS ARTICLE – ARTICLES DE SYNTHÈSE

MEDICAL SCIENCES

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UREAPLASMA IN PREGNANCY. IS THERE ANY RISK FOR PRETERM LABOR?

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Keywords:
Ureaplasma, preterm birth, pregnancy outcomes, inflammation, NAAT, fetal membranes.

Introduction. *Ureaplasma species, particularly Ureaplasma urealyticum and Ureaplasma parvum, inhabit the lower genital tract of sexually active women and have been linked to adverse reproductive outcomes. This review highlights their role in preterm delivery, along with detection challenges and pathogenic mechanisms.*

Material and methods. *This review compiles data from 25 studies, encompassing a total of approximately 15,700 patients. These studies include retrospective and prospective cohorts, cross-sectional designs, and case-control studies. Key parameters evaluated included impact of Ureaplasma species on pregnancy outcomes, such as preterm labor and chorioamnionitis.*

Results. *The studies reviewed (2000–2024) included 10 retrospective, 8 prospective, 4 cross-sectional, and 3 case-control designs. Ureaplasma parvum was found in 40.5% of healthy women and Ureaplasma urealyticum in 20.3%. Intra-amniotic infection increased preterm delivery risk (OR: 2.76–3.0), with preterm birth rates ranging from 26% to 58.6%. Ureaplasma induces pro-inflammatory cytokines, activates neutrophils and TLR-9, and increases prostaglandin and matrix metalloproteinase activity, weakening fetal membranes and triggering preterm labor.*

Conclusions. *Ureaplasma spp. significantly contribute to preterm delivery, primarily through inflammatory processes and membrane damage. Further research with prospective randomized studies is recommended.*

Cuvinte-cheie:
Ureaplasma, naștere prematură, rezultate ale sarcinii, inflamație, NAAT, membrane fetale.

UREAPLASMA ÎN SARCINĂ. FACTOR DE RISC PENTRU NAȘTEREA PREMATURĂ?

Introducere. *Speciile de Ureaplasma, în special Ureaplasma urealyticum și Ureaplasma parvum, colonizează tractul genital inferior al femeilor active sexual și, în timp, au fost asociate cu diverse complicatii reproductive. Aceast review analizează rolul speciilor de Ureaplasma în nașterea prematură, concomitent cu posibilele dificultăți de identificare și mecanismele patogenice.*

Material și metode. *Aceast review sintetizează date din 25 de studii, care au inclus 15.700 de paciente. Studiile analizate cuprind cohorte retrospective și prospective, studii transversale și studii de caz-control. Principalele aspecte evaluate sunt impactul speciilor Ureaplasma asupra rezultatelor sarcinii, în special în travaliul prematur și corioamniotită.*

Rezultate. *Materialele analizate (2000–2024) includ 10 studii retrospective, 8 prospective, 4 transversale și 3 studii de caz-control. Astfel, Ureaplasma parvum a fost identificată la 40,5% dintre femeile sănătoase, iar Ureaplasma urealyticum la 20,3%. Infecția intra-amniotică a crescut riscul de naștere prematură (OR: 2,76–3,0), cu rate ale nașterii premature între 26% și 58,6%. Ureaplasma determină producerea de citokine proinflamatorii, activează neutrofilele și receptorul TLR-9, crescând producția de prostaglandine și activitatea metaloproteinazelor matriceale, ceea ce duce la slăbirea membranelor fetale și declanșarea travaliului prematur.*

Concluzii. *Speciile de Ureaplasma contribuie semnificativ la provocarea nașterii premature, în principal prin mecanisme inflamatorii și deteriorarea membranelor fetale, de aceea, sunt necesare cercetări suplimentare prin studii prospective randomizate.*

INTRODUCTION

Numerous asymptomatic, healthy individuals have *Ureaplasma* species (*Ureaplasma* spp.) colonization in their genitourinary tract. Mycoplasmas are rarely the only organisms isolated from a genitourinary specimen, therefore determining whether they are co-isolates or pathogens that cause illness can occasionally be challenging. Publicly available research on these species pathogenicity frequently has significant design flaws. These species have historically been challenging and complex to detect. Recognition of *Ureaplasma urealyticum* (*U. urealyticum*) in unfavorable pregnancy outcomes is rising. Adverse outcomes in a pregnant woman include chorioamnionitis, preterm premature rupture of membranes, spontaneous preterm labor, spontaneous abortions and even stillbirth. These microorganisms may not be necessary for pathological conditions to arise from the vaginal flora on their own. Additional factors may also need to be present in order for certain events to happen.

MATERIAL AND METHODS

This review synthesizes data from studies published between 2000 and 2024. We were particularly interested in the type of study, study design, the number of patients involved, methods used to detect *Ureaplasma* spp., and key findings related to *Ureaplasma* spp. colonization and pregnancy outcomes.

We conducted a comprehensive search across multiple databases (e.g., PubMed, Scopus, and Web of Science) using a combination of Boolean operators and keywords to identify relevant studies. The search terms included variations of "*Ureaplasma*," "preterm birth," "pregnancy outcomes," and "infection." The following Boolean operators were used:

- "*Ureaplasma* and preterm birth"
- "*Ureaplasma* or *Mycoplasma* and pregnancy"
- "*Ureaplasma* and infection and preterm labor"

We did not apply any language restrictions to the search, but studies published in English and widely spoken languages were prioritized for inclusion. The search was last updated in May, 2024 to ensure that the most current research was included. We used the PRISMA flow diagram to visually represent the study selection process (fig. 1). This diagram is included in the supplementary materials for clarity.

Studies were included if they met the following criteria:

1. Investigated the presence and effects of *Ureaplasma* spp. in pregnant women.
2. Reported outcomes related to preterm birth.
3. Utilized reliable detection methods such as NAAT or culture-based techniques.

Data from the selected studies were extracted and categorized. We were particularly interested in:

- Study type (retrospective, prospective cohort, cross-sectional, case-control).
- Number of patients included in each study.
- Detection methods used and their accuracy.

Descriptive statistics were used to summarize the data from the selected studies. Odds ratios (OR) and percentages were calculated to quantify the association between *Ureaplasma* colonization and adverse pregnancy outcomes. The statistical significance of these associations was assessed to determine the reliability of the findings. To mitigate publication bias, we conducted a comprehensive search without language restrictions.

There was significant heterogeneity in the reporting methods used across the included studies. While most studies relied on PCR for detecting *Ureaplasma* species, other methods such as bacterial cultures or serological tests were also used. This variation in diagnostic standards may introduce bias and affect the comparability of study results.

We acknowledge that the differences in diagnostic techniques and the lack of uniformity in defining preterm birth and other pregnancy outcomes may contribute to heterogeneity and potential bias in the findings.

RESULTS

This review analyzed 25 studies published between 2000 and 2024 (fig.1), involving 15,700 patients. The studies included 10 retrospective, 8 prospective cohort, 4 cross-sectional, and 3 case-control designs (tab. 1).

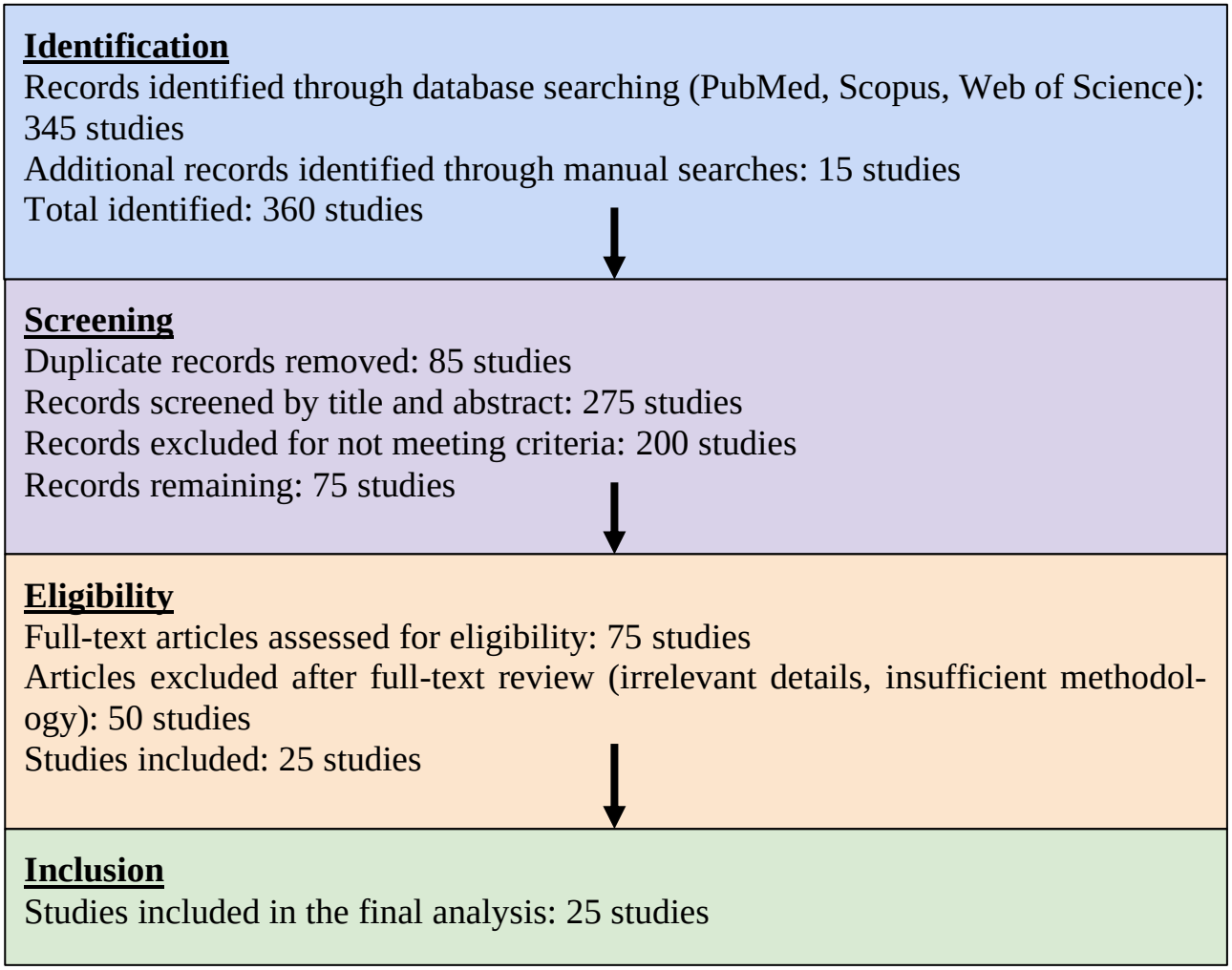

Figure 1. PRISMA diagram. Summary of study selection.

Ureaplasma parvum was detected in 40.5% of healthy women, while *Ureaplasma urealyticum* was found in 20.3%. Detection using NAAT was found to be superior to culture-based methods due to its speed and accuracy. The studies consistently showed that intra-amniotic infection with *Ureaplasma* increased the risk of preterm delivery, with odds ratios ranging from 2.76 to 3.0. Preterm birth rates among *Ureaplasma*-positive women varied from 26% to 58.6%. In a prospective cohort, 58.6% of women with second-trimester *Ureaplasma* infection experienced preterm labor, compared to 4.4% of uninfected women. Detection of *Ureaplasma parvum* in the vagina was identified as a significant risk factor for preterm birth with an odds ratio of 3.0. Vaginal colonization with *Ureaplasma parvum* in the first trimester increased the risk of spontaneous preterm birth with an odds ratio of 1.7. Intra-amniotic inflammation was present in 25% of cases with *Ureaplasma* DNA. The Gardnerella Lactobacillus *Ureaplasma* test demonstrated sensitivities of 37.9% for predicting preterm birth before 37 weeks and 44.4% for predicting preterm birth before 34 weeks. 68% of newborns born to carrier mothers were carriers as well. Infection rates among newborns were 100% for Ureaplasma parvum, and 28.5% for *Ureaplasma urealyticum*. *Ureaplasma* infections were found to induce pro-inflammatory cytokines, activate neutrophils and TLR-9, and increase prostaglandin and matrix metalloproteinase activity, leading to fetal membrane weakening and rupture.

DISCUSSIONS

Ureaplasma is one of the common species found in the lower genital tract of sexually active women. The first publications about colonization with Ureaplasma in women date back to 1954. The first publication discussing *Ureaplasma* was by Shepard MC in 1960, who reported the recovery of pleuropneumonia-like organisms from the

urogenital tract. This study laid the groundwork for understanding *Ureaplasma* as a significant pathogen in human health (1).

Ureaplasma is a very small, atypical bacterium, the detection of which was quite challenging in the past. With the development of new techniques, questions about the harmlessness of *Ureaplasma* infection are being raised. *Ureaplasma* spp. is a bacterium belonging to the class Mollicutes, which consists of 8 genera, including *Mycoplasma*. The two most commonly observed species are *U. urealyticum* and *U. parvum* (2).

Ureaplasmas are among the smallest microorganisms without a cell wall, which is why gram-staining is not reliable. The pleomorphic nature of *Ureaplasma* species results from their lack of structural integrity, allowing individual organisms to vary in size from 100 nm to 1 µm. Originally identified as tiny-form pleuropneumonia-like organisms, *Ureaplasma* spp. were also known as T-mycoplasmas. However, urease, an enzyme that hydrolyzes urea to provide 95% of its energy needs, distinguishes *Ureaplasma* from other *Mycoplasma* species. Ammonia is produced when urea is hydrolyzed, which increases the proton electrochemical potential and initiates the synthesis of ATP from scratch. One characteristic that sets *Ureaplasma* spp. apart in culture is the generation of ammonia. Numerous techniques have been reported for serotyping *Ureaplasma* spp., including the use of rabbit antisera in growth inhibition tests, immunoperoxidase tests, enzyme-linked immunosorbent assays, and colony indirect epi-immunofluorescence. Multiple cross-reactions between serovars and the absence of standardized reagents have contributed to the poor results obtained from these tests (3).

The *retrospective* study by Kusanovic JP et al., 2020, was designed to compare the identification and susceptibility of *Ureaplasma* spp. and *Mycoplasma hominis*. They compared NAAT) with the culture-based method, followed by antibiotic susceptibility testing. The results were then compared in terms of identification accuracy, time to result, and susceptibility profile. The study highlighted the importance of rapid and accurate identification of *Ureaplasma* spp. and *Mycoplasma hominis* in managing high-risk pregnancies. The faster turnaround time of NAAT makes it a valuable tool for timely clinical decision-making, especially in acute settings (4). The retrospective nature of the study and its focus on high-risk pregnancies may introduce selection bias, as well as potential information bias from the use of medical records for data collection.

Ureaplasma is one of the common species found in the lower genital tract of sexually active women. Rumyantseva T. et al., 2018, *in a cross-sectional study* including 2,594 female patients, found that *U. parvum* was detected in 40.5% of healthy women, while *U. urealyticum* was found in 20.3% of healthy women (5). As a cross-sectional study, the design limits causal inferences and may be subject to information bias, as it provides a snapshot of the population at one point in time and may not accurately reflect causal relationships or variations over time. This study shows that even asymptomatic pregnant women can be colonized with *Ureaplasma* spp., highlighting that colonization can occur without symptoms at the beginning of pregnancy.

In gynecology, *Ureaplasma* spp. has been widely linked to pelvic inflammatory disease, urinary tract infections, and bacterial vaginosis. The bacterial burden of *Ureaplasma* spp. in females with bacterial vaginosis can be significantly higher than in those without this condition. Mollicutes do not cause inflammatory vulvovaginitis. There has been speculation about *Ureaplasma* working in symbiosis with other BV pathogens. Although not in pure culture, *Ureaplasma* species have been directly isolated from affected fallopian tubes.

The *cross-sectional study* by Cox C. et al., 2016, aimed to determine the clinical significance of four mollicutes species: *Mycoplasma genitalium, Mycoplasma hominis, U. urealyticum*, and *U. parvum*, in the context of non-chlamydial, non-gonococcal urethritis. The study found a significantly higher prevalence of *U. parvum* in non-gonococcal urethritis patients (17.3%) (6). This study indicates that, among the four mollicutes species examined, *U. parvum* was the most frequently associated with complications. This finding could help guide screening options for pregnant women, particularly in high-risk populations. By focusing on *U. parvum*, healthcare providers may be able to implement more specific and timely interventions to improve pregnancy outcomes. This study may be subject to selection bias, as it is a cross-sectional study that examines a specific patient group without random sampling, limiting the generalizability of its findings.

In the *retrospective study* by Zeng J. et al., 2022, out of the 1,736 patients examined, 461 (26%) were found to be positive for *U. urealyticum* (7). This retrospective study may be prone to recall bias, as it relies on historical patient data and may not have accounted for all relevant variables, potentially affecting the accuracy of the reported prevalence rates.

Ureaplasma infections also occur when the woman is pregnant. Usually, the causative organism is detected after the onset of adverse outcomes or after the delivery has occurred (8).

The *prospective cohort* by Abele-Horn M. et al., 2000, examines the impact of *U. urealyticum* colonization on pregnancy outcomes. It included 172 women with *U. urealyticum* and 123 women without the infection. Results showed that higher colonization levels were significantly associated with decreased birth weight and gestational age, and increased rates of chorioamnionitis and preterm delivery. High-density colonization was identified as an independent risk factor for these adverse outcomes, while low colonization levels had no significant effect (9). This study may be subject to selection bias, as it compares women with *U. urealyticum* colonization to those without, potentially overlooking confounding factors that could influence pregnancy outcomes, such as other infections or underlying health conditions.

The study by Gerber S. et al., 2003, aimed to investigate the relationship between intra-amniotic *U. urealyticum* in asymptomatic second-trimester pregnant women and subsequent pregnancy outcomes, particularly PTB. The researchers obtained transabdominal amniotic fluid from 254 asymptomatic women at 15-17 weeks of gestation (wg) and tested it for *U. urealyticum* using polymerase chain reaction (PCR). They found that *U. urealyticum* was identified in 29 subjects (11.4%). Subsequent PTB occurred in 17 (58.6%) of the *U. urealyticum*-positive women compared to 10 (4.4%) of the *U. urealyticum*-negative women, a statistically significant difference ($P < .001$). PTB was documented in 7 (24.1%) of the *U. urealyticum*-positive women compared to only 1 (0.4%) of the *U. urealyticum*-negative women, which was also statistically significant ($P < .0001$). The study further revealed that *U. urealyticum*-positive women had a higher prevalence of PTB in a prior pregnancy (20.7%) compared to the negative women (2.7%; $P = .0008$) (10). This study may be subject to selection bias, as it only included asymptomatic women, potentially excluding those who showed symptoms of infection and might have different outcomes.

Kataoka S. et al., 2006 in a *prospective cohort* explored the relationship between *U. urealyticum* and PTB. It involved 1,040 women initially, with singleton pregnancies less than 11 wg. However, after excluding some participants for various reasons such as induced abortions and unavailability for follow-up, a total of 877 women were analyzed for the final results. *U. parvum* was detected in 52.0% of the women. *U. urealyticum* was detected in 8.7% of the women. Detection of *U. parvum* in the vagina was identified as a significant risk factor for late abortion or PTB. Women with *U. parvum* had an odds ratio (OR) of 3.0 for experiencing these outcomes, with a 95% confidence interval from 1.1 to 8.5, indicating a statistically significant increase in risk (11). The study's observational design and lack of control group may introduce selection bias and confounding factors that could influence the results regarding PTB rates.

The study by Harada K. et al., 2008, involved 145 participants, comparing 100 women with full-term deliveries and 45 women with preterm deliveries. It was a clinical investigation analyzing the presence of *U. urealyticum* in vaginal secretions. The study found that *Ureaplasma* infection was significantly higher in the preterm delivery group (51.1%) compared to the full-term group (30.0%). The presence of this bacterium was associated with an increased production of IL-8 and apoptotic cell death, suggesting a potential causative link to preterm delivery outcomes (12). This study may be affected by selection bias, as the inclusion of only women with full-term or preterm deliveries may not account for other factors influencing *Ureaplasma* infection.

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The *cross-sectional comparative study* by Jones HE et al., 2009, investigated the role of intrauterine infection in preterm delivery, analyzing bacterial DNA in the placenta and fetal membranes from 74 women. The groups included PPROM <32 weeks, PTL with intact membranes <32 weeks, indicated preterm delivery <32 weeks, and term deliveries. Bacterial prevalence was significantly higher in the preterm groups, especially PTL with intact membranes (89%) and PPROM (55%), compared to term deliveries (14). This study may suffer from selection bias, as the groups are based on different types of preterm deliveries (PPROM, PTL, and indicated preterm delivery), which could introduce variability in the factors contributing to PTB, potentially skewing the results on bacterial prevalence.

The observational cohort study by Agger WA et al., 2014, investigated the link between urogenital infections and PTB among 676 pregnant women from various urban and rural settings. Results showed an 8% overall PTB rate, with higher rates in large urban areas (12.1%) compared to midsize urban (8.8%), small city (9.4%), and rural areas (2.3%). *U. parvum* infections were particularly prevalent in large urban sites, correlating with increased PTBs. Significant risk factors included prior PTB (aOR 2.76) and urinary tract infection (aOR 2.62), while protective factors included good health (aOR 0.42) and group B streptococcal infection treatment (aOR 0.38) (15). This study may be subject to confounding bias, as various factors such as prior PTB, urinary tract infections, and urban versus rural settings could influence the results, making it difficult to isolate the specific impact of *U. parvum* on PTB.

The retrospective cohort study by Freitas AC et al. examined the relationship between vaginal microbiota composition and spontaneous PTB. Conducted as a retrospective cohort study, it included 46 pregnant women who delivered preterm and 170 who delivered at term. *Ureaplasma* species were found in 14 out of 46 (30%) women who had PTBs, with all testing positive for *U. parvum* and none for *U. urealyticum* (16). This study may have selection bias, as the sample of 46 women with PTBs might not be representative of the broader population, potentially skewing the findings regarding the relationship between *Ureaplasma* species and PTB.

The study by Payne MS. et al., 2016, found that detection of *U. parvum* was significantly higher in women who experienced spontaneous preterm birth (PTB) compared to those who delivered at term. Specifically, *U. parvum* was detected in 77% of preterm cases versus 36% at term. This association was even stronger when the *U. parvum* genotype SV6 was present, with detection in 54% of preterm cases compared to 15% at term. Additionally, smoking was found to increase the likelihood of detecting these organisms (17). This study may have confounding bias due to the influence of smoking on the likelihood of detecting *U. parvum*, which could have contributed to the observed association with PTB.

The prospective multicenter study by Rittenschober-Böhm J. et al., 2017, analyzed the impact of first-trimester vaginal colonization by *Ureaplasma* biovars on PTB outcomes in 4,330 pregnant women. The results showed that *U. parvum* was detected in 37% of the women. The rate of spontaneous PTB in this group was 10.4%, with an odds ratio (OR) of 1.7 (95% confidence interval [CI] 1.3, 2.2; $p < 0.001$), indicating a significantly increased risk. *U. urealyticum* was detected in 5.9% of the women, with a PTB rate of 8.9% and an OR of 1.4 (95% CI 0.9, 2.3; $p = 0.193$), which was not statistically significant. Compared to women with negative PCR results for *Ureaplasma*, who had a 6.4% rate of preterm birth, the study concluded that vaginal colonization with *U. parvum* is a statistically significant and independent risk factor for spontaneous PTB, with an adjusted OR of 1.6 (95% CI 1.2, 2.1; $p < 0.001$), regardless of other risk factors (18).

Another study by Judith Rittenschober-Böhm J. et al., 2019, showed that vaginal colonization with *U. parvum* serovar 3 significantly increases the risk of spontaneous PTB at very low (<32 weeks, $P < 0.005$) and extremely low (<28 weeks, $P < 0.005$) gestational ages. The presence of serovar 3 was most common, found in 43.3% of *U. parvum* positive samples, compared to 31.4% for serovar 6 and 25.2% for serovar 1. The study suggests a targeted approach for women with serovar 3 colonization, especially those with a history of PTB or bacterial vaginosis (19). This study may have selection bias, as it focused on women with a history of PTB or bacterial vaginosis, which could influence the generalizability of the findings to the broader pregnant population.

A *case-control study* by Oliveira CNT. et al., 2020, aimed to investigate the presence of *Ureaplasma*

spp. in placental tissue and its association with adverse pregnancy outcomes. PCR was utilized to identify Mollicutes in cervical mucus and placental tissue samples. *U. parvum* was found in 66.3% of placental tissue samples from women who had spontaneous abortions. A positive correlation was observed between the presence of *U. parvum* in placental tissue and abortion. The study included 98 women who miscarried and 20 women who had healthy pregnancies. This study suggests that *Ureaplasma* can reach the maternal-fetal surface and contribute to unwanted pregnancy outcomes (20). This case-control study may be subject to selection bias, as the comparison between women who miscarried and those with healthy pregnancies may not fully account for other confounding factors, such as maternal health conditions or environmental influences, which could also affect pregnancy outcomes.

The study led by Peretz A. et al., 2020, investigated the prevalence and transmission of *Ureaplasma* species among pregnant women, along with the potential implications for pregnancy outcomes and newborn health. The study included 214 pregnant women who were tested for vaginal pathogen carriage using standard culture and PCR assays, and pharyngeal swabs were collected from the newborns of carrier mothers. A total of 19 (8.8%) women were found to be carriers of *Ureaplasma* species, with 4.19% testing positive for *U. parvum* and 2.32% for *U. urealyticum*. Carriage was more common in younger women, with 10.5% of women aged 18-29 being carriers, compared to 7.5% of women aged 30-39. No women over the age of 40 were found to carry *Ureaplasma.* Among the women who carried *Ureaplasma*, 5 (26.3%) delivered preterm. Specifically, 3 out of 5 women carrying *U. urealyticum* and 1 out of 9 women carrying *U. parvum* delivered preterm (21). This study may be subject to selection bias, as the sample of 214 pregnant women may not be representative of the general population, particularly since carriage of *Ureaplasma* was more common in younger women. Additionally, the reliance on standard culture and PCR assays for pathogen detection may introduce detection bias, as the sensitivity of these methods can vary depending on microbial load, potentially leading to false negatives or overestimation of *Ureaplasma* prevalence.

Bartkeviciene D. et al., 2020, conducted a *retrospective study* to analyze the impact of *Ureaplasma* infections on pregnancy complications. The study included 50 pregnant women with signs of threatened preterm delivery. Samples from the endocervical canal and cervix surface were tested for several pathogens, including *Ureaplasma* species. The study found that 46% of the patients had premature rupture of membranes, and 76% experienced preterm delivery. *Ureaplasma* infections were significantly associated with premature rupture of membranes ($p < 0.004$), placental inflammation ($p < 0.025$), and newborn respiratory distress syndrome ($p < 0.019$) (22). The small sample size and potential selection bias from focusing on a single hospital setting may limit the generalizability of the findings.

The study by Kacerovsý M. et al., 2022, was a prospective cohort study involving 115 women, aged 22-35 weeks of gestation, complicated by PTB. The diagnosis of microbial invasion of the amniotic cavity was made using molecular biology techniques in addition to culture methods. The level of interleukin-6 in the amniotic fluid was used to measure intra-amniotic inflammation. Sterile inflammation was found in 14% of the women, while 25% had intra-amniotic infection. DNA from *Ureaplasma* spp. was found in the cervical fluid of 51% of the participants. Women with intra-amniotic infection had greater levels of *Ureaplasma* spp. and *Mycoplasma hominis* DNA (42%) compared to women with sterile intra-amniotic inflammation (7%) and those without intra-amniotic inflammation (7%; $p = 0.001$) (23). The study's retrospective design may introduce recall and selection bias, as it relies on past medical records and does not control for confounding variables in a non-randomized setting.

The *prospective cohort study* by Payne MS. et al., 2021, included 936 women who provided midvaginal swabs between the 12th and 23rd weeks of gestation, which were analyzed using quantitative PCR to detect 23 microbial DNA targets associated with PTB risk. The study found that the overall PTB rate was 12.6%, with a spontaneous PTB rate of 6.2% for those under 37 weeks and 2.9% for those under 34 weeks. The rate of preterm premature rupture of membranes (PPROM) was 4.2%. The final predictive model, called the Gardnerella Lactobacillus Ureaplasma test, demonstrated sensitivities of 37.9% for predicting PTB before 37 weeks and 44.4% for predicting PTB before 34 weeks (24). This study may

be subject to detection bias due to its reliance on quantitative PCR for detecting microbial DNA, which may not fully account for the variability in microbial load or composition. Additionally, the relatively low sensitivity of the predictive model (37.9% for PTB before 37 weeks and 44.4% for PTB before 34 weeks) could introduce measurement bias, as it might fail to accurately predict PTB, leading to potential misclassification of patients at risk. This could affect the generalizability and clinical applicability of the findings.

The study conducted by Matasariu DR. et al., 2020, included 1,301 pregnant women with ruptured membranes and pregnancies over 17 weeks, observed from January 2010 to December 2019. The prevalence of *U. urealyticum* infection was 57.3% in women between 17-23 weeks, 49.7% between 24-28 weeks, 40.7% between 29-32 weeks, 40.2% between 33-36 weeks, and 45.1% in those ≥37 weeks. The infection was significantly associated with adverse pregnancy outcomes, including PTB and chorioamnionitis (25). The study may be impacted by recall bias, as the retrospective design relies on patient histories and the potential for confounding factors due to the absence of randomization.

The research conducted by Przybylski M. et al., 2024, was a retrospective study involving 201 pregnant women who were hospitalized at the Obstetrics and Gynecology Department of Poznan Regional Hospital between 2019 and 2022. The study showed a higher occurrence of PTB among the infected group (31.1%) compared to the non-infected group (20%). PPROM occurred in 40% of *Ureaplasma*-positive patients preceding preterm delivery, compared to 20% in non-infected cases, indicating a significant effect of the infection on this specific complication. The effectiveness of antibiotic therapy did not show a clear benefit, as PTB and pregnancy loss rates were similar in treated (35.7%) and untreated patients (31.6%) (26). This study may be subject to bias due to its retrospective design, which could be influenced by incomplete patient records, selective reporting of PTB cases, or differences in treatment protocols between the infected and non-infected groups.

This *retrospective observational study* by Marti DT. et al., 2024, included 71 pregnant women who experienced PTBs and 94 women with genital infections who delivered at term. The odds ratio (OR) for PTB associated with this pathogen is reported as 2.76, with a p-value of 0.009, indicating a statistically significant association. This suggests that the presence of *U. urealyticum* in pregnant women substantially increases the risk of delivering preterm (27). The retrospective design and the comparison of two distinct groups (PTBs and term deliveries with genital infections) could introduce confounding variables, such as differences in maternal health, socioeconomic factors, or other infection-related conditions, potentially affecting the likelihood of PTB and introducing selection bias.

The study by Prodan-Barbulescu C. et al., 2024, conducted between 2019 and 2023, is a retrospective case-control study comparing vaginal microbiota from 89 women who delivered preterm and 106 women who delivered at term. The analysis centered on vaginal cultures taken during the third trimester, comparing various microbiological and immunological parameters between the two groups. *U. urealyticum* was significantly associated with increased PTB risk, with an odds ratio of 2.43 ($p = 0.001$). This study provides robust evidence that the presence of *U. urealyticum* in the vaginal microbiota is critically associated with the risk of PTB. It underscores the potential benefits of targeted microbial management as part of strategies to reduce PTB rates (28). This study may be subject to recall and selection bias, as it relies on retrospective data and the comparison of preterm and term birth groups, which could involve unaccounted-for differences in other factors affecting PTB risk, such as socioeconomic status or access to prenatal care.

The mechanism by which *Ureaplasma* species contribute to preterm birth (PTB) involves several complex processes:

1. Induction of Pro-inflammatory Cytokines and Chemokines**:**
   Ureaplasma infection induces the production of pro-inflammatory cytokines and chemokines in the amniotic fluid and fetal membranes. This inflammatory response can activate matrix metalloproteinases (MMPs), which degrade the extracellular matrix of the fetal membranes, weakening them and making them more susceptible to rupture (29).
2. Neutrophil Activation**:**

The infection also activates neutrophils, which release enzymes and reactive oxygen species that further damage the fetal membranes. Neutrophils can form neutrophil extracellular traps (NETs) that contribute to tissue damage and inflammation (30).

3. Prostaglandin Production:
Ureaplasma infection increases the production of prostaglandins, which are known to induce uterine contractions. Elevated levels of prostaglandins in the amniotic fluid can lead to the premature initiation of labor (31).
4. Cervical Epithelial Damage:
Ureaplasma can ascend from the lower genital tract to the upper genital tract, leading to cervical epithelial damage. This damage promotes further infection and inflammation, contributing to cervical remodeling and shortening (32).

In addition, *Ureaplasma* species contribute to PTB through the activation of Toll-Like Receptor 9 (TLR-9). TLR-9 is an innate immune receptor that recognizes unmethylated CpG motifs in bacterial and viral DNA, triggering an immune response. In the case of *Ureaplasma* infections, bacterial DNA activates TLR-9 on immune cells like macrophages and dendritic cells. This activation initiates a signaling cascade involving MyD88, which leads to the activation of NF-κB and the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β (33).

Once the infection ascends to the choriodecidual area and crosses the fetal membrane, *Ureaplasma* spp. move placentally into the amniotic cavity. In addition to their direct impact, they raise the levels of many cytokines and other inflammatory mediators (34).

The activation of TLR-9, a DNA sensor, by neutrophil extracellular traps and ERK signaling facilitates the fetal membrane response. During infection, neutrophils drawn to the membranes have the ability to spread inflammation and weaken the tissue. This can cause damage at the maternal-fetal interface, raising the risk of early fetal membrane rupture and PTB in women with an intrauterine infection (35).

An increase in IL-6 concentration has been linked to the presence of *U. parvum* and *U. urealyticum*, while an increase in IL-12p70 concentration is associated with *U. parvum* presence. Regarding gene expression, the presence of *U. parvum* led to the downregulation of genes associated with the immune response, while the spontaneous abortion group showed an elevation of genes linked to the activation of apoptosis. Taken together, these findings demonstrate that *U. parvum* colonizes the placentas of pregnant women at any gestational age and may be connected to spontaneous abortion (36).

Ureaplasma causes preterm premature rupture of membranes (PPROM) by infecting the amniotic fluid. This was demonstrated by measuring intra-amniotic inflammatory responses in pregnant women. White blood cell counts and amniotic fluid matrix metalloproteinase-8 concentrations were used to measure the degree of the intra-amniotic inflammatory response, while the amount of white blood cells and C-reactive protein in the mother's blood during amniocentesis reflected the maternal inflammatory response (37).

The study by Tong M. et al. (2021) investigated the role of activated neutrophils in propagating fetal membrane inflammation and weakening through ERK and TLR-9 signaling. The researchers found that neutrophils contribute to this process by releasing neutrophil extracellular traps (NETs) that activate TLR-9. The findings suggest that targeting neutrophil activation and these specific signaling pathways could potentially prevent inflammation-induced weakening of fetal membranes, reducing the risk of PPROM and related complications (38).

A study conducted by Tripathy S. et al. (2024) examined the effects of *U. parvum* infection on the chorioamnion membranes in a non-human primate model. The experimental group was inoculated with *U. parvum* (10^5 CFU/mL) at the choriodecidua, while the control group received sterile media. Significant increases in the expression of MMP-9 and PTGS2 were noted in the fetal membranes, indicative of an inflammatory response. More notably, there was a marked increase in the expression of inflammasome components like NLRP3, NLRC4, AIM2, NOD2, and the adaptor ASC (PYCARD), alongside pro-inflammatory cytokines such as IL-1β and IL-18 (39).

The study by Tantengco OAG et al. investigates the impact of *U. parvum* on exosome biogenesis and the proteomic profile of exosomes in ectocer-

vical epithelial cells. *U. parvum* was able to colonize ectocervical epithelial cells, demonstrating colocalization with CD9-positive intraluminal vesicles, which are indicative of exosome compartments. The proteomic analysis revealed that exosomes derived from infected cells had decreased protein abundance and exhibited distinct protein profiles compared to those from uninfected cells. Key proteins like clathrin, ALIX, CD9, and CD63, which are involved in exosome formation and release, were found to be decreased. Proteins such as TSG101, Rab5, Rab35, and UGCG, which play roles in vesicular trafficking and lipid biosynthesis, were increased in infected cells. This study enhances our understanding of how *U. parvum* interacts with host cells at a molecular level, particularly through modifications in exosome biogenesis and protein cargo. These findings underscore the importance of exosomal processes in the pathophysiology of *U. parvum* infections and their potential consequences for female reproductive health (40).

CONCLUSIONS

1. The compiled studies from 2000 to 2024 demonstrate a significant association between *Ureaplasma* spp. colonization and adverse pregnancy outcomes, particularly PTB.
2. Detection using NAAT was found to be superior to culture-based methods due to its speed and accuracy. The studies consistently showed that intra-amniotic infection with *Ureaplasma* spp. increased the risk of preterm delivery, with odds ratios ranging from 2.76 to 3.0.
3. *Ureaplasma* infections were found to induce pro-inflammatory cytokines, activate neutrophils and TLR-9, and increase prostaglandin and matrix metalloproteinase activity, leading to fetal membrane weakening and rupture.
4. Prospective randomized studies are recommended to validate these findings and develop targeted therapeutic strategies to mitigate the risks associated with *Ureaplasma* spp. infections. By improving detection and management protocols, healthcare providers can better support maternal and neonatal health, ultimately reducing the incidence of preterm births and related complications.

CONFLICT OF INTEREST

There is no conflict of interest regarding the material presented in the paper.

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GENETIC DIVERSITY ANALYSIS OF THE SARS-CoV-2 VIRUS: A LITERATURE REVIEW

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Keywords: *SARS-CoV-2, COVID-19, genetic monitoring, mutation variants, sequencing, S protein.*

Introduction. *The continuous evolution of the SARS-CoV-2 virus through the accumulation of genetic mutations has led to the emergence of variants with different characteristics, including increased transmissibility, heightened resistance, and changes in disease severity.*

Material and methods. *The research was conducted using open-access international databases such as PubMed, Google Scholar, and national libraries, employing the keywords: SARS-CoV-2, COVID-19, genetic monitoring, mutation variants, sequencing, S protein.*

Results. *Currently, the WHO identifies five major genetic variants of concern (VOCs): Alpha, Beta, Gamma, Delta, and Omicron. The Alpha variant became globally dominant in early 2021 and was replaced by the Delta variant in the summer of 2021. The Delta strain has over 13 mutations, nine of which are found in the S protein. The genome of the Omicron variant contains more than 30 mutations in the conserved domain of the Spike protein. The Omicron variant caused a sharp increase in the number of COVID-19 cases worldwide and was responsible for a record 15 million new infections reported worldwide in one week.*

Conclusions. *The continuous evolution of the SARS-CoV-2 genome poses new challenges for public health. It is essential to study the virus's genetic characteristics to understand mutations, immune evasion, and the persistent effects of infection, with the aim of optimizing prevention and treatment strategies.*

Cuvinte-cheie: *SARS-CoV-2, COVID-19, monitorizarea genetică, variante de mutații, secvențierea, proteina S.*

ANALIZA DIVERSITĂȚII GENETICE A VIRUSULUI SARS-CoV-2: REVIZUIREA LITERATURII

Introducere. *Evoluția continuă a virusului SARS-CoV-2 prin acumularea mutațiilor genetice a generat variante cu diferite caracteristici, inclusiv o transmisibilitate crescută, rezistență sporită și modificări în severitatea bolii.*

Material și metode. *Cercetarea a fost efectuată folosind bazele de date internaționale cu acces deschis – PubMed, Google Academic și bibliotecile naționale, utilizând cuvintele cheie: SARS-CoV-2, COVID-19, monitorizarea genetică, variante de mutații, secvențierea, proteina S.*

Rezultate. *În prezent, OMS identifică cinci variante genetice majore de îngrijorare (VOC): Alpha, Beta, Gamma, Delta și Omicron. Varianta Alpha a devenit dominantă la nivel global la începutul anului 2021 și a fost înlocuită cu varianta Delta din vara anului 2021. Tulpina Delta are mai mult de 13 mutații, dintre care nouă se găsesc în proteina S. Genomul variantei Omicron are mai mult de 30 de mutații în domeniul conservat al proteinei Spike. Varianta Omicron a provocat o creștere bruscă a numărului de cazuri de COVID-19 la nivel mondial și a fost responsabilă pentru un record de 15 milioane de noi infectări raportate în lume în decurs de o săptămână.*

Concluzii. *Evoluția continuă a genomului SARS-CoV-2 impune noi provocări pentru sănătatea publică. Este esențial să se studieze caracteristicile genetice ale virusului pentru a înțelege mutațiile, evaziunea imunității și efectele persistente ale infecției, în vederea optimizării strategiilor de prevenire și tratament.*

INTRODUCTION

At the end of 2019, a new coronavirus subtype, named SARS-CoV-2 (Severe Acute Respiratory Syndrome – Coronavirus 2), was identified as the cause of a cluster of pneumonia cases in Wuhan, China. The virus rapidly spread worldwide, and on March 11, 2020, the World Health Organization (WHO) officially declared the COVID-19 pandemic. The initial impact on public health was devastating, with healthcare systems worldwide overwhelmed by the large number of cases. Travel restrictions, quarantines, and lockdowns became common measures to limit the spread of the virus. In addition to these measures, the pandemic had significant effects on the global economy, disrupting international trade, the workforce, and education, while reshaping the norms of social and professional interactions (1, 2).

The Coronaviridae family, to which SARS-CoV-2 belongs, also includes other epidemiologically significant viruses such as SARS-CoV and MERS-CoV, characterized by a high frequency of genomic alterations (mutations, deletions, recombinations). Since the initial sequencing of its genome in January 2020, SARS-CoV-2 has undergone thousands of unique mutations. Most of these mutations do not affect the virus's virulence or transmissibility, but the most notable ones occur in the Spike protein, particularly in the receptor-binding domain (RBD). These mutations can alter how the RBD binds to the cellular receptor, angiotensin-converting enzyme 2 (ACE2), often increasing the virus's infectivity and leading to the emergence of new genetic variants of SARS-CoV-2 (3 – 6).

The global response to the pandemic included unprecedented international cooperation in research and the rapid development of vaccines, illustrating a new model of global collaboration. However, significant challenges arose, including logistical issues in vaccine distribution, vaccine hesitancy, and disparities in access to medical resources. These aspects highlight the need for continued research to address critical questions left unanswered by the pandemic and to develop strategies to mitigate its effects.

It is important to conduct a literature review for a deeper understanding of the genetic evolution of the SARS-CoV-2 virus and its impact on the COVID-19 pandemic in order to summarize, systematize data, and provide a holistic picture of the current state of knowledge. This can help identify general trends and patterns that might be missed when examining individual publications. These arguments highlight the versatility and importance of conducting a literature analysis to further improve research, practical measures, and response strategies to global health challenges.

The aim of this study was to analyze the existing specialized literature on the genetic characterization and evolution of SARS-CoV-2, with a focus on genomic mutations, the emergence of new variants with epidemiological potential, and their impact on public health.

MATERIAL AND METHODS

For this study, international open-access databases such as PubMed and Google Scholar were used. Source identification was guided by relevant keywords and the following search strategies: *Nidovirales*, deletion 69/70 AND S protein, Concerning Variants AND evolution of SARS-CoV-2, genome characteristic OR genetic monitoring AND COVID-19 AND mutation variants, sequencing AND whole genome AND SARS-CoV-2 virus. To ensure comprehensiveness and relevance of identified materials, additional references were obtained through manual review of bibliographies and citations from initially selected articles. Exclusion criteria: articles published before 2020 to ensure data timeliness, articles lacking a methodology or presenting it unclearly. Inclusion criteria: only relevant articles published in English and Romanian were included to facilitate in-depth analysis. Regarding study types, articles classified as Systematic Review, Prevalence Study, and Qualitative Study were selected to provide a comprehensive overview and robust data analysis.

Therefore, the text of the articles was evaluated based on variables such as the study's aim, methodology, year of completion, and results obtained. From the collected information, the most relevant and recent studies offering clear perspectives on the genetic diversity of the SARS-CoV-2 virus and its impact on public health were selected. These sources were analyzed to highlight emerging trends, significant variations in the virus, and their implications for vaccination and treatment. In this regard, a total of 278 scientific papers were

analyzed, from which, according to selection criteria, 60 publications were analyzed to obtain information about a wide range of genetic characteristics of the COVID-19 causative agent, studying the virus genome mutation mechanisms and the spread of its new strains, of which 15 articles were examined in depth regarding the genetic characterization of VOC variants (fig. 1).

This rigorous methodology enables a comprehensive and systematic evaluation of the literature, essential for understanding the complexity and genetic implications of SARS-CoV-2 in the current global context.

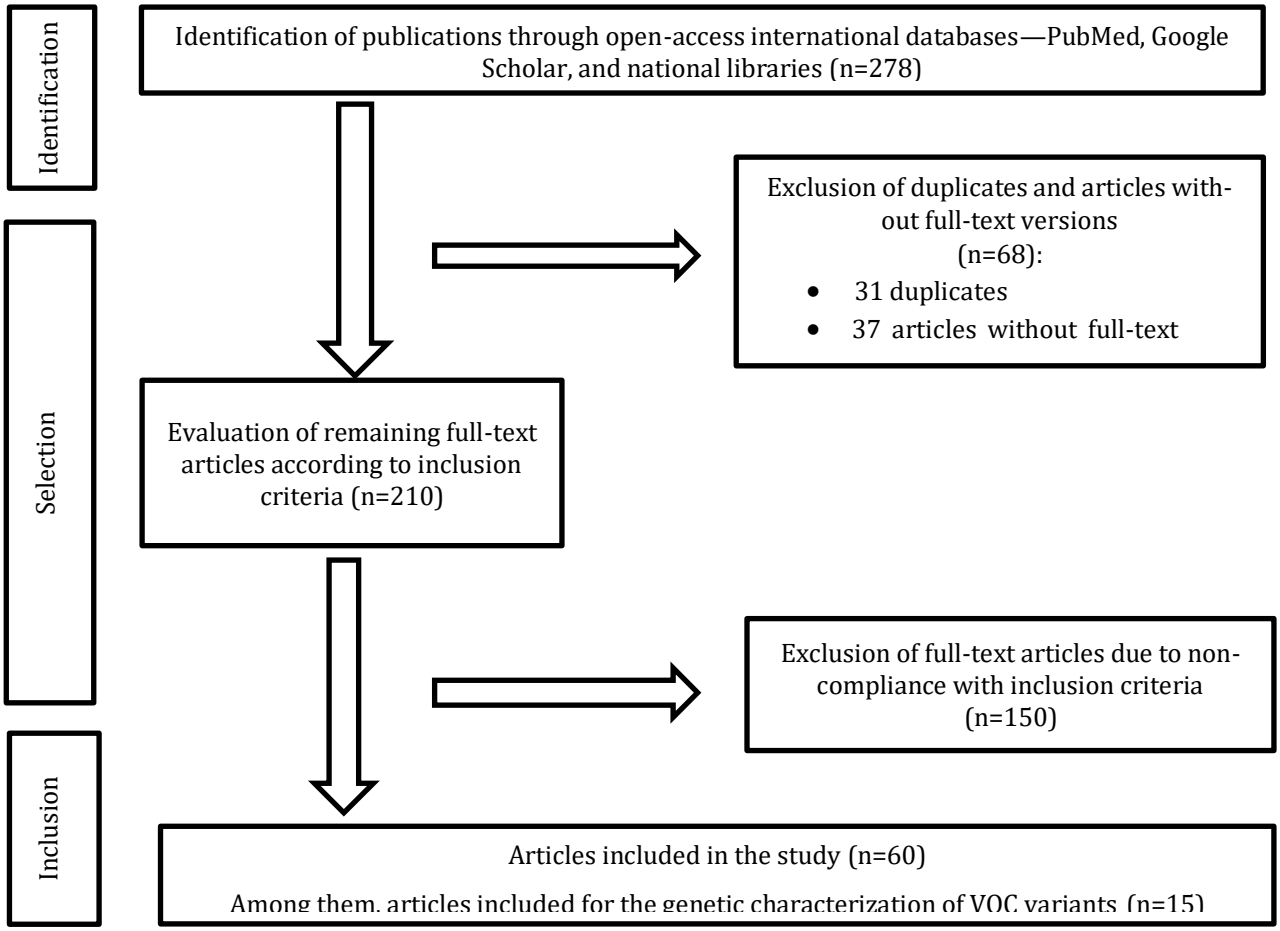

Figure 1. Literature search algorithm.

RESULTS

SARS-CoV-2 is a single-stranded RNA virus, with a genome length of ~29.9 kb. The viral genome consists of six open reading frames (ORFs) common to coronavirus and a series of other accessory genes (7 – 10).

According to phylogenetic analysis, SARS-CoV-2 is more similar to SARS-CoV than to MERS-CoV. It's worth noting that, based on homology modeling studies, SARS-CoV-2 was found to be 96.2% homologous with BatCoV RaTG13, a bat coronavirus from the species *Rhinolophus affinis* (8, 9).

The genome of the SARS-CoV-2 virus encodes 29 proteins, including 16 non-structural proteins (NSP1 – NSP16), necessary for the viral life cycle, 4 structural proteins, and 9 auxiliary protein factors (ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF9c, and ORF10). The structural N protein, together with viral RNA, forms the virus's nucleocapsid, while the S (Spike), E (envelope), and M (membrane) proteins together form the viral envelope. SARS-CoV-2 has an exceptionally high mutation rate, with numerous mutations – particularly in the Spike gene – correlated with increased transmission rates of SARS-CoV-2, enhanced fusogenic properties, and greater pathogenicity of the virus, as well as the emergence of new variants that could reduce the effectiveness

of existing COVID-19 vaccines and antibody-based therapies. The S protein is responsible for SARS-CoV-2 attachment and entry by binding to host receptors. The ACE2 protein has been identified in various organs, including the respiratory system, gastrointestinal tract, lymph nodes, thymus, bone marrow, spleen, liver, kidneys, and brain, suggesting that the virus has tropism for different organs and tissues. Mutations in the Spike protein, particularly D614G, increase the virus's adaptability by evading vaccine effects, resulting in higher survival and spread rates of the virus. This mutation is found in the S region of the following clades: G/GR/GRY/GH/GV, and it is associated with a high host infection rate due to efficient transmission (11, 12, 13).

Thus, the examined viruses have been scientifically proven to undergo slight and rapid modifications, including their virulence and, to some extent, their antigenic structure, which complicates diagnosis and treatment. Coronaviruses can exhibit genetic variability due to mutations occurring in the viral genome. Genetic mutations are transcription errors of RNA polymerase and can generate new antigenic variants and a limited variation in pathogenic potential (14, 15).

The various clinical presentations in COVID-19 patients are caused by mutations in the SARS-CoV-2 genome. The high frequency of genetic mutations leads to the emergence of new variants, a variation that may explain the differences observed in symptoms and disease severity. Altered ACE2 binding interactions or shifted tissue tropism may arise from a mutation among viral descendants, resulting in aggressive infections (16).

As a result, due to the continuous emergence of multiple SARS-CoV-2 variants, the US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have independently created classification systems to define emerging viral mutations in several subgroups based on their impact on transmissibility, lethality, and response to therapy. Although there are differences between the two classifications, some alignments exist regarding the first group of variants of concern (VOC), which possess a set of proven characteristics, such as increased infectiousness, severe disease, higher mortality, and a significant reduction in neutralization by antibodies formed in response to previous infection or vaccination. Currently, under WHO classification, the Delta (B.1.617.2) and Omicron (B.1.1.529) variants belong to this category. The second group, variants of interest (VOI), includes variants with specific genetic markers associated with changes in receptor binding, reduced antibody neutralization, increased transmissibility, decreased treatment efficacy, and a potentially anticipated increase in disease severity. The third group consists of variants under monitoring (VUM), for which evidence suggests a potential impact on transmission rates and treatment efficacy, although their prevalence has declined over time to practically zero. There is another category in the CDC classification: variants of high consequence (VOHC), for which there is compelling evidence that existing diagnostic, prevention, and treatment strategies are much less effective than for those that circulated previously (17).

Variant of concern (VOC):

A series of bibliographic sources highlight the characteristics of SARS-CoV-2 mutations related to phenotypic changes compared to the original virus. These mutations span various levels of structural organization, with the most studied being those impacting the sequence level of different viral proteins. One of the first variants reported during the COVID-19 pandemic was D614G in the Spike protein, associated with increased viral load, immune escape, potential drug resistance, and heightened pathogenicity. This amino acid substitution has persisted in the current variants. It has been noted that the region encoding the receptor-binding domain (RBD) of the Spike protein is prone to accumulating changes in SARS-CoV-2; many studies report substitutions along this region, including N501Y, E484K, N439K, S477N, S399P, and K417V. It was hypothesized that changes in this region could alter the binding affinity of SARS-CoV-2 to ACE2. Another reported variant in the Spike protein was P681H, located near the furin cleavage site and associated with increased transmissibility and infectivity of SARS-CoV-2. The main variants of concern exhibit changes in sequences related to the Spike protein, in the RBD and RBM (receptor-binding motif), and at the furin cleavage site (18).

The relevant criteria for inclusion in VOC are: viral mutation variants for which there is evidence of increased transmissibility, more severe disease (e.g., higher rates of hospitalization or mortality), significant reduction in neutralization by antibodies formed during a prior infection or vaccination, reduced treatment effectiveness, vaccine effect-

tiveness, failed diagnostic measures previously performed (compared to earlier variants). Currently, according to WHO, this category includes the Alpha (UK), Beta (South African), Gamma (Brazilian), and Delta (Indian) variants (10, 15).

These SARS-CoV-2 viral mutation variants have captured researchers' interest as strains that, in addition to multiple point mutations, possess more significant mutations driving the virus's evolution toward increased contagiousness, replication capacity, pathogenic potential, and immune response evasion (19 – 23).

Variants of SARS-CoV-2

✓ **Alpha Variant (B.1.1.7)**

The Alpha variant (B.1.1.7), the first strain classified as a VOC, was identified in southeast England in September 2020 and became globally dominant by early 2021. The Alpha variant exhibits a 70% increase in transmissibility due to key modifications, particularly the emergence of the first Spike mutation (D614G), as well as mutations in the RBM (N501Y) and near the furin cleavage site (P681H), which could enhance ACE2 affinity and impact infection development and transmission. This could have contributed to the rapid spread and dominance of this variant worldwide before the emergence of the Delta variant (19, 24, 25, 26, 27, 28).

Marisa A. P. Donnelly and co-authors noted that in December 2020, the Alpha lineage of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (a Variant of Concern (VOC), also known as B.1.1.7) was first detected in California and Colorado. By the end of April 2021, Alpha had become the predominant circulating lineage in all regions of the United States and other countries worldwide. Surveillance and modeling suggested that Alpha exhibited increased transmissibility within communities compared to non-Alpha lineages circulating at that time (29).

✓ **Beta Variant (B.1.3.51)**

The Beta strain was first detected in the Nelson Mandela Metropolitan Municipality (South Africa) in October 2020. The Beta variant features the N501Y mutation in the Spike protein, similar to the Alpha strain, along with K417N and E484K mutations, which occur in the binding site. The E484K amino acid substitution helps the virus evade neutralizing antibodies, potentially negatively impacting vaccine efficacy. The E484K spike mutation has been linked to a case of reinfection with the Beta variant of SARS-CoV-2 in Brazil, which researchers believe was the first reinfection case associated with this mutation (30).

Cocherie Théophile and co-authors emphasized that the Beta variant, like the Alpha variant, carries the N501Y substitution, but it is distinct due to the absence of the 69/70 deletion and the presence of E484K and K417N/T substitutions. The K417N/T substitutions impact a neutralizing antibody target epitope in the RBD. These substitutions result in the loss of a salt bridge between the RBD and ACE2 and increase the dissociation constant of their binding. This represents a detrimental mutation in terms of SARS-CoV-2 infectivity, leading to negative natural selection of previously existing strains. This variant was selected due to its ability to evade the humoral immune response developed in the general population, associated with mutations like N501Y or E484K that restore the virus's infective potential. The E484K substitution affects a contact point between the RBD and ACE2, resulting in a conformational rearrangement that tightens the binding interface between the RBD and ACE2 and forms new hydrogen bonds, reducing the dissociation constant. Additionally, the E484K substitution impacts one of the key sites for viral recognition by neutralizing antibodies, lowering their affinity whether derived from vaccines, convalescent plasma, or monoclonal antibody treatments (19, 31).

✓ **Gamma Variant (P.1)**

The Gamma strain (P.1) was first identified on January 6, 2021, by the National Institute of Infectious Diseases (NIID) in Japan in four Japanese individuals returning from the Amazonas state in Brazil. Cowling and Lewi Stone reported that the Gamma variant triggered a second wave of the coronavirus epidemic in Manaus, the capital of Amazonas, despite over 70% of the city's population having developed antibodies following the outbreak in May 2020 caused by another coronavirus variant. The situation was exacerbated by Brazilian President Jair Bolsonaro's opposition to vaccinations, his characterization of the coronavirus as a minor flu, and his disregard for calls to impose a state of emergency or implement strict measures such as mask mandates and self-isolation. The damages inflicted by the new wave of the Gamma strain on residents in tropical regions were so devastating that, at the peak of the out-

break, the healthcare system was overwhelmed and unable to cope with the massive number of patients suffering from severe and critical forms of the disease (32).

The genomic analysis of the Gamma (P.1) SARS-CoV-2 strain revealed that this sublineage exhibits up to 12 mutations in the Spike protein, including N501Y (shared with the Alpha and Beta strains) and E484K (also present in the Beta strain). However, specialists also observed that new mutations appeared in the Gamma variant's genome in the Spike protein K417T, which were not detected in previous strains and which allow the virus to bind more firmly to human cells and, in some cases, evade antibodies. Research has shown that the Gamma strain is three times more contagious than the "Wuhan" coronavirus and is capable of overcoming immunity in those who have recovered from the disease. Moreover, studies indicate that this variant affects young people and pregnant women more severely than other SARS-CoV-2 variants. Furthermore, Mendiola-Pastrana and co-authors highlighted three major genomic alterations in the Gamma (P.1) variant – K417T, E484K, and N501Y – that enhance its affinity for the ACE2 receptor and contribute to an estimated 40% increase in transmissibility compared to earlier variants (33, 34).

✓ **Delta Variant (B.1.617.2)**

The Delta variant (Phylogenetic Assignment of Named Global Outbreak Lineages designated as Pangolin lineage B.1.617.2) of SARS-CoV-2 virus was first detected in India on September 7, 2020. It was classified by the World Health Organization as a variant of concern (VOC) on May 11, 2021, and quickly surpassed other SARS-CoV-2 variants by November 2021, accounting for over 98% of new infections globally (35).

Taylor and co-authors, along with Ong S. and collaborators, noted that this variant exhibits biological and clinical implications, including an increased risk of hospitalization, a longer duration of viral shedding by infected individuals, lower Ct values in PCR tests, higher affinity for the ACE2 receptor, mechanisms to evade the effects of antibodies, and a 50% higher transmissibility rate (19, 36, 37).

The genome of the Delta strain contains more than 13 mutations, nine of which are found in the Spike protein, a surface protrusion of the virus that aids its attachment to human cells. K. Suresh studied the evolution of viruses and identified two mutations located in the receptor-binding domain region, which enable the virus to bind more firmly to cells. The emergence of new mutations in the Delta variant accounted for the increased spread of the virus during the second half of 2021, which significantly declined by December (38).

Kang Min and collaborators emphasized that, compared to the wild-type virus, the Delta variant exhibits 10 specific mutations – T19R, G142D, 156del, 157del, R158G, L452R, T478K, D614G, P681R, and D950N – which may be responsible for its competitive advantages over other variants. The authors noted that the spike mutation of residue 452 located at the receptor-binding domain could enhance immune evasion and resistance to neutralizing antibodies, while P681R in the S1/S2 regions of the S gene could influence proteolytic processing. All these mutations could lead to increased affinity for the ACE2 receptor and resistance to neutralizing antibodies, resulting in increased transmissibility (19).

At the same time, Gomari MM et al. reported that this lineage carries a wide range of mutations, some of which, such as N501Y and P681H, strongly impact the function of the Spike protein. It has been demonstrated that the N501Y substitution in the Spike protein enhances ACE2 binding and cellular infectivity in animal models, while the P681H substitution in the Spike protein affects the furin cleavage site (39).

At the same time, Cocherie T. and collaborators observed that the Delta variant is more competitive than the Alpha variant. In their work, they highlighted that the L452R substitution facilitates the creation of a salt bridge between R454 and D467, which is responsible for conformational changes and a more stable S protein. This conformational change reduces interaction with certain neutralizing antibodies, influencing the cellular immune response and partially blocking the HLA-dependent immune system (MHC class I), thereby contributing to the progression of infection. The T478K substitution results in the replacement of a neutral amino acid with a positively charged basic amino acid at the RBD-ACE2 interface, increasing the interaction strength between RBD and ACE2. Furthermore, it was observed that the combination of L452R and E484Q enhances the RBD-ACE2 binding strength and, consequently, the infectivity of the viral particle. The authors

concluded that this increased transmissibility is associated with heightened virulence. The Delta variant had previously shown fewer symptomatic forms, and an increased risk of severe illness and hospitalization, especially in the unvaccinated populations (35, 40).

✓ **Omicron Variant (B.1.1.529)**

In November 2021, a SARS-CoV-2 variant named Omicron, classified under Pangolin lineage B.1.1.529, was identified in South Africa. Omicron is the most modified SARS-CoV-2 variant, and its near-total transmissibility and immune evasion capabilities have raised global concerns. Due to these characteristics, Omicron rapidly replaced Delta as the dominant variant in multiple regions (41, 42, 43).

This variant features over 30 mutations in the conserved domain of the Spike (S) protein, some of which—69–70del, T95I, G142D/143–145del, K417N, T478K, N501Y, N655Y, N679K, and P681H—are also present in the Alpha, Beta, Gamma, and Delta genome variants, along with 19 mutations in the non-Spike conserved proteins. By the end of January 2022, additional subvariants, BA.2 (B.1.1.529.2) and BA.3 (B.1.1.529.3), were detected in several European countries. The BA.2 subvariant differs from BA.1 in 50 amino acids. Significant differences in amino acid content, particularly in the S protein, between these two subvariants indicate that BA.2 may possess virological characteristics distinct from BA.1. By January 2022, BA.2 had overtaken the BA.1 sublineage in Asia and Europe, suggesting that BA.2 is more infectious due to its enhanced transmission capacity, binding affinity, and immune evasion ability. Since its discovery, the Omicron variant has led to a sharp rise in global COVID-19 cases, accounting for a record 15 million new COVID-19 cases reported worldwide in a single week (39, 44, 45, 46, 47, 48, 49).

The Omicron variant uses the endosomal pathway for cellular penetration. Experimental evidence has shown that Omicron, compared to the Delta variant and the so-called wild-type strain (Wuhan-Hu-1), exhibits a higher tropism for the nasal cavity and bronchial epithelium but a lower tropism for human alveolar cells. Additionally, the Omicron variant is characterized by predominant accelerated replication in the upper respiratory tract and a reduced ability to fuse viral and cellular membranes, which ultimately explains the increased contagiousness of the virus and, at the same time, a milder progression of the disease (39 – 49).

J.A. Lewnard et al. demonstrated that among individuals diagnosed with COVID-19 and monitored in outpatient settings, infection with an Omicron variant was associated with a significantly lower risk of progression to severe clinical forms, including hospitalization, symptomatic hospitalization, intensive care unit admission, mechanical lung ventilation, and mortality, compared to infection with the Delta variant (39 – 49).

Chatterjee S. and co-authors found that the BA.1 sublineage of the Omicron variant was the most widespread globally, but BA.2 progressively replaced BA.1 in many countries, while the transmissibility of BA.3 remained very limited, with the fewest reported cases. Two additional lineages, BA.4 and BA.5, were detected in South Africa in January and February 2022. These sublineages became predominant during the fifth wave of the COVID-19 pandemic that started in South Africa, replacing BA.2, with more than 50% of cases attributed to BA.4 (35%) and BA.5 (20%). Omicron has more mutations than any other variant. These mutations facilitate stronger binding to host cell receptors compared to other reported variants. It also evades most antibodies that block the virus or neutralizing antibodies produced by vaccinated individuals or individuals infected with other variants (43, 50).

Subsequently, Tamura T. and co-authors described that the BQ.1.1 sublineage of the Omicron variant, a descendant of BA.5, became predominant in Western countries in December 2022. The authors noted that this sublineage contains all the convergent substitutions, such as R346T, K444T, L452R, N460K, and F486V, which enhance the binding affinity of the SARS-CoV-2 S protein to the human angiotensin-converting enzyme 2 (ACE2) while also contributing to the evasion of humoral antiviral immunity induced by vaccination and natural SARS-CoV-2 infection. Furthermore, due to ongoing mutations in the Omicron variant genome, a recombinant variant named XBB emerged. The Omicron XBB variant likely arose from the recombination of two BA.2 descendants, BJ.1 and BM.1.1.1, as well as a descendant of BA.2.7516. While the BQ.1 lineage became dominant in Europe, XBB established dominance in In-

dia and Singapore. Subsequently, on October 28, 2022, the WHO classified XBB as a subvariant of Omicron under monitoring (43, 51).

In the article presented by Dinah V. Parums, a detailed study is described regarding the new sublineage of the Omicron variant, EG.5 (Eris), which was first recorded by the World Health Organization on February 17, 2023, and designated as a variant under monitoring (VUM) on July 19, 2023. This sublineage and its derivatives – EG.5.1, EG.5.1.1, and EG.5.2 – are descendants of XBB.1.9.2, sharing the same amino acid spike profile as XBB.1.5 (Kraken). However, the authors noted that EG.5 (Eris) includes an additional amino acid mutation, F456L, in the Spike protein compared to its parental subvariants, while the EG.5.1 subvariant contains another Spike mutation, Q52H. Subsequently, following WHO risk assessments on August 8, 2023, EG.5 (Eris) and its sublineages were designated as a variant of interest (VOI) (25, 43, 52).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused millions of deaths and substantial morbidity worldwide since 2019. The intensive scientific effort to understand the biology of SARS-CoV-2 has resulted in a daunting number of genomic sequences. We have witnessed evolutionary phenomena, including the emergence of variants with distinct phenotypes, such as transmissibility, severity, and immune evasion (53).

Currently, this virus has attained the status of the most studied virus: during the pandemic, an enormous amount of genomic sequences was obtained, providing extensive information about this pathogen, which has enabled not only the development of strategies to combat it but also a deeper understanding of its biology, characteristics, and mutation dynamics. Each new variant or sublineage of the virus has been and continues to be studied in detail. Moreover, while initially, many believed that the virus would become more transmissible but less virulent as mutations accumulated, in reality, the new sublineages of SARS-CoV-2 mutate very rapidly, gaining an increasing number of opportunities to evade all forms of immunity, penetrate more easily into human cells, and continue to cause severe damage.

Markov P.V. et al. predict that as the Omicron variant continues to circulate, immunity induced by a combination of vaccination and prior infection will provide protection against severe illness upon reinfection. However, an alternative scenario exists: a new variant could emerge with a completely different set of mutations and properties, allowing the virus to evade immunity created by prior infections or vaccines. This could result from the accelerated evolution of the virus during long-term persistence in immunocompromised individuals. At the same time, predicting the virulence of new strains is challenging; it is quite possible that variants may arise that cause severe disease in more people than the Omicron variant (54, 55).

DISCUSSIONS

Compared to their hosts, RNA viruses have mutation rates that can be over a million times higher due to their limited ability to correct replication errors (56, 57, 58, 59, 60). The survival and adaptability of RNA viruses depend on their ability to overcome harmful mutations and evolve into forms that provide competitive advantages, such as better adaptation to their hosts. SARS-CoV-2 undergoes genetic evolution as it adapts to its new human hosts, resulting in mutations in the viral genome that can potentially modify the virus's pathogenic potential.

Based on the analysis of scientific publications, it was established that from the early days of the COVID-19 pandemic, multiple research directions were initiated, including a detailed examination of the SARS-CoV-2 causative agent and its mutations over time and space (tab. 1). This information is extremely important because it helps understand the mechanisms of pathogenesis and resistance of the causative agent and the actual mutation directions, which have been observed since the early days of the pandemic. The genomic changes of the Alpha variant (B.1.1.7) were linked to mutations in seven genes and some proteins, but these were likely neutral concerning protein function (1, 2 in tab. 1). It was assumed that the observed mutations influence the clinical presentation and disease severity (3, 4 in tab. 1). Examining the genomic characterization of the Beta variant (B.1.3.51), it was found that mutations in the RBD region led to the loss of the salt bridge between RBD and ACE2, thus increasing their dissociation con stant. Amino acid metabolism modification contributes to the increased viral nucleic acid quantity in the upper respiratory tract (5, 6 in tab. 1).

Table 1. Analysis of articles regarding the genetic characteristics of VOC variants.

Nr.	Authors	Content of the article	Year of publication
Genomic characteristics of the Alpha variant (B.1.1.7)			
1.	A. Nagy, S. Pongor, B. Gyorffya	Mutations in seven genes: L54F, D614G, and V1176F in the spike glycoprotein (S), A97V and P323L in RNA polymerase, Q57H and G251V in ORF3a, P13L, S194L, R203K, G204R, and I292T in the nucleocapsid phosphoprotein, I33T in the ORF6 protein, and mutations S1197R and T1198K in the NSP3 protein.	2021
2.	S Isabel, L. Grana-Miraglia, J. M. Gutierrez et al.,	Analysis of over 1,225 SARS-CoV-2 genomes from December 2019 to March 2020 revealed the presence of the D614G missense mutation in the SARS-CoV-2 Spike protein. The authors suggested that the mutation is most likely neutral concerning the protein's function.	2020
3.	C. P. Morris, Chun Huai Luo, A. A. M. Schwartz et al.	It was assumed that the N501Y mutation in variants B.1.1.7, P1, and B.1.351 could affect ACE2 binding and have an impact on disease severity.	2021
4.	R. A. Mansbach, S.Chakraborty, Kien Nguyen et al.	The amino acid substitution in Spike at residue 614 from aspartic acid (D) to glycine (G) (D614G) is more transmissible and contributes to an increase in viral nucleic acid quantity in the upper respiratory tract.	2021
Genomic characteristics of the Beta variant (B.1.3.51)			
5.	Cocherie T., Zafilaza K., Leducq, V. et al.	The K417N/T substitutions affect a neutralizing antibody target epitope of the RBD, leading to the loss of a salt bridge between the RBD and ACE2 and an increased dissociation constant of their binding.	2022
6.	Cele S., Gazy I., Jackson L. et al.	The E484 substitution is a binding site for highly potent neutralizing antibodies. Mutations causing substitutions at E484 have emerged as immune escape mutations and have conferred broad cross-resistance to monoclonal antibody panels and plasma neutralization from convalescent individuals.	2021
Genomic characteristics of the Gamma variant (P.1)			
7.	Mendiola-Pastrana IR., Lopez-Ortiz E., Rio de la Loza-Zamora J.G. et al.	The Gamma strain (P.1) exhibits three major modifications in the viral genome—K417T, E484K, and N501Y—that confer affinity for the ACE2 receptor and contribute to an estimated 40% increase in transmissibility compared to the earlier variants.	2022
8.	Paul M., Chun Huai Luo, A. Amadi et al.	The genomes of the Beta (B.1.351) and Gamma (P.1) variants display mutations in the S protein: N501Y and E484K, which increase the binding affinity to angiotensin-converting enzyme 2 (ACE2).	Iulie 2021
9.	M. Gomari, P. Tarighi, E. Choupani et al.	The genome of the P.1 variant contains the N501Y, E484K, and K417T substitutions, the most important amino acid mutations, which can induce conformational changes in the Spike protein.	2023
Genomic characteristics of the Delta variant (B.1.617.2)			
10.	Min Kang, Hualei Xin, Jun Yuan et al.	Compared to the wild-type virus, the Delta variant has nine or ten characteristic mutations: T19R, G142D, 156del, 157del, R158G, L452R, T478K, D614G, P681R, and D950N.	2022
11.	M. M. Gomari, P. Tarighi, E. Choupani et al.	The Delta variant has a number of mutations, some of which, N501Y and P681H, affect the function of the Spike protein. The N501Y substitution enhances the binding of the Spike protein to ACE2, while the P681H substitution affects the furin cleavage site.	2023
12.	Th.Cocherie, K. Zafilaza, V. Leducq et al.	The L452R substitution affects the RBD region and leads to the formation of a salt bridge between R454 and D467, responsible for a conformational change, which impacts the cellular immune response by modifying the 448-456 region of the S protein.	2023

Nr.	Authors	Content of the article	Year of publication
Genomic characteristics of the Omicron variant (B.1.1.529)			
13.	D. Setiabudi, Y.Sribudiani, K. Hermawan et al.	This variant has more than thirty mutations in the conserved region of the Spike protein (S), including 69–70del, T95I, G142D/143–145del, K417N, T478K, N501Y, N655Y, N679K, and P681H, which overlap with those found in the Alpha, Beta, Gamma, or Delta variants.	2022
14.	Sh. Pather, Sh.A. Madhi, B.J.Couling et al.	Essential mutations of different sublines of the Omicron variant with biological significance: del69–70, G142D, del143–145, R346K, S371L, N440K, G446S - Resistance to neutralizing antibodies; L452R, L452Q, N501Y - Increased binding to ACE2; F486V, E484A – Escape from neutralizing antibodies; Q493R - Increased binding to ACE2 and escape from neutralizing antibodies; H655Y, P681H - Increased binding to ACE2, transmissibility, and enhanced endosomal entry; N969K - Reduced fusogenicity in the S2 domain; del3674–3676, del3675–3677 - Protein stability; del27–29 - Suppression of immune response.	2023
15	Fan. Y, Asao. S, Furbank. R et al.	BA.1 and BA.2 have 12 mutations in the RBD, including G339D, S373P, S375F, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, and Y505H. S371L, G446S, and G496S were identified only in BA.1, while R346K was found in one member of this group, namely BA.1.1. BA.2 possesses two unique mutations in the RBD, including S371F and R408S, and shares T376A and D405N with BA.3. The authors state that some of these mutations were also found in previous variants.	2022

Examining the genome of the Gamma variant (P.1), changes were observed that contribute to the increased transmissibility, estimated to be 40% higher compared to earlier SARS-CoV-2 variants, and induce conformational changes in the Spike protein (7-9 in tab. 1). Compared to the wild-type virus, the Delta variant has up to ten characteristic mutations, some of which affect the Spike protein function and other proteins, impacting the cellular immune response (10-12 in tab. 1). It was found that the genome of the Omicron variant has more than thirty mutations in the conserved domain of the Spike protein, including 69–70del, T95I, G142D/143–145del, K417N, T478K, N501Y, N655Y, N679K, and P681H, which overlap with those found in the Alpha, Beta, Gamma, or Delta variants. Importantly, these mutations trigger protective mechanisms, immune response suppression, and antibody formation (13-15 in tab. 1).

Peter V. Markov and coauthors offer hope of understanding the processes that generate this diversity, predicting the possible future evolution ary trajectories of the virus, and developing means of prevention and treatment. To facilitate such possibilities, there is an urgent need to critically review the key factors of SARS-CoV-2 evolution and to explain the processes that generate diversity and novelty in the virus (53).

In this context, it is important to understand the mechanisms that generate genetic variations in SARS-CoV-2, which underlie processes within the host and at the population level. To understand how major lineages, such as variants of concern (VOC), are generated, bibliographic data have been analyzed and included in five tables according to the number of SARS-CoV-2 variants.

Studying the genetic characteristics of the SARS-CoV-2 virus provides valuable opportunities for the development of more effective treatments, the adaptation of diagnostic tests, and the next generations of vaccines. Additionally, understanding the dynamics and molecular evolution mechanisms of different mutated variants is crucial for anticipating and combating the pandemic spread.

CONCLUSIONS

1. Coronaviruses are RNA viruses with large genomes, which give them persistence in a variety of hosts and environments.
2. SARS-CoV-2 has the ability to adapt and coexist long-term in the human population.

3. The continuous evolution of the SARS-CoV-2 genome has generated new variants with significant public health impacts.
4. Studies on mutations and persistent effects are essential, and collaboration between researchers, authorities, and the pharmaceutical industry is crucial for the prevention of COVID-19 and the development of therapy.

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THE IMPORTANCE OF TRAINING FAMILY PHYSICIANS IN PROMOTING PHYSICAL ACTIVITY AND SPORTS

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Keywords: *physical activity, sports medicine, prevention, training, family medicine.*

Introduction. *Training family doctors in promoting physical activities and assisting individuals engaged in sports can significantly contribute to the primary prevention of non-communicable diseases. However, current training in this field, both in university and postgraduate programs, is often insufficient or even absent. The study aims to improve training programs for family physicians in the field of promoting physical activities by developing a model of continuing education program for them.* ***Material and methods.*** *A bibliographic study was conducted on the importance of training family physicians in promoting physical activity and sports. The study utilized the PubMed/MEDLINE, Google Scholar, and ResearchGate databases, covering the period from 2004 to 2024, using the following keywords: physical activity promotion, sports medicine, prevention, training, and family medicine.* ***Results.*** *In Moldova's medical education system, it is crucial to implement educational interventions that integrate topics from sports medicine and physical activity promotion into undergraduate and postgraduate training. Our recommendations focus on developing appropriate curricula, providing continuing education sessions, and establishing partnerships with experts in sports medicine. Consequently, we propose a project for designing a training program for family physicians to enhance their role in promoting physical activity and sports.* ***Conclusions.*** *To effectively promote physical activities and support individuals engaged in sports, it is essential to develop and implement continuous training programs for family doctors, tailored to local needs and resources.*

Cuvinte-cheie: *activitate fizică, medicină sportivă, prevenție, instruire, medicina de familie.*

IMPORTANȚA INSTRUIRII MEDICILOR DE FAMILIE ÎN PROMOVAREA ACTIVITĂȚILOR FIZICE ȘI A SPORTULUI

Introducere. *Instruirea medicilor de familie în promovarea activităților fizice și în asistența persoanelor care practică sportul poate contribui semnificativ la profilaxia primară a maladiilor netransmisibile. Cu toate acestea, pregătirea actuală în acest domeniu în programele universitare, cât și în cele postuniversitare este de cele mai multe ori insuficientă sau chiar absentă. Prezentul studiu are ca obiectiv îmbunătățirea programelor de instruire a medicilor de familie în domeniul promovării activităților sportive prin elaborarea unui model de instruire continuă a acestora.* ***Material și metode****. A fost efectuat un studiu bibliografic cu referire la importanța instruirii medicilor de familie în promovarea activităților fizice și a sportului, utilizând bazele de date PubMed/MEDLINE, Google Scholar și Research Gate, în perioada 2004-2024. Cuvintele cheie utilizate au fost: promovarea activității fizice, medicina sportivă, prevenție, instruire, medicina de familie.* ***Rezultate.*** *Pentru învățământul medical din Republica Moldova este de mare importanță implementarea intervențiilor educaționale care vizează introducerea temelor din domeniul medicinei sportive și promovării activităților fizice în pregătirea universitară și postuniversitară. Recomandările noastre includ dezvoltarea unor programe de studii adecvate, furnizarea de sesiuni de educație continuă și crearea de parteneriate cu experți în domeniul medicinei sportive. Prin urmare, propunem un proiect de elaborare a unui program de formare pentru medicii de familie în domeniul promovării activității fizice și a sportului.* ***Concluzii.*** *Pentru promovarea activităților fizice și asistența persoanelor ce practică sportul este esențial să se dezvolte și să se implementeze programe de instruire continuă pentru medicii de familie adaptate nevoilor și resurselor locale.*

INTRODUCTION

An important aspect of the work of primary healthcare specialists should be the promotion of physical activity – the most effective and accessible means of reducing sedentary behavior while also providing clinical benefits in the primary and secondary prevention of diseases (1, 2, 3). Furthermore, these specialists have the best knowledge of the patient's history and, therefore, possess a high level of credibility regarding the health indications and advice provided to prevent deficiencies. Promoting physical activity is a process that encourages the adoption of an active lifestyle, recognized for its preventive impact on non-communicable diseases, while sports medicine, on the other hand, focuses on the assessment, prevention, and treatment of conditions associated with sports practice. Collaboration and discussions between family physicians and patients present an opportunity for counseling on a healthy lifestyle, and recommendations for physical activity offer an excellent chance to engage in promotional discussions between healthcare providers and patients (4, 5, 6). Primary healthcare physicians contribute to the overall health of the community by promoting physical activity and strategies for preventing injuries.

The activity of family physicians is multifaceted. Due to their professional responsibilities, family physicians must possess knowledge and practical skills related to the health of individuals engaged in sports, as well as the benefits of physical activities for the general population (7). They are often required to offer consultations to children and young people participating in various sports and issue a medical certificate stating that the athlete is fit to participate in sports.

It is well known that participation in physical activity and sports requires official medical certification. A sports medical certificate can only be issued by a specialist in sports medicine (8). In the Republic of Moldova, there is only one Sports Medicine Center located in Chisinau, and most athletes and individuals engaged in sports seek medical assistance from local healthcare institutions (family physician centers, private clinics, etc.) (9). Therefore, family physicians largely decide whether an individual is fit to participate in sports. An unqualified medical conclusion that is not based on specific knowledge in the field could represent a professional error with a significant impact on individuals engaged in either competitive or recreational sports (10).

Monitoring the health of both professional and amateur athletes should focus on the prevention of illnesses and injuries while promoting a healthy lifestyle (11). To carry out more effective professional activities, future family physicians will need to deepen their knowledge of sports medicine during their postgraduate training (12).

Optimizing training programs will benefit patients by providing guidance on safe exercise practices, injury prevention, and the importance of an active lifestyle (12, 13). Additionally, practice has shown that implementing preventive measures is an important part of the professional activities of family physicians (14, 15, 16). These measures include various activities in the fields of hygiene, epidemiology, health promotion, and health education, among others.

Thus, the paper aims to analyze bibliographic sources regarding the necessity of improving the knowledge level of family physicians in promoting physical activity and sports, along with the development of a model for enhancing a training program.

MATERIAL AND METHODS

To achieve the proposed aim, an advanced literature search was conducted in major international databases, including PubMed/MEDLINE, Google Scholar, and ResearchGate. The keywords used for the publication searches were physical activity promotion, sports medicine, prevention, training, and family medicine. Using these search terms, publications in English and Romanian from the period 2004–2024 were analyzed. The inclusion criteria were: original articles and research addressing physical activity promotion in primary care, training programs for family physicians and their relevance in chronic disease prevention, family physicians' competencies, health assessment of athletes and individuals engaged in recreational sports, and counseling on physical activity related to the roles of family physicians and sports medicine specialists. A total of 353 article titles and abstracts were reviewed, out of which 226 were excluded due to lack of full-text availability or insufficient direct relevance to the topic. To identify relevant information for the

study, 58 sources were analyzed and synthesized. The data from these articles were selected, classified, evaluated, and synthesized based on the following criteria: author/citation, study design, assessments/data, limitations, and key findings. The reported results were compiled in a narrative format. The findings are significant as they propose a training program development project for family physicians focused on physical activity promotion and sports.

RESULTS

The healthcare sector presents a unique opportunity to promote a healthy lifestyle through physical exercise among the general population, as well as by providing medical assistance to individuals who engage in regular sports activities, whether professional or amateur. Family physicians frequently interact with their patients, with most individuals visiting their healthcare providers at least once a year, which allows for a comprehensive approach to decision-making regarding physical activity for preventive or training purposes (17, 18, 19). Nowadays, health promotion activities are becoming increasingly relevant, particularly for the younger generation, as this population segment is the most vulnerable to risk factors and the most receptive to education and the development of a healthy lifestyle (11, 20).

It is well known that regular exercise and physical activity improve health, well-being, and help manage a range of chronic diseases that patients face today. However, there is a gap between these well-documented theoretical benefits and their practical implementation, largely due to deficiencies in the training and education of specialists at the primary healthcare level (21, 22, 23).

According to recent data presented by Sousa J.R., Afreixo V., Carvalho J., et al., who summarized the analysis of study programs and the survey of beneficiaries from medical schools, it was determined that integrating physical activity education into medical programs presents many challenges that require an understanding of the complex interplay between organizational dynamics, faculty perspectives, and educational priorities (10).

The integration of physical activity and sports aspects into continuing medical education programs can help address the ongoing educational needs of physicians who may not have received sufficient training during their undergraduate studies. *Exercise is Medicine* and the *American College of Sports Medicine* have established that medical students should gain experience in four critical areas by the end of their training: assessing needs and applying physical exercise, endurance training, counseling, and behavioral strategies (24, 25).

Despite the benefits of training family physicians in sports medicine, several challenges remain. The analysis of study programs has shown that the training of family physicians does not include topics such as assessing patients' physical condition, counseling for safe sports activities, doping prevention, and managing sports-related conditions. Among the challenges faced by family physicians in sports medicine are limited resources for education and training, varying interests among medical students, and the need for continuous professional development to keep up with medical advances (26). In several developed countries, lifelong learning strategies have been implemented by integrating sports medicine topics into curricula (27). These strategies include developing specific modules within continuing medical education programs for physicians, covering aspects such as exercise physiology, injury prevention, and post-traumatic recovery (24, 28). Organizing periodic events, such as workshops and seminars, is of major importance, as they provide both theoretical knowledge and practical applicability by involving family physicians, sports physicians, and physiotherapists (29, 30). This approach can help integrate specialized knowledge into general medical practice.

For medical education in the Republic of Moldova, it is also crucial to implement targeted educational interventions by incorporating sports medicine and physical activity promotion topics into undergraduate and postgraduate training. Our proposals include developing an adapted curriculum, organizing continuous training sessions, and establishing partnerships with experts in sports medicine.

Thus, we propose a project to develop a training program for family physicians in promoting physical activity and sports (tab. 1). The objectives of the program will enable the optimization of healthcare by promoting physical activities and effectively monitoring individuals who participate in sports.

Table 1. Stages for developing a continuing education program for family physicians in promoting physical activity and sports.

Assessment of training needs in the Republic of Moldova
• Identification of knowledge and competency gaps among family physicians • Consultation with experts (specialists in sports medicine, rehabilitation, physiotherapy, etc.)
Course development
• Identification of key competencies that family physicians need to acquire, such as assessing patients' physical condition, preventing doping, preventing injuries, and managing sports-related conditions. • Inclusion of topics such as exercise physiology, sports nutrition, medical rehabilitation, and pain management. • Use of a combination of teaching methods, including theoretical courses, seminars, and case studies.
Course implementation
• Organization of training sessions that combine theoretical courses with practical exercises. • Provision of educational materials, such as guides, manuals, and access to relevant databases. • Teaching staff: hiring experts in sports medicine to guide and coordinate the training program.
Course evaluation
• Use of tests and practical assessments to measure the skills acquired by participants. • Collection of feedback from participants to continuously improve the course.
Integration into professional practice
• Providing continuous resources and consultancy for physicians applying new knowledge in their daily practice. • Collaborating with Sports Medicine Centers and other institutions to facilitate the integration of knowledge into clinical practice.
Promotion and support of the course
• Informing family physicians about the importance of sports medicine and the benefits of participating in the training program. • Offering continuing education credits or other incentives for participation in the training.
Monitoring and continuous improvement
• Periodic evaluation of the course's effectiveness and updating the curriculum based on new research and trends in sports medicine. • Adjusting the program based on participant feedback and developments in the field.

Thus, family physicians and sports medicine physicians must maintain continuous collaboration to ensure the health of registered athletes. Training family physicians in sports medicine can bring significant benefits to the healthcare system, including improved management of chronic conditions, injury prevention, and the promotion of a healthy lifestyle. Educating family physicians in sports medicine is essential for enhancing primary care and treatment outcomes for athletes and physically active individuals. By integrating sports medicine into primary care physicians' training programs, healthcare systems can better meet the diverse health needs of our populations, promote lifelong physical activity, and contribute to the overall well-being of our communities (31, 32).

DISCUSSIONS

The analysis conducted in this study makes a significant contribution by proposing a preliminary model of continuing medical education, based on a comprehensive synthesis of the literature and interdisciplinary consultations, aimed at enhancing family physicians' competencies in physical activity promotion.

The main health policy documents adopted in our country – the National Strategy "Health 2030" and the National Program for the Prevention and Control of Priority Non-Communicable Diseases in the Republic of Moldova for 2023-2027 – establish the intensification of citizens' physical activity as a key objective for strengthening public health (33, 34). Regular physical activity is a

strong preventive factor against cardiovascular diseases, cancer, and related conditions such as hypertension, obesity, diabetes, and mental health disorders (35, 36).

The family physician team serves as the first point of contact for patients within the healthcare system, providing primary and continuous medical care, including health promotion services at the individual, family, and community levels. Considering the ongoing reforms in primary healthcare and public health, strengthening capacities in joint health promotion activities and disease prevention presents a valuable opportunity (37).

Primary healthcare provides an appropriate setting for physical activity counseling, as it serves as the first point of contact between family physicians and the population, regardless of social status or economic background. Assessing physical activity as part of medical consultations is one of the most effective ways to promote it (1, 38). The lack of quality daily physical education in many schools has contributed to the obesity epidemic in numerous countries (39). The importance of an active lifestyle, smoking cessation, proper nutrition, and regular exercise cannot be overlooked.

Family physicians should encourage physical exercise at every visit, set physical activity goals, and monitor related behaviors (3, 40).

Several international organizations recommend incorporating physical activity counseling into the daily practice of primary healthcare services, regardless of the presence or absence of chronic conditions (35, 36). The American College of Sports Medicine, in collaboration with the American Medical Association, launched the "Exercise is Medicine" initiative, emphasizing that physical inactivity should be considered a "vital sign" in primary care. This means that physical activity should be assessed in clinical settings alongside other clinical indicators, such as blood pressure and body mass index (41).

Similarly, in the United Kingdom, primary healthcare providers are encouraged to identify patients who are not sufficiently active and subsequently offer physical activity counseling, especially to those diagnosed with a chronic condition (e.g., diabetes) (42). This initiative has demonstrated the success of integrating physical activity into primary care through the specific training of physicians and can serve as a model for adapting a similar approach in the Republic of Moldova.

It is very important for family physicians to have basic knowledge of sports medicine. By definition, sports medicine is a specialty that deals with the health of individuals and athletes for educational, preventive purposes and to foster healthy individual interests and abilities for fulfilling an active social role (43, 44). Sports medicine encompasses not only the treatment of injuries but also preventive care, performance optimization, and health promotion. Family physicians trained in sports medicine can provide comprehensive care that addresses the physical, psychological, and nutritional needs of athletes (8, 38). It has become an essential field in improving patients' health and quality of life, increasingly recognized for its benefits in preventing and treating health issues related to physical activity (25, 45). In this context, family physicians play a crucial role in assessing and recommending interventions related to sports and physical exercise.

A family physician trained in aspects of sports medicine can immediately initiate an appropriate treatment plan, facilitate rehabilitation, and monitor the recovery process. In the treatment of sports injuries, timely diagnosis and intervention are crucial to preventing long-term complications. It is essential for a family physician to understand the role, responsibilities, and content of the sports medical examination, contemporary methods for clinical, instrumental, functional, and laboratory evaluation of body systems, as well as the methodology and specific aspects of assessing and interpreting examination and testing results to accurately evaluate physiological capacities (8, 46). Establishing a clinical, functional, and differential diagnosis for organizing the rehabilitation process of athletes is also a key component (8, 47).

Primary care and sports medicine are complementary fields that can work together effectively to support individuals' health and performance, whether they are professional athletes or casual sports participants (48). While the family physician focuses on overall health and disease prevention, the sports physician ensures that individuals engaging in sports train optimally and safely, addressing their specific physiological needs (49).

This collaboration can aid both in injury prevention and in maximizing long-term physical performance.

The activities of the family physician should focus on promoting health through a holistic approach across all aspects (physical, psycho-emotional, social, and cultural) throughout life, in conjunction with other healthcare services and public health interventions aimed at slowing down or even preventing various chronic non-communicable diseases (50, 51). Promoting physical exercise alongside other health maintenance methods (nutrition, recreation, psychological counseling) within interdisciplinary approaches at the primary care level aims to support a healthy lifestyle throughout life (52). The family physician can provide nutritional advice tailored to the individual needs of patients, encouraging the consumption of foods rich in essential nutrients and the avoidance of unhealthy products. For athletes, the focus can be on adjusting caloric intake and balancing proteins, carbohydrates, and fats according to the type and intensity of physical activity (38).

The use of banned substances or those at risk of doping endangers the health of athletes and individuals engaged in recreational sports (53, 54). Health specialists do not possess the necessary level of knowledge and practical skills regarding anti-doping. Most doctors are unaware of the international regulations and those developed by Moldova concerning anti-doping activities, the list of prohibited doping substances and methods in sports, as well as the sanctions in case of doping (55). The development and implementation of undergraduate and postgraduate programs addressing anti-doping can significantly contribute to reducing the consumption of banned substances. Medical professionals trained in anti-doping can provide beneficial support to athletes by offering accurate information on the issue and positively influencing their values and behaviors (56, 57). Developing such programs within the undergraduate and postgraduate training system for health specialists, including family medicine, and applying them in the training process can greatly contribute to the success of anti-doping policies (58).

Integrating methodologies for promoting physical activity and the behavior of individuals who practice sports into primary healthcare can reduce costs by avoiding unnecessary referrals to specialists and optimizing the allocation of medical resources. A family physician with specialized training can provide primary healthcare to individuals engaged in sports and promote physical activity for primary and secondary prevention.

The main limitations of the study include the lack of direct empirical data to validate the proposed educational model and reliance on the available literature. At the same time, the model provides a solid foundation for developing pilot programs in medical education institutions. Practical implementation would require adapting the curriculum to local resources and context, as well as involving public health institutions and sports medicine centers.

In light of the analysis conducted, the results suggest that training family physicians in promoting physical activity can become a central element of national public health strategies. By implementing an adapted educational program, these objectives can be achieved with a positive impact on community health.

CONCLUSIONS

1. The professional activities of family physicians are diverse and include the implementation of numerous measures for the prevention and monitoring of communicable and non-communicable diseases. They play a central role in primary and secondary prevention by promoting physical activity, and proper training of family physicians can reduce unjustified referrals to specialists and increase the efficiency of medical care.
2. In order to carry out high-quality professional activities, family physicians need to be trained in the comprehensive care of individuals who practice sports and in promoting physical activity within the general population. Developing courses focused on assessing the health status of physically active patients, preventing injuries, and the principles of sports nutrition is crucial to meet current demands.

CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

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PERCEPTIONS OF FAMILY PHYSICIANS REGARDING PATIENTS' SELF-MEDICATION

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Keywords: *self-medication, family physicians, self-treatment, self-care, patient education, drug interactions, polypharmacy.*

Introduction. *Self-medication is the practice of using medications to treat self-diagnosed conditions without prior consultation with a healthcare specialist. This phenomenon is widespread globally, reaching a rate of over 90% in some countries. The objective of the study was to explore and analyze the perceptions of family physicians in the Republic of Moldova regarding self-medication.* ***Material and methods****. The study was conducted using descriptive, quantitative, and cross-sectional methods. Data were collected from November 2023 to March 2024 on a sample of 346 family physicians from the Republic of Moldova.* ***Results****. It was found that 87.6% of physicians frequently or very frequently encounter patients who resort to self-medication, and 68.79% of physicians have a negative attitude toward this phenomenon. No statistically significant differences were observed between the region, work environment, or work experience of the physicians and the frequency of patients practicing self-medication (p>0.05). A trend was noted of an intensified negative attitude toward self-medication with increasing work experience (p<0.05). At the same time, 55.2 % of physicians identified the lack of awareness of the risks associated with self-medication as the main factor driving patients to engage in this practice.* ***Conclusions.*** *Self-medication is frequently observed in the Republic of Moldova, with a primary factor being the lack of awareness, making public education on this issue imperative. The negative attitude toward self-medication increases with the physician's work experience and is influenced by their own practices. Medical professionals play a decisive role in preventing the risks of self-medication through informing, providing therapeutic advice, and educating patients.*

Cuvinte-cheie: *automedicație, medici de familie, autotratament, autoîngrijire, educarea pacientului, interacțiuni medicamentoase, polifarmacie.*

PERCEPȚII ALE MEDICILOR DE FAMILIE PRIVIND AUTOMEDICAȚIA PACIENȚILOR

Introducere. *Automedicația este practica de a utiliza medicamente pentru a trata afecțiuni autodiagnosticate, fără consultul în prealabil al unui specialist din domeniul sănătății. Aceast fenomen este foarte răspândit la nivel global, atingând o rată de peste 90% în unele țări. Obiectivul studiului a fost de a explora și de a analiza percepțiile medicilor de familie din Republica Moldova privind automedicația.* ***Material și metode****. Studiul a fost realizat apelându-se la metodele descriptivă, cantitativă, transversală. Datele au fost colectate în perioada noiembrie 2023 – martie 2024, pe un eșantion de 346 de medici de familie din Republica Moldova.* ***Rezultate****. S-a constatat că 87,6% dintre medici au întâlnit frecvent sau foarte frecvent pacienți care apelează la automedicație, iar 68,79% dintre doctori manifestă o atitudine negativă față de acest fenomen. Nu s-au relevat diferențe statistice semnificative între regiunea, mediul de activitate sau stagiul de muncă al medicilor și frecvența atestării pacienților care practică automedicația (p>0,05). S-a observat o tendință de intensificare a atitudinii negative față de automedicație odată cu creșterea experienței de muncă (p<0,05). Totodată, 55,2% dintre medici au identificat ca principalul factor ce determină recurgerea la automedicație lipsa conștientizării riscurilor pe care aceasta le prezintă.* ***Concluzii.*** *Automedicația este frecvent atestată în Republica Moldova, iar un factor principal în practicarea acesteia constă în lipsa conștientizării, fapt pentru care educația populației în acest sens devine imperativă. Atitudinea negativă față de automedicație crește odată cu experiența de muncă a medicului și este dependentă de propriile practici ale acestuia. Lucrătorii medicali au un rol decisiv în prevenirea riscurilor de automedicație prin informare, oferire de sfaturi terapeutice și educare a pacienților.*

INTRODUCTION

Self-medication is a major global challenge involving the entire healthcare system. Today, understanding and accurately assessing self-medication are becoming increasingly important topics. The rapid development of technology, ease of access, and exchange of information has led to a rise in both self-diagnosis and self-medication. Self-medication is a widespread practice across all age groups – youth, adults, and the elderly – and is frequently encountered worldwide (1). Some authors estimate the global prevalence of self-medication to be between 32.5% and 81.5% (2), while others report even broader ranges, up to 100% in certain regions (3).

Self-medication is a complex phenomenon that cannot be fully encompassed by current definitions (4). According to the World Health Organization, "self-medication involves the use of medicines by consumers to treat self-recognized disorders or symptoms, or the intermittent or continuous use of a prescribed medication for chronic or recurrent diseases or symptoms" (5). Self-medication is an essential component of self-care, contributing to health maintenance, disease prevention, and treatment (6). The concept of self-medication includes not only the use of over-the-counter medicines by individuals for themselves but also administering these medications to other family members, particularly infants, children, or the elderly (5). The International Pharmaceutical Federation and the World Self-Medication Industry define self-medication as "the use of non-prescription medicines by individuals on their own initiative." (7).

Self-medication carries both benefits and risks. While it can be helpful to patients and healthcare professionals, it can also cause them harm (1). Inappropriate self-medication occurs when people use medications irresponsibly, such as taking prescription drugs without medical consultation, using leftover medications prescribed for other conditions, sharing medications with friends or family, or using expired medications (8). Recent data reveal a significant increase in adverse reactions associated with self-medication during the COVID-19 pandemic. Comparative results by Gras and his team indicate that in 2020, 3.7% of reported adverse reactions were linked to self-medication, whereas in 2019, this proportion was only 1.6% (9). Awareness of the responsibility for self-medication must be shared by all involved parties, including pharmaceutical workers, healthcare professionals, the general population, and each individual consumer (10).

In the Republic of Moldova, few studies have explored family physicians' attitudes toward self-medication, with existing research covering narrower aspects and conducted over 10 years ago, such as Safta et al. (11) and Ghicavîi et al. (12). In this context, the aim of the present study is to explore both the attitudes and practices of family physicians toward self-medication, enabling the identification of aspects that help minimize and prevent risks associated with self-medication. The primary hypothesis is that family physicians perceive self-medication as a common practice with significant health risks for patients, yet they may not fully understand the benefits that responsible self-medication can offer.

In this study, for the first time, detailed insights were identified regarding family physicians' opinions on the reasons and factors that drive patients to self-medicate, as well as the consequences of this practice observed by physicians and other important aspects of self-medication. These insights aim to support the development of a set of recommendations to minimize and prevent the risks associated with self-medication.

MATERIAL AND METHODS

General objectives

The main objective of this study was to explore and analyze the perceptions of family physicians in the Republic of Moldova regarding self-medication.

Research design

The study was descriptive, quantitative, and cross-sectional, aimed at providing a detailed and comprehensive analysis of family physicians' perceptions regarding self-medication.

Participants

The study included 346 family physicians from the Republic of Moldova, working in primary healthcare institutions in urban and rural areas across various regions of the country (Chișinău municipality, Center, North, and South). The sample size was calculated using a specific formula for representative sampling in descriptive studies of finite and small populations.

Instrument used
To explore family physicians' opinions on self-medication, a questionnaire comprising 26 questions was developed. The questions were organized into four distinct sections designed to collect information on: general data, opinions and attitudes, practices associated with self-medication, and relevant aspects related to self-medication control. A total of 349 questionnaires were received, three of which were deemed invalid. Data collection took place between November 2023 and March 2024.

Ethical aspects of the research
The study followed research ethics principles, and the participation of physicians was voluntary. The questionnaires were anonymous, ensuring data confidentiality.

Data and statistical analysis
Descriptive statistics were used to analyze the results, and the percentage distribution of responses was shown for each response option. Quantitative analysis was conducted using Excel. To determine the statistical significance of associations between variables, the chi-square test (χ^2) was used.

RESULTS

Of the total participants, 129 physicians (37.28%) were from rural areas and 217 (62.72%) from urban areas. Most participants have over 20 years of work experience (56.94%), while 22.3% have up to 10 years of experience, and one in five physicians (20.81%) reported experience between 11 and 20 years. The majority of physicians (87.6%) indicated that they frequently or very frequently encounter patients who practice self-medication. Only 12.1% of physicians encounter this situation occasionally, while only 0.3% encounter it rarely. No physician reported never encountering patients who practice self-medication. There are no statistically significant differences based on the physician's region, work setting, or professional experience in relation to the frequency of encountering patients who self-medicate ($p>0.05$).

The evaluation of the general opinion on self-medication revealed that the majority of family physicians (68.79%) have a negative attitude toward this practice. In contrast, 12.43% of respondents have a positive attitude, accepting self-medication to some extent, while 18.79% are neutral or undecided.

The data analysis revealed that physicians who never practice self-medication or do so only occasionally have the highest proportion of negative attitudes, at 76.00% and 74.46%, respectively. In contrast, those who frequently (59.83%) or always (60%) engage in self-medication show lower proportions of negative attitudes. At the same time, physicians who frequently or always practice self-medication exhibit a higher proportion of positive attitudes (18.8% and 20.0%, respectively) compared to those who practice it occasionally (8.15%) or never (8%).

The attitude towards self-medication varies depending on the physicians' experience. More than half (54.55%) of physicians with up to 10 years of experience have a predominantly negative attitude towards self-medication, while 14.28% have a positive attitude. Among those with 11 to 20 years of experience, 72.22% exhibited a negative attitude towards self-medication, whereas 13.89% are more inclined to accept it. Physicians with over 20 years of experience show a negative attitude in 73.10% of cases, while 11.17% hold a positive attitude. Thus, it is evident that the negative attitude towards self-medication increases with years of work experience ($p<0.05$, $p=0.02$).

The attitude of family physicians also varies depending on the environment in which they work, with those in rural areas exhibiting a more negative attitude towards self-medication (75%) compared to those in urban areas (65%). However, this relationship is not statistically significant ($p>0.05$, $p=0.134$).

Physicians were encouraged to express their opinions on self-medication in various contexts. The highest scores (calculated using the Likert scale) were attributed to the statements: self-medication should be approached with caution (1.34); self-medication is acceptable with proper patient education, in well-defined situations, and for certain types of medication (0.84); it is recommended only for OTC (over-the-counter) medications (0.6). The most negative attitude was expressed towards self-medication with prescription medications, which scored 0.18. These results suggest that physicians consider self-medication acceptable only under strict conditions, emphasizing the need for heightened caution and proper patient education.

While 61.8% of family physicians have a negative attitude towards patients who use alternative

sources (such as the internet or relatives) to seek information about treatments before consulting a doctor, 24.3% display a neutral attitude. The practice of requesting advice from a pharmacy for OTC medications without medical consultation also generated predominantly negative or neutral reactions: 57.23% and 28.32%, respectively. On the other hand, physicians showed openness to consulting patients even for the most minor ailments, with the majority (61.6%) expressing a positive or very positive attitude, indicating an appreciation for these behaviors, while the percentage of those with a negative attitude was relatively low (11.6%) (fig. 1).

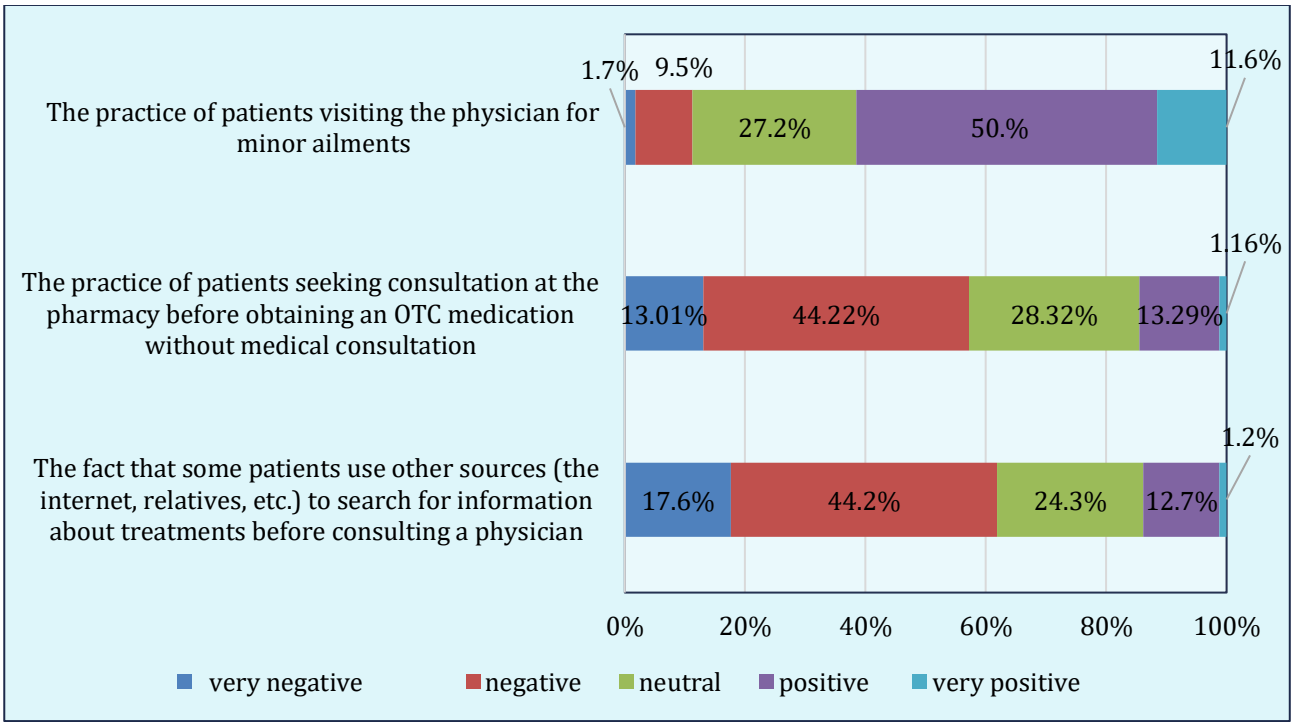

Figure 1. Physicians' attitudes towards patients' practices regarding medication information, %.

Physicians' attitudes towards self-medication vary depending on the category of medication. Only 21.7% of physicians have a negative or very negative attitude towards the purchase of OTC medications without prior medical consultation. In contrast, 63.4% disapprove of the purchase of RX medications based on a prior consultation. The attitude is even stricter in the case of purchasing RX medications based on advice from relatives or information found online, with 91.9% of physicians expressing a negative or very negative opinion. For antibiotics, 92.6% of physicians showed a negative attitude towards their use without appropriate medical consultation. In this context, physicians highlighted significant concerns regarding self-medication, particularly for certain groups of medications. Antibiotics were identified by 93.1% of physicians as posing serious or very serious risks, followed by medications for sleep disorders and anxiety (86.7%) and nonsteroidal anti-inflammatory drugs (75.43%). Moderate consequences were most frequently associated with medications for colds and flu (54.0%) and those for digestive tract issues (50.3%). Vitamins and dietary supplements were considered relatively harmless (57.3%), while 55.5% of physicians estimated minor or negligible risks for phytotherapy. Using the Likert scale, a total coefficient was calculated for each opinion regarding medications and the negative consequences (side effects, worsening health conditions, etc.) that may arise. The highest coefficient (4.34) was attributed to antibiotics, suggesting that physicians consider this group of medications to have the most severe negative consequences, while phytotherapy was deemed the safest, with the lowest coefficient (2.25).

According to the data obtained in the study, 74% of physicians always ask patients about previ-

ously used medications, 23.4% do so frequently, while 2.6% only occasionally. According to physicians, the conditions for which patients most often resort to self-medication are: cold and flu (97.7%); various types of pain (88.2%); and digestive problems (75.1%) (fig. 2).

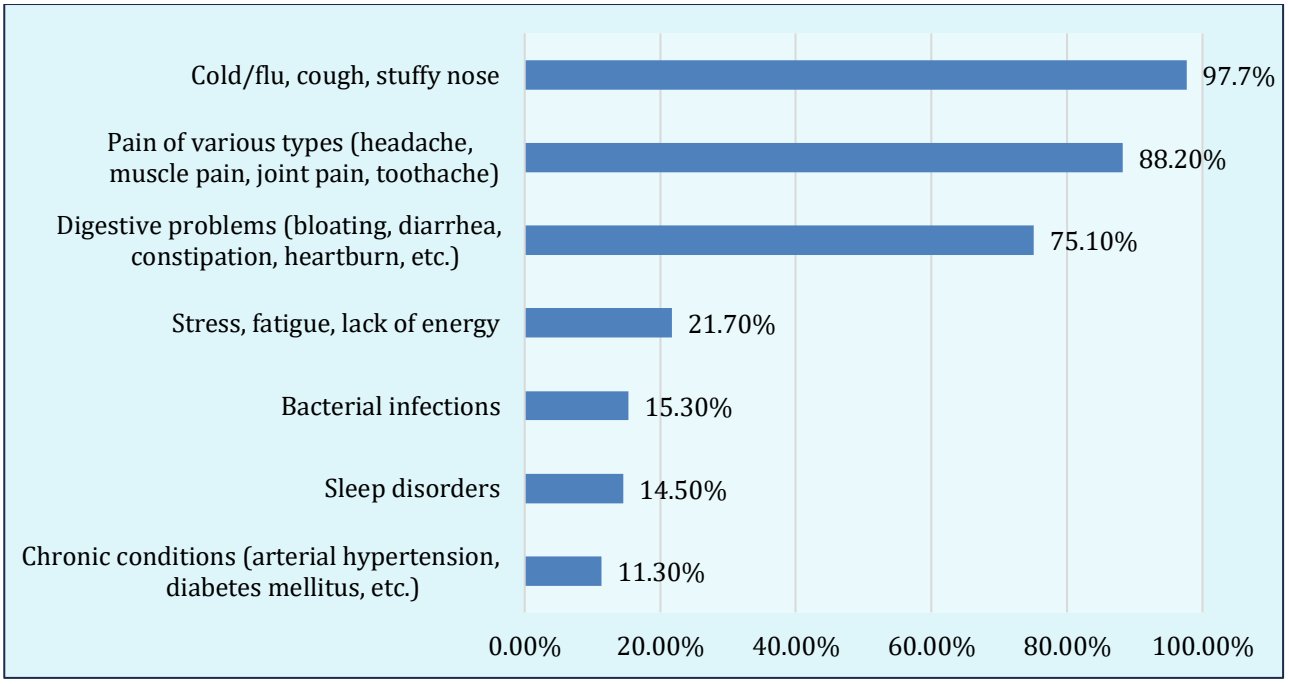

Figure 2. Situations in which patients resort to self-medication, %.

In the opinion of family physicians, the main factors driving patients to self-medication are the lack of awareness about its risks (55.2%), the accessibility of OTC medications (48.3%), the desire to avoid crowded medical institutions, and a lack of time (42.8%). Other influencing factors include patients' belief that the condition is minor (37.3%), prior experience with a specific medication (34.4%), and difficulties scheduling medical appointments (27.7%). Physicians acknowledge that self-medication has both benefits and risks. Only 0.9% of physicians stated that self-medication poses no risks, while the majority highlighted risks such as worsening the patient's condition (68.8%), antibiotic resistance (66.2%), delayed diagnosis (65.0%), undesirable side effects (48.8%), accidental overdosing, and drug interactions (42.8%). The benefits of self-medication, according to physicians, include active patient participation in their healthcare (52.3%), avoiding work absences for minor symptoms (43.1%), patient autonomy in managing minor symptoms (41.9%), and reducing the strain on the healthcare system (39.3%). Additionally, self-medication can increase the availability of medical services in rural or remote areas (22%) and contribute to saving medical resources (19.9%).

While 66.7% of physicians always assess compliance with instructions for OTC medications, 71.9% consistently provide education to patients regarding self-medication, and 57.5% evaluate patients' knowledge about self-medication. Although 65.3% of physicians consider that patients are not sufficiently informed about the risks of self-medication, 52.6% do not have enough time for detailed discussions (fig. 3).

The vast majority of physicians (88.2%) support the idea of stricter regulations on the dispensing and sale of RX medications. Key measures for regulating and controlling self-medication include implementing stricter rules for dispensing medications (80.6%), developing tools or technologies for monitoring medication purchases through a centralized system (62.7%), and enforcing stricter regulations on medication advertising (60.7%). Educating patients through awareness and public information campaigns is considered extremely important, and encouraging the reporting of adverse reactions is seen as useful for controlling self-medication (48.8%). In contrast, involving pharmacists in this process is less popular (46.2%).

The majority of respondents (54.6%) believe that

responsibility for informing patients should be shared between family physicians and pharmacists, with regular information exchange. Family physicians also see an important role for specialist physicians in educating and informing patients (27.7%). Only 8.4% of respondents support the idea that the responsibility should rest solely with pharmacists or family physicians (2.0% each), highlighting the importance of an interdisciplinary and collaborative approach in managing self-medication.

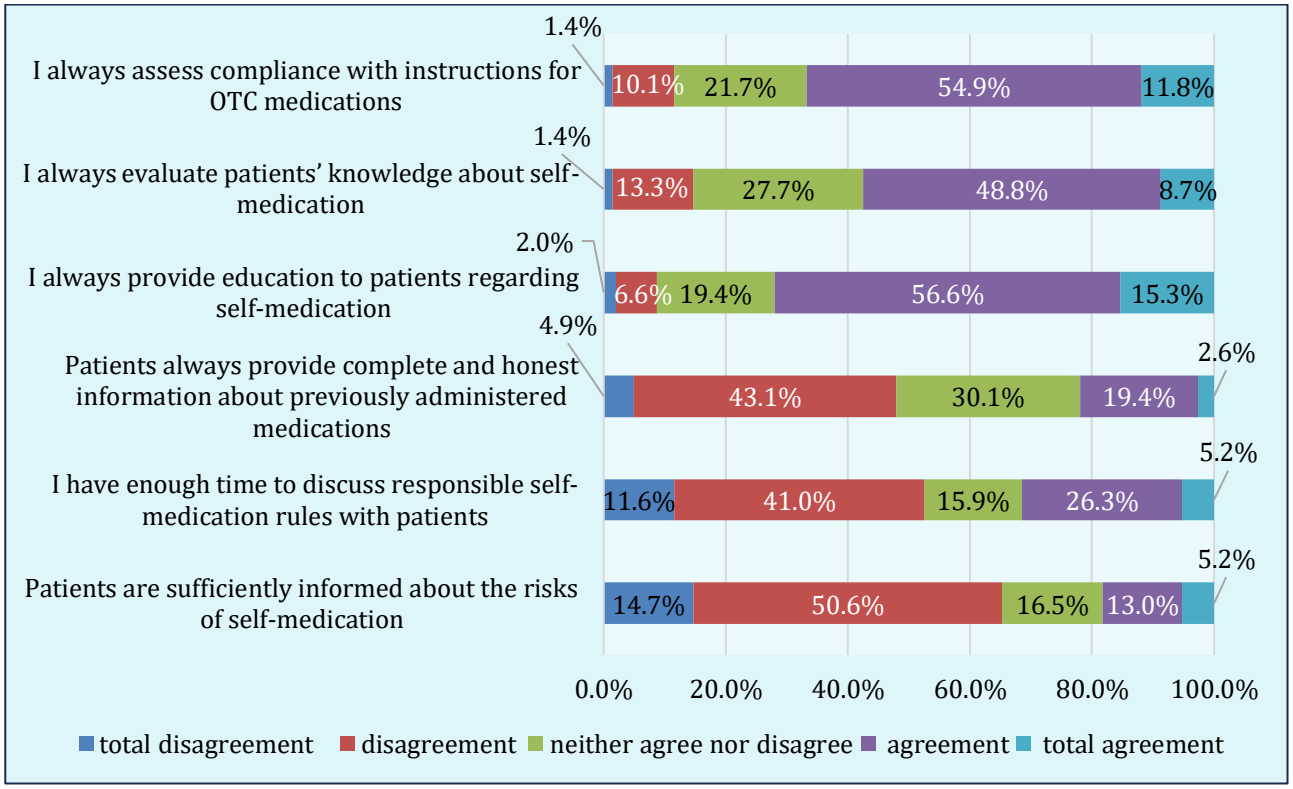

Figure 3. Physicians' opinions on specific aspects of self-medication, %.

DISCUSSIONS

Studies on self-medication are generally more common among patients. However, some research suggests that physicians consider self-medication an acceptable practice for minor issues, while being aware of potential risks such as misdiagnosis or adverse drug reactions (11). In the Republic of Moldova, no recent studies have been conducted exploring the attitudes of family physicians towards self-medication. For example, a 2011 study reported that 60.94% of physicians rejected self-medication, but did not specify the specialties of the participating physicians (12). Another study, from 2014, found that 87.5% of physicians held a negative attitude towards self-medication, though it included doctors from various specialties (13).

Family physicians, being in closer contact with patients and directly involved in managing self-medication, can provide more precise information about this phenomenon. Therefore, the results of this study offer valuable insights into current perceptions. Thus, we observe that 68.79% of the interviewed physicians have a negative attitude, which reflects an awareness of the risks associated with self-medication. This finding aligns with trends observed in studies from other countries, although direct comparison is limited due to differences in design. For example, a study conducted in Jordan on 695 adults (44.5% from the medical field, 55.5% from outside the medical field) found that 65.3% of respondents disagreed with the idea that physicians accept self-medication (14).

Focusing exclusively on family doctors and exploring their attitudes towards self-medication in detail provides a deep understanding, offering a specific and current perspective that can contribute to the development of policies aimed at reducing the risks associated with self-medication.

CONCLUSIONS

1. In the Republic of Moldova, self-medication is a widespread practice, particularly common in minor ailments. Patients practice it for various reasons, including avoiding overcrowding in medical institutions and lack of time. However, lack of risk awareness and easy access to over-the-counter medications are critical factors. The majority of family physicians adopt a negative attitude towards self-medication, emphasizing the need for stricter regulations and better patient education.
2. The hypothesis of the study has been confirmed, and in order to reduce the risks associated with self-medication and promote the responsible use of medications, it is essential to implement concrete measures, including stricter regulations and broader health education.

LIMITATIONS OF THE STUDY

This study evaluates self-medication exclusively from the perspective of family physicians. Another direction for future research would be to investigate the perceptions of other stakeholders involved, such as pharmacists, specialist doctors, and patients.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

ETHICAL APPROVAL

There is no ethical approval.

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HEALTH LITERACY, MYTHS AND STIGMA AMONG PATIENTS WITH PARKINSON'S DISEASE IN THE REPUBLIC OF MOLDOVA

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Keywords: *Parkinson's Disease; Health literacy; Self-stigma.*

Introduction: *Health literacy one's capacity to ensure appropriate health-related decisions based on acquired knowledge, affects the quality of life for Parkinson's Disease (PD) patients. This study establishes a baseline of health literacy, myths, and stigma among PD patients in the Republic of Moldova.*

Material and Methods: *Conducted at the "Diomid Gherman" Institute of Neurology and Neurosurgery (2022-2023), this cross-sectional study used descriptive and inferential statistics (Chi-square test; CI 95%). 103 PD patients (52.4% women, 47.6% men; average age 65.5 years) were included and presented the Knowledge, Attitude and Practices questionnaire.*

Results: *PD patients attribute the disease to stress (61.2%), altered brain blood flow (49.5%), poor brain oxygenation (44.7%), and toxic substances (13.6%), with accent in those with lower education (p=0.001). 30.1% associate tremors with PD, and 21.4% believe PD limits life expectancy. Treatment concerns include 15.5% viewing medication as "toxic", 6.8% believing L-dopa accelerates disease progression. Self-stigma includes feelings of shame (46.6%), fear of judgment (44.7%), isolation (32.0%), and reduced independence (65%).*

Conclusions: *The study reveals limited health literacy and significant self-stigma among PD patients in Moldova, highlighting misconceptions and social impacts of the disease, especially in less educated individuals. Enhancing health literacy and addressing stigma are crucial for improving patient care.*

Cuvinte-cheie: *Boala Parkinson, alfabetizare în domeniul sănătății, autostigmatizare.*

ALFABETIZAREA ÎN DOMENIUL SĂNĂTĂȚII, MITURILE ȘI STIGMATIZAREA PACIENȚILOR CU BOALA PARKINSON ÎN REPUBLICA MOLDOVA

Introducere: *Alfabetizarea în sănătate - capacitatea de a lua decizii corecte în legătură cu sănătatea proprie, bazată pe cunoștințe, influențează calitatea vieții pacienților cu Boala Parkinson (BP). Acest studiu evaluează nivelul de alfabetizarea în sănătate, miturile și stigma asociate cu BP în Republica Moldova.*

Materiale și metode: *Studiul a fost realizat la Institutul de Neurologie și Neurochirurgie „Diomid Gherman" (2022-2023), utilizând o metodologie de tip transversal cu elemente de statistică descriptivă și inferențială (testul Chi-square, CI 95%). Au participat 103 pacienți cu BP (52,4% femei, 47,6% bărbați; vârsta medie 65,5 ani) cărora le-a fost propus chestionarul Cunoștințe, Atitudini și Practici.*

Rezultate: *Pacienții din Moldova atribuie BP stresului (61,2%), fluxului sanguin cerebral alterat (49,5%), oxigenării cerebrale insuficiente (44,7%) și substanțelor toxice (13,6%); mai accentuate la subiecții cu nivel scăzut al educației (p=0,001). 30,1% asociază tremorul cu BP, iar 21,4% cred că BP limitează speranța de viață. Îngrijorările legate de tratament includ 15,5% care consideră medicamentele „toxice" și 6,8% care cred că L-dopa accelerează progresia bolii. Stigma de sine include sentimente de rușine (46,6%), frica de judecată (44,7%), izolare (32,0%) și independență redusă (65%).*

Concluzii: *Studiul relevă o alfabetizare în sănătate limitată și o stigma de sine semnificativă printre pacienții cu BP din Moldova, evidențiind concepțiile greșite și impactul social al boli, în special la cei cu nivel redus al educației. Îmbunătățirea alfabetizării în sănătate și abordarea stigmei sunt esențiale pentru îmbunătățirea îngrijirii pacienților.*

INTRODUCTION

The establishment of the diagnostic of Parkinson's disease (PD) as a chronic disease impacts the patient and his family. The health-related quality of life of those individuals is defined by their understanding of the pathology and the requirements involving treatment and maintenance of the symptoms. Additionally, of great contribution is the image they have of themselves and the way they are perceived in the society. The afore mentioned elements delineate the impact of health literacy and myth circulation in community and the consequently formed stigma around PD (1).

Health literacy accounts for a multidimensional construct that reflects one's capacity to make appropriate health-related decisions. The term equivalates the degree of education of patients translated by their cognitive and social skills required to extract, process and use information about their health (2). One's capacity to choose the best care options can be reflected through one's knowledge, attitudes and practices regarding their diagnosis, an approach we choose through this study focused on patients with PD. Correspondingly, low health literacy in PD was shown to be unfavorable on several levels being associated with poorer clinical status, higher hospitalization rates and burden for the caregivers (3). The lack of understanding of PD lead, overtime, to vulgar constructs explaining its causes, evolution and treatment options that were widely widespread in the community, but wrong in essence. Those represent myths – flawed knowledge that needs to be unlearned to ensure best medical practice. Their broad dissemination in society reflects diminished health literacy – individuals either lack correct medical knowledge or choose to follow cultural beliefs over best medical advice.

Stigma refers to the product of misconceptions and attitudes towards an individual leading to one's undervalue implying their lack or loss of qualities. Thus, we can distinguish two forms: enacted-stigma – that corresponds to socially and institutionally constructed stigma; and self-stigma which represents the internalized feelings of a person exposed to the negative outcomes of enacted-stigma (4). Low health literacy in the community creates a favorable milieu for both kinds of stigma, especially in the context of chronic disorders such as PD (3–5). The way one is perceiving themselves with the disease is key, therefore several contributing factors – deter-minants, can influence the severity of stigma such as: feeling ashamed, impaired indepen-dency, questioning self's mental capacities, compromising symptoms in social situations, fear of isolation in the community and distancing from relatives (1, 6).

Therefore, based on the previously reported gaps in the understanding of PD due to low health literacy (7) and its frequent association to stigma (1), more research into this field is required. Our investigation on the subject showed there is limited international literature on this topic and no publication in the Republic of Moldova. Knowledge Attitude Practice (KAP) studies evaluating Parkinson's disease among Moldovan neurologists and medical workers were conducted (8–10). Thus, we aimed to consider a similar approach (KAP questionnaires), but focusing on PD patients, to establish a baseline of health literacy and myths that circulate in the community of people with the disease and to identify determinants of self-stigma.

MATERIAL AND METHODS

The research was carried out at the *Diomid Gherman* Institute of Neurology and Neurosurgery from January 2022 to December 2023 and represents a cross-sectional study. The study group included patients diagnosed with Parkinson's disease who were able to read, comprehend and independently complete a KAP survey (Knowledge, Attitudes and Practices). The KAP questionnaires were developed, validated, and implemented according to WHO guideline. The questionnaires included open and closed questions upon the knowledge of PD patients about their disease, attitudes, and practices. A total of 103 questionnaires were completed and analyzed: 52.4% (n=54) women and 47.6% (n=49) men, with an average of 65.49±8.38 years old. The studied sample was stratified based on two key factors: level of education (categorized as more or less than 12 years) and gender, to ensure balanced representation across these variables. The data about the knowledge of the patients about the diagnosis, treatment and evolution of PD was extracted from the KAP questionnaires (a quantitative study) and help determine the level of health knowledge.

The myths and stigma determinants were extracted from the in-depth interviews conducted to 10 patients with PD – qualitative study. Descriptive statistics were used to summarize the demographic characteristics of the participants. For inferential analysis, Pearson ***Chi-square tests*** (CI 95%) were used to examine associations between categorical variables, such as gender, education level, and knowledge of Parkinson's disease. All data were analyzed using Microsoft Excel statistical package.

RESULTS

Knowledge, Attitudes, Practices and Myths surrounding Parkinson's disease

The degree of health literacy in PD patients was evaluated based on the knowledge, attitudes and practices they reported regarding the disease. Results are reported in the following compartments (tab. 1, fig.1):

1. *Knowledge and myths about the etiology of PD*. When asked about the etiology of the disease, most of the respondents (61.2%) considered that PD is caused by stress or strong emotions, only 13.6% believed it is the contact with toxic substances. Although the majority of subjects (64.1%) knew there was no relationship between infections and PD, a small percentage of subjects (3.9%) believed that there was. An individual response (1.0%) stated PD as a contagious condition. A recurrent opinion among the participants is that altered blood flow to the brain (49.5%) and lack of brain oxygenation (44.7%) leads to PD. This opinion was more frequent in subjects with lower education levels (p=0.001), and had a tendency to prevail in male population specifically regarding the change in blood flow (p=0.052). The majority of educated patients knew PD is not the result of another disease (56.5% vs.9%, p<0.001), whilst a third of them did not know about any connection between PD and other diseases (78.9% vs. 37%,p<0.001). Just over a half of respondents (55.3%) believed that PD affects not only the elderly, this was noted by 71.7% of people with higher education (p=0.018), while a total of 25.2% believed that it is closely related associated with old age.
2. *Knowledge about the prognostic of PD.* A significant number of patients (40.8%) were convinced PD caused a shorter life span, 24.3% believed PD has a fast progression, 5.8% thought it's a life-threatening disease. Stratification based on the education level showed the patients with lower education were more likely to believe PD reduces life expectation (p=0.004) and has rapid progresssion (0.026).
3. *Knowledge and myths about the symptomatology of PD.* The major part of the responders (91.3%) were aware the main symptoms of PD include tremor and bradykinesia. However, a third of them (30.1%) took tremor as the definitory sign confirming PD, particularly in less educated individuals (42.1% vs. 26.1%, p=0.001).
4. *Knowledge, attitudes, and practices upon the diagnostic tools.* A considerable number of patients are convinced that PD can be diagnosed either through brain neuro-imagistic exam (60.2%) or lab exam (29.1%). Patients with higher education levels were more reticent to the diagnostic possibilities of those diagnostic tools (MRI - 75.4% vs. 41.3%, p<0.001; blood work – 36.8% vs. 19.6%, p=0.001). No statistically significant results were observed among genders.
5. *Knowledge, attitudes, and practices regarding treatment options.* Opinions about antiparkinsonian medication were divided: several participants (15.5%) consider medication to be "toxic"; 6.8% associate L-dopa treatment to accelerate the disease progression; 6.8% believed L-dopa action to subside only the first 5 years after diagnosis. Very few respondents from both lower (8.8%) and higher (4.3%) education backgrounds believed in the efficacy of L-dopa medication, surpris

Table 1. Health literacy determinants registered in Parkinson's disease patients.

	Stratification based on education level			Stratification based on gender		
Parameters	**Education <12 years Nr ±SD**	**Education > 12 years Nr ±SD**	**p**	**Males Nr ±SD**	**Females Nr ±SD**	**p**
Mean age	63.19 ±9.109	68.33 ±6.419	0.002*	65.8 ±7.705	65.2 ±9.021	0.722
Disease duration	6.16 ±3.401	6.57 ±4.708	0.612	6.35± 4.280	6.33 ±3.812	0.797

Years of education	9.96 ±1.451	15.87 ±2.655	<0.001*	12.45 ±3.506	12.75 ±3.712	0.713
	% (Nr)	**% (Nr)**	**df, p**	**% (Nr)**	**% (Nr)**	**df, p**
Knowledge and myths about the etiology of PD						
			PD is caused by stress or strong emotions			
Yes	64.%(37)	56.5%(26)		57.1%(28)	64.8%(35)	
No	7%(4)	21.7%(10)		16.3%(8)	11.1%(6)	
I don't know	28.1%(16)	21.7%(10)	2, 0.093	26.5%(13)	24.1%(13)	2, 0.663
			PD is caused by contact to toxic substances			
Yes	10.5%(6)	17.4%(8)		18.4%(9)	9.3%(5)	
No	42.1%(24)	52.2%(24)		42.9%(21)	50.0%(27)	
I don't know	47.4%(57)	30.4%(14)	2, 0.195	38.8%(19)	40.7%(22)	2, 0.392
			PD is caused by infections			
Yes	1.8%(1)	6.5%(3)		2%(1)	5.6%(3)	
No	61.4%(35)	67.4%(31)		59.2%(29)	68.5%(37)	
I don't know	36.8%(21)	26.1%(12)	2, 0.279	38.8%(19)	25.9%(14)	2, 0.288
			PD is caused by altered blood flow to the brain			
Yes	61.4%(35)	34.8%(16)		59.2%(29)	40.7%(22)	
No	5.3%(3)	34.8%(16)		20.4%(10)	16.7%(9)	
I don't know	33.3%(19)	30.4%(14)	2, 0.001*	20.4%(10)	42.6%(23)	2, 0.052
			PD is caused by poor brain oxygenation			
Yes	52.6%(30)	34.8%(16)		53.1%(26)	37.0%(20)	
No	5.3%(3)	41.3%(19)		22.4%(11)	20.4%(11)	
I don't know	42.1%(57)	23.9%(11)	2, 0.001*	24.5%(12)	42.6%(23)	2, 0.135
			PD is an elderly disease			
Yes	35.1%(20)	13.0%(6)		30.6%(15)	20.4%(11)	
No	42.1%(24)	71.7%(33)		53.1%(26)	57.4%(31)	
I don't know	22.8%(13)	15.2%(7)	2, 0.018*	16.3%(8)	22.2%(12)	2, 0.446
			PD is contagious			
Yes	1.8%(1)	0%(0)		0%(0)	1.9%(1)	
No	78.9%(45)	91.3%(42)		81.6%(40)	87.0%(47)	
I don't know	19.3%(11)	8.7%(4)	2, 0.199	18.4%(9)	11.1%(6)	2, 0.382
			PD is the result of another disease			
Yes	5.3% (3)	6.5%(3)		6.1%(3)	5.6%(3)	
No	9%(15.8)	56.5%(26)		34.7%(17)	33.3%(18)	
I don't know	78.9%(57)	37%(46)	2, <0.001*	59.2%(29)	61.1%(33)	2, 0.978
Knowledge about the prognostic of PD						
			PD reduces life expectancy			
Yes	49.1%(28)	30.4%(14)		46.9%(23)	35.2%(19)	
No	17.5%(10)	47.8%(22)		28.6%(14)	33.3%(18)	
I don't know	33.3%(19)	21.7%(10)	2, 0.004*	24.5%(12)	31.5%(17)	2, 0.471
			PD is a fatal disease			
Yes	8.8%(5)	2.2%(1)		8.2%(4)	3.7%(2)	
No	64.9%(37)	84.8%(39)		73.5%(36)	74.1%(40)	
I don't know	26.3%(15)	13.0%6()	2, 0.065	18.4%(9)	22.2%(12)	2, 0.587
			PD has rapid progression			
Yes	29.8%(17)	17.4%(8)		20.4%(10)	27.8%(15)	
No	26.3%(15)	52.2%(24)		40.8%(20)	35.2%(19)	
I don't know	43.9%(25)	30.4%(14)	2, 0.026*	38.8%(19)	37.0%(20)	2, 0.667
			PD patients can have a long and active life			
Yes	26.3%(15)	67.4%(31)		51%(25)	38.9%(21)	
No	33.3%(19)	6.5%(3)		24.5%(12)	18.5%(10)	
I don't know	40.4%(23)	26.1%(12)	2, 0.001*	24.5%(12)	42.6%(23)	2, 0.153

Knowledge, attitudes, and practices upon the treatment options						
PD medication is toxic						
Yes	8.8%(5)	23.9%(11)		14.3%(7)	42.6%(23)	
No	38.6%(22)	50%(23)		46.9%(23)	40.7%(22)	
I don't know	52.6%(30)	26.1%(12)	2, 0.012*	38.8%(19)	16.7%(9)	2, 0.814
Dopaminergic drugs accelerate PD progression						
Yes	8.8%(5)	4.3%(2)		2%(1)	11.1%(6)	
No	45.6%(26)	76.1%(35)		59.2%(29)	59.3%(32)	
I don't know	45.6%(26)	19.6%(9)	2, 0.007*	38.8%(19)	29.6%(16)	2, 0.154
Levodopa acts only during the first 5 years of PD						
Yes	8.8%(5)	4.3%(2)		6.1%(3)	7.4%(4)	
No	15.8%(9)	43.5%(20)		30.6%(15)	25.9%(14)	
I don't know	75.4%(43)	52.2%(24)	2, 0.008*	63.3%(31)	66.7%(36)	2, 0.862
Levodopa side effects outpass its benefits						
Yes	8.8%(5)	4.3%(2)		8.2%(4)	5.6%(3)	
No	35.1%(20)	69.6%(32)		51.0%(25)	50%(27)	
I don't know	56.1%(32)	26.1%(12)	2, 0.002*	40.8%(20)	44.4%(24)	2, 0.843
*statistically significant results (p<0.05)						

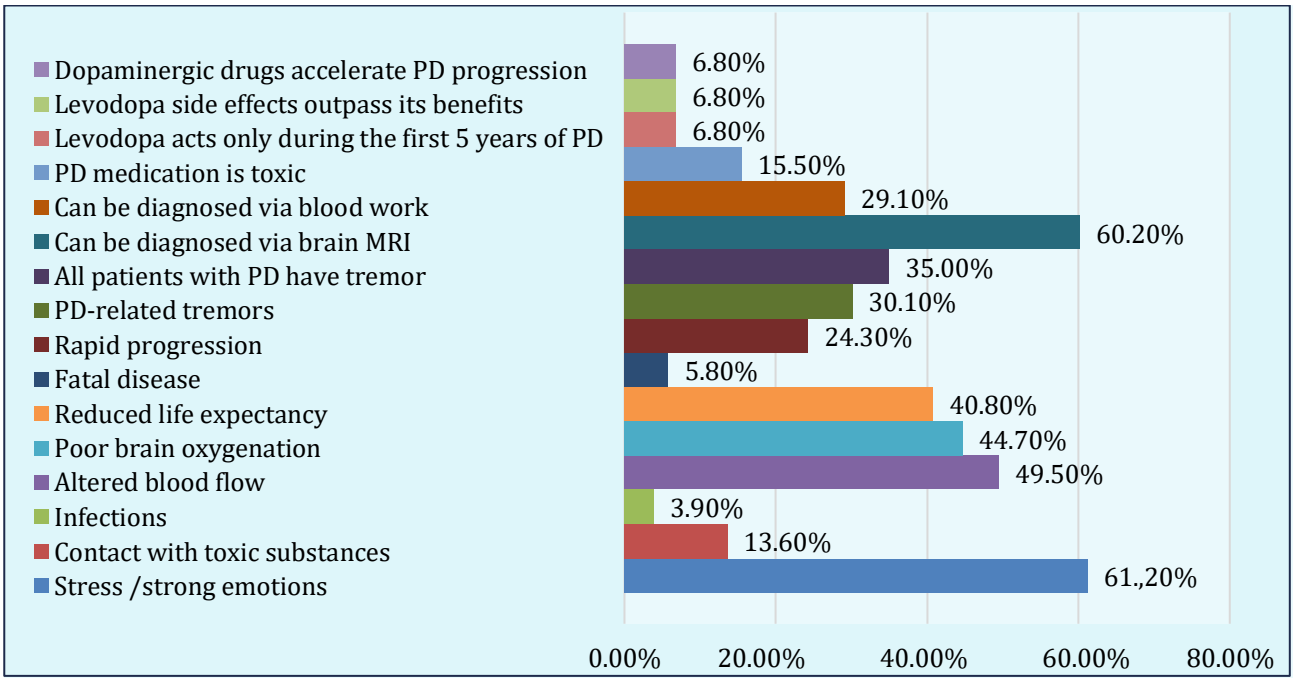

Figure 1. Health literacy determinants registered in Parkinson's disease patients.

ingly a majority of higher educated individuals (69.6%) believed its side effects out passed its benefits (p=0.002).

Parameters influencing self-stigma

A significant proportion of diagnosed patients (46.6%) stated "It's a shame to have Parkinson's Disease", mostly seen in less educated subjects (p=0.001). 49.5% stated "It is shameful to walk using crutches or walking frames", this idea also prevailed among those with lower education (p=0.001) (tab. 2).

A third of the subjects interviewed (33.0%) are convinced that PD caused dementia – 47.8% out of the patients with higher degrees supported this idea (p=0.001); meanwhile two thirds (65.0%) believed it caused dependency upon other's help – result rather constant among subjects from different educative backgrounds and gender. 44.7% stated PD made them subjected to judgement form others, a concern in 52.6% of the less educated (p=0.028). Additionally, 30.1% said PD al-

Table 2. Self-stigma determinants in Parkinson's disease patients.

	Stratification based on education level			*Stratification based on gender*		
Parameters	**Education <12 years**	**Education > 12 years**	**p**	**Males**	**Females**	**p**
	% (Nr)	**% (Nr)**	**df, p**	**% (Nr)**	**% (Nr)**	**df, p**
			PD is caused by a mental illness			
Yes	38.6%(22)	52.2%(24)		46.9%(23)	42.6%(23)	
No	14.0%(8)	28.3%(13)		14.3%(7)	25.9%(14)	
I don't know	47.4%(27)	19.6%(9)	2, 0.010*	38.8%(19)	31.5%(17)	2, 0.332
			PD causes dementia			
Yes	21.1%(12)	47.8%(22)		30.6%(15)	35.2%(19)	
No	17.5%(10)	32.6%(15)		24.5%(12)	24.1%(13)	
I don't know	61.4%35()	19.6%(9)	2, 0.001*	44.9%(22)	40.7%(22)	2, 0.874
			All PD patients use wheelchairs or are bedridden			
Yes	29.8%(17)	17.4%(8)		22.4%(11)	25.9%(14)	
No	15.8%(9)	41.3%(19)		32.7%(16)	22.2%(12)	
I don't know	54.4%(31)	41.3%(19)	2, 0.013*	44.9%(22)	51.9%(28)	2, 0.494
			PD causes loss of independency			
Yes	61.4%(35)	69.6%(32)		63.3%(31)	66.7%(36)	
No	22.8%(13)	28.3%(13)		26.5%(13)	24.1%(13)	
I don't know	15.8%(9)	2.2%(1)	2, 0.066	10.2%(5)	9.3%(5)	2, 0.937
			PD causes altered relationships with family and friends			
Yes	45.6%(26)	10.9%(5)		26.5%(13)	33.3%(18)	
No	54.4%(31)	82.6%(38)		67.3%(33)	66.7%(36)	
I don't know	0%(0)	6.5%(3)	2, 0.001*	6.1%(3)	0(0)	2, 0.157
			PD causes social isolation			
Yes	43.9%(25)	17.4%(8)		30.6%(15)	33.3%(18)	
No	49.1%(28)	76.1%(3)		36.3%(31)	59.3%(32)	
I don't know	7%(4)	6.5%(3)	2, 0.014*	6.1%(3)	7.4%(4)	2, 0.910
			It's a shame to use crutches and walking frames			
Yes	66.7%(38)	28.3%(13)		40.8%(20)	57.4%(31)	
No	31.6%(18)	69.6%(32)		57.1%(28)	40.7%(22)	
I don't know	1.8%(1)	2.2%(1)	2, 0.001*	2%(1)	1.9%(1)	2, 0.240
			Fear of judgement in the community			
Yes	52.6%(30)	34.8%(16)		38.8%(19)	50.0%(27)	
No	19.3%(11)	43.5%(20)		38.8%(19)	22.2%(12)	
I don't know	28.1%(16)	21.7%(10)	2, 0.028*	22.4%(11)	27.8%(15)	2, 0.187
			It's a shame to have PD			
Yes	64.9%(37)	23.9%(11)		34.7%(17)	57.4%(31)	
No	35.1%(20)	71.7%(33)		63.3%(31)	40.7%(22)	
I don't know	0%(0)	4.3%(2)	2, 0.001*	2%(1)	1.9%(1)	2, 0.068

*statistically significant results ($p<0.05$)

ters relationships among close and distant family members, 32.0% affirmed "PD leads to social isolation" (fig. 2).

Patient statements with regards to PD

Some of recurrent themes emerged from the in-depth interviews. When asked about what Parkinson's disease is, all patients said it's "an old age disease", seven out of ten stated it's "when there is tremor in your hands" and that it represents "a mental illness".

Stress was widely regarded as a cause, with varying degrees of belief: "the disease appeared because I was always stressed," "this tremor started after a big scare and never went away," and "the daily struggles of life made me sick." Some pati-

ents explained the origin of the disease based on their understanding of medical information: "one of my neck vessels is shorter than the other, so that made my brain sick," and "a few years ago, during an investigation (after a Doppler ultrasound), my doctor told me that my neck veins are not symmetric, so the blood doesn't reach my brain properly."

Living with PD is a significant source of distress for patients: "I feel bad for my children because they have to take care of me," "We used to have big family gatherings when we were younger, but now I feel embarrassed to attend because I struggle to eat properly," "I rarely see my neighborhood friends anymore – they might think I'm drunk because of my tremor."

Regarding treatment, many respondents expressed reluctance: "The medication doesn't work; I feel even worse," "I stopped taking the drugs my doctor prescribed." Two patients believed that dopaminergic treatment worsened their symptoms: "I feel worse when I take levodopa/carbidopa (active compounds substituted for brand name); I experience strange sensations on the left side of my face."

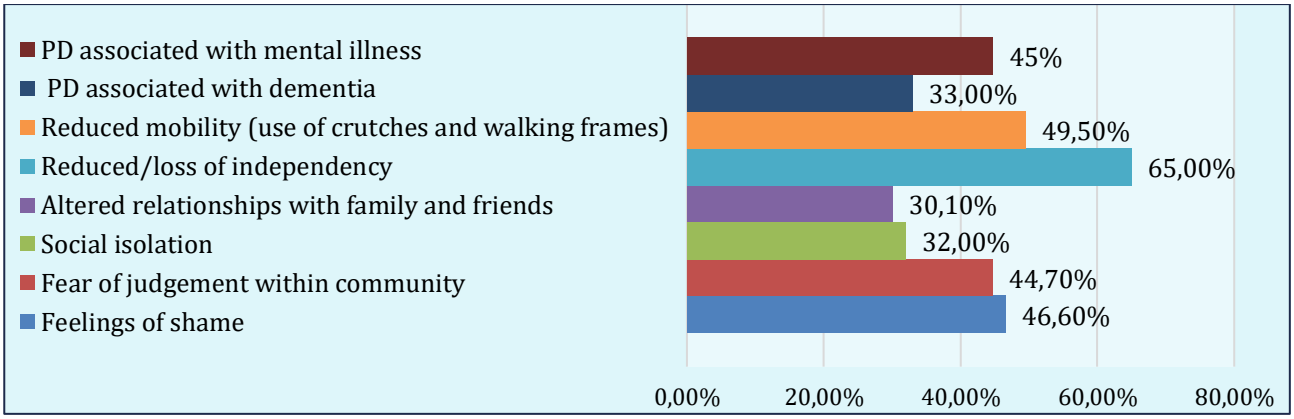

Figure 2. Self-stigma determinants identified in Parkinson's disease patients

DISCUSSIONS

Based on the collected responses, most individuals believed their condition to result from exposure to extremely stressful situations (61.2%) or to happen in the context of mental disorders (44.7%). This association might be due to the increased self-reported severity of PD symptoms in relation to acute and chronic stress exposure and the diminished effect of medication in that context (11). The pathophysiological explanation resides in the loss of the dopamine-dependent adaptative mechanisms involved in the stress management in the central nervous system. Although the neuroplastic abilities of the nigro-striatal system are compromised and may predispose to PD they don't mandate the onset of the disease (12). Patients also associated PD to disrupted blood flow (49.5%) or poor oxygenation (44.7%), especially in the patients with lower levels of education (p=0.001), probably as result of embedded myths in the community that cervical blood vessels' asymmetry of flow is at the basis of an umbrella of neurological disorders, as highlighted the statements form the in-depth interviews. A minority of respondents thought PD is a contagious (1%) or infective disease (3.9%). Those findings show a profound lack of knowledge and misinformation of the patients about the nature of their disease – a synucleinopathy.

In addition, our results showed that a third of the respondents (35%) – 42.1% of those from a lower educative background (p=0.001); believe tremor to be the hallmark sign of PD. A similar observation was made in a study made in Tabuk City, Saudi Arabia, where 93.66% of the respondents portrayed tremor as a common trait of PD(13). Low awareness about the various phenotypes of the disease may lead to disbelief in the accuracy of the diagnosis and create reluctance in following diagnostic procedures and initiation of treatment. Furthermore, the general misconception that PD is an old age only disease (1, 14, 15) – myth registered in up to 25.2% of the questioned subjects; can cause hesitancy in younger patients towards accepting and adhering to treatment along to accentuated self-stigma as per the feeling of loss of their value to the familial cell/society.

The efficacy of therapeutic approaches is highly questioned among patients, some of them being concerned about the toxicity of the medication (15.5%) or believe L-Dopa has more side-effects than benefits (6.8%) and causes a faster progression of the disease (6.8%). This erroneous understanding may be a consequence of: ineffective communication and education of the patient about the way L-Dopa functions; wrong posology; unawareness of the side effects and the lack of their management or prevention. Data showed that most of the subjects with higher education levels had statistically significant greater confidence into antiparkinsonian medication. A KAP study evaluating practices of neurologists in the Republic of Moldova about management of PD showed negative approaches in regard to L-Dopa treatment – 30.4% of them delaying as much as possible initiation of the treatment (8). Thus, the practitioners' reticence into prescribing the appropriate medication regimen can reflect upon the assurance patients have in its overall need. Some of the uncertainty surrounding L-dopa may be the result of earlier studies on the oxidative stress induced by PD treatment on substantia nigra which was latter disproved but persists in a minority of the medical community (16).

A significant number of patients believe PD influences negatively life expectancy (40.8%), followed by 24.3% concerned about the rapid progression of the disease. However, a greater number of educated subjects had positive perspectives about life with PD diagnosis (p=0.001). The subject of mortality and disease associated risks must not be ignored - early disclosure of all aspects of the disease including complications and mortality rates is the first step into ensuring the patient and its family is prepared (3, 17). Complementary, patients must be informed of the major threat surrounding PD, notably: aspiration pneumonia as a result to dysphagia and immobility, especially as the disease progresses(18). Preparation in advance of the patient and relatives is key into providing qualitative years lived with the disease.

The findings exposed above are in alignment to the results obtained in a study lead at the University of Pennsylvania's Parkinson's Disease and Movement Disorder Center in 2015, were 30% of respondents had poor health literacy although they had higher degrees of education (3). A scoping review profiled various barriers to providing appropriate care for PD patients, which included low health literacy, exacerbated by the belief held by most patients that treatment related discussion should be solely initiated by healthcare providers (17). This observation shows the impact the initial disclosure of the diagnostic can have – probably the first time the patient has ever heard about PD. Clear description of the clinical presentation, etiology, disease evolution and management options are of essence. Health literacy of the patients with PD is of utter most importance as symptoms can be confusing, sometimes the disease is fully installed at young age and medication regimens are rather complex. Insufficient explanations can result in wrong conceptualization of the disease, low adherence to treatment and decreased life quality. In the previously conducted KAP study, up to 64.4% of the Moldovan neurologists disclosed lacking theoretical skills and 62.2% practical skills with PD patients (10), fact that could contribute to the overall poor health literacy in PD patients in the Republic of Moldova, as a variety of erroneous perceptions about the disease prevailed in the studied sample.

Furthermore, the research allowed the evaluation of the effect several determinants of self-stigma have on subjects diagnosed with PD. Fear of losing independency represents the greatest concern of patients (65%) followed by mobility impairment in 49.5% of cases. Other key factors of concern re-emerging are of psychosocial nature, such as: feelings of shame 46.6%, fear of community judgement 44.7%, associating PD to mental illnesses. Approximately a third of the respondents expressed anticipation of social isolation (32%) and strained relationships with friends or family members (30.1%).

Self-stigma in patients with PD is the result of the stereotypes and the discrimination individuals experience in their community(4,15). Elements such as the degree of self-compassion and health literacy proved to strongly influence the degree of self-stigma(3,4). A review of publications realized by a Luxembourg team of researchers, through a thematic synthesis, identified 87 determinants of self-stigma which included the ones described in our study (6). In addition, the typical symptoms associated to PD (tremor, rigidity, bradykinesia, on/off phenomenon, incontinence, drooling or troubles swal-

lowing) along to the increased clumsiness caused by the progression of the disease is a source of embarrassment and patients have a tendency to try and dissimulate them(15,16). In a Kenyan research, upon questioning a patient with incipient stage of PD disclosed being afraid of showing symptoms in the future, thus manifesting anticipatory-stigma (14). Social interactions can also suffer as a result of the symptoms of PD. Patients may be mistaken to be drunks due to postural instability or their intentions may be misunderstood in regard to their hypo-/amimia(1). Those could cause social avoidance of the diagnosed individual and emphasize enacted stigma.

CONCLUSIONS

1. This research showed limited health literacy among PD patients by revealing widespread misconceptions and myths regarding diagnostic procedures, clinical presentation, disease progression, and treatment efficacy – factors that ultimately affect adherence to best clinical practices. Additionally, patients exhibited signs of self-stigma driven by their symptoms and disease progression, which negatively impacted their family and social relationships. These findings were more pronounced in individuals with lower levels of education.
2. Thus, the tendency of patients to rationalize their symptoms by associating them to familiar concepts reflects gaps in the medical care provided. Effective communication of the diagnosis, along with patient and family education on the etiology, progression, treatment, and management of PD, is essential to reducing frustration, addressing misunderstandings, and increasing awareness of the condition's specific challenges.

CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

ETHICAL APPROVAL

The research was approved by the Committee of Ethics in Research of the *Diomid Gherman* Institute of Neurology and Neurosurgery (No. 1 from 24.02.2022).

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REQUIREMENTS FOR AUTHORS

Rules of drafting

The manuscript (written in English and French) should be in accordance with the guidelines published in: *Uniform Requirements for Manuscripts Submitted to Biomedical Journal (1994) Lancet 1996, 348, V2; 1-4* (www.icmje.org). The manuscripts should be written in font Cambria, size 11 points, spaced at 1.0, fully justified alignment, fields 2 cm on all sides. All pages must be numbered consecutively (in the right bottom corner) and continuously. Abbreviations should be explained at first occurrence in the text and should not be excessively used. The manuscripts must not exceed the number of words (without the title, affiliation, abstract and references): review articles – 4,500 words; research articles – 3,000 words; expert opinions – 2,500 words; case presentation – 1,700 words; experimental and clinical notes – 1,300 words; book reviews and presentations – 2,000 words; teaching articles – 4,000 words. The volume of tables and figures should not exceed ⅓ from the volume of the manuscript. The journal reserves the right to make any other formatting changes. Rejected manuscripts are not returned.

All manuscripts submitted for publication should be accompanied by two abstracts: in the language of origin of the article and English.

Title and authors

The title should be as short as possible (maximum – 120 signs with spaces), relevant for the manuscript content. The names of the authors should be written in full: name, surname (*e.g.:* Jon JONES). Affiliation should include: Department/Unit/Chair, University/Hospital, City, Country of each author. Beneath the affiliation, the author`s details and contact information – e-mail address (*e.g.:* corresponding author: Jon Jones, e-mail: jon.jones@gmail.com).

The structure of the manuscript

The manuscript should comprise the following subheadings (capitalized):

- **SUMMARY**
- **INTRODUCTION** (will reflect the topicality and the general presentation of the problem studied, purpose and hypothesis of the study)
- **MATERIAL AND METHODS**
- **RESULTS**
- **DISCUSSIONS**
- **CONCLUSIONS**
- **CONFLICT OF INTERESTS**
- **ACKNOWLEDGEMENT** (optional)
- **ETHICAL APPROVAL** (specify the presence or absence of a positive opinion from the ethics committee: no, date, institution ad informed consent)
- **REFERENCES**

The **summary** should contain 1,600 signs with spaces:

- **Introduction**
- **Material and methods**
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- **Key words:** 3-5 words

The summary should not include tables, charts, and bibliographic notes; information not included in the article.

Figures. The text included in figures should be written in font Cambria, 10 point. Each figure should be accompanied by a heading and legend. They should be numbered with Arabic numerals and placed in parentheses (*e.g.:* fig. 1). Both the title (*e.g.* Figure 1) and legend are centred, below the figure.

Tables. The text included in tables should be written in font Cambria, 10 point. Each table should be accompanied by a heading. Tables should be inserted into the text and adjusted to the width of the page. The tables are numbered in Arabic numerals and mentioned in body text in parentheses (*e.g.* tab. 1). The title of the table is centred on the top of the table (*e.g.* Table 1).

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Titlul ar trebui să fie cât mai scurt posibil (maximum - 120 de semne cu spaţii), elocvent pentru conţinutul manuscrisului. Numele autorilor vor fi scrise deplin: prenume, nume de familie (*ex:* Ion RUSU). Afilierea va include: Secţia/Departamentul/Catedra, Universitatea/Spitalul, Oraşul, Ţara pentru fiecare autor. Se vor menţiona obligatoriu, mai jos, datele autorului corespondent şi informaţiile de contact – adresa de e-mail (*ex:* autor corespondent: Ion Rusu, e-mail: ion.rusu@gmail.com).

Structura manuscrisului

Manuscrisul va cuprinde următoarele subtitluri (scrise cu majuscule):

- **REZUMAT** (vezi cerinţele mai jos)
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- **MATERIAL ŞI METODE**
- **REZULTATE**
- **DISCUŢII**
- **CONCLUZII**
- **CONFLICT DE INTERESE**
- **MULŢUMIRI ŞI FINANŢARE** (optional)
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- **REFERINŢE**

Rezumatul va conţine până la 1600 de semne cu spaţii şi va cuprinde:

- **Introducere**
- **Material şi metode**
- **Rezultate**
- **Concluzii**
- **Cuvinte cheie**: 3-5 cuvinte

În rezumat nu vor fi incluse tabele, grafice şi note bibliografice; informaţii care nu sunt prezentate în studiu.

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Structure du manuscrit

Le manuscrit comprendra les sous-titres suivants (avec lettres majuscules):

- **RÉSUMÉ** (voir les exigences ci-dessous)
- **INTRODUCTION** (reflétera l'actualité et la présentation générale du problème étudié, le but et l'hypothèse de l'étude)
- **METHODES**
- **RESULTATS**
- **DISCUSSIONS**
- **CONCLUSIONS**
- **CONFLIT D'INTERETS**
- **REMERCIEMENTS ET FINANCEMENT**
- **APPROBATION ÉTHIQUE** (préciser la présence ou l'absence d'avis favorable du comité d'éthique: no, date, institution et consentement éclairé)
- **REFERENCES**

Le **résumé** contiendra 1600 signes avec espaces:

- **Introduction**
- **Méthodes**
- **Résultats**
- **Conclusions**
- **Mots clés**: 3-5mots.

Le résumé ne comprendra pas des tableaux, graphiques et des notes bibliographiques; des informations non présentées dans l'étude.

Figures. Le texte inclus dans les figures doit être écrit avec police Cambria, taille 10 points. Chaque figure doit être accompagné par un titre et une légende. Ceux-ci seront numérotés avec des chiffres arabes et mentionnés dans le texte entre parenthèses (*ex:* fig. 1). Le titre (*ex:* Figure 1) et la légende de la figure doivent être centrés, au-dessous de la figure.

Tableaux. Le texte inclus dans les tableaux doit être écrit avec police Cambria, taille 10 points. Chaque tableau doit être accompagné par un titre. Les tableaux seront numérotés avec des chiffres arabes, mentionnés dans le texte entre parenthèses (*ex:* tab. 1), et seront insérés dans le texte, sans dépasser la largeur d'une page. Le titre du tableau sera placé au-dessus du tableau, centré (*ex:* Tableau 1).

Les **références** doivent être numérotées dans l'ordre où elles apparaissent dans le texte. La citation de la source de référence sera de style *AMA*, placée à la fin de l'article et n'inclura que des références citées dans le texte (mentionnant le numéro de référence entre parenthèses rondes). Si la même référence est citée plusieurs fois, elle sera transmise dans le texte avec le même numéro que celui de la première citation. Le nombre total de références ne dépassera pas 50 sources. La responsabilité pour l'exactitude des données est à la charge de l'auteur. Il faut indiquer dans le manuscrit seulement les références vraiment consultées par les auteurs. Les composants des sources de référence doivent être rédigés strictement selon les exigences.

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Подготовка рукописи (разработанной на английском и французском языках) будет осуществляться в соответствии с инструкциями, опубликованными в: *Uniform Requirements for Manuscripts Submitted to Biomedical Journals (1994) Lancet 1996, 348, V2; 1-4* (www.icmje.org). Авторы должны использовать шрифт Cambria, размер 11 точек, с интервалом 1,0, выравнивание по ширине, поля 2 см со всех сторон. Все страницы должны быть пронуме-рованы последовательно (в правом нижнем углу) и включать непрерывную нумерацию страниц. Сокращения должны быть объяснены при первом появлении в тексте и не должны использоваться чрезмерно. Объем рукописей не должен превышать (без названия, принадлеж-ности, резюме и литературы): для обзорных статей/рефератов – 4500 слов; для научных ста-тей – 3000 слов; для экспертных заключений – 2500 слов; для презентации случаев из клини-ческой/лабораторной практики – 1700 слов; для экспериментальных и клинических заметок – 1300 слов; для рецензий и презентаций книг – 2000 слов; для учебных статей – 4000 слов. Объем таблиц и рисунков не должен превышать ⅓ от объема рукописи. Журнал оставляет за собой право вносить любые другие изменения форматирования. Отклоненные рукописи не возвращаются.

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Название и авторы

Название должно быть как можно короче (максимум – 120 знаков с пробелами), но дос-таточно информативным для содержания рукописи. Фамилии авторов будут написаны полностью: имя, фамилия (*например:* Иван ИВАНОВ). Принадлежность будет включать: Отделение/ Департамент/Кафедра, Университет /Больница, Город, Страна для каждого автора. Данные соответствующего автора и контактная инфор-мация – адрес электронной почты (*например:* контактная информация: Иван Иванов. e-mail: ivan.ivanov@gmail.com) будут обязательно ниже.

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Рукопись будет включать в себя следующие подзаголовки (они должны быть заглавными):

- **РЕЗЮМЕ** (см. требования ниже)
- **ВВЕДЕНИЕ** (будет отражать актуаль-ность и общее представление изучаемой проблемы, цель и гипотезу исследования)
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Резюме должно содержать 1600 знаков с пробелами и будет включать в себя следующие подзаголовки:

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Таблицы. Текст, включенный в таблицы, должен быть написан в Cambria, размер 10 пунктов. Каждая таблица должна сопровождаться заголовком. Они должны вставляться в текст, не превышая ширину страницы. Должны быть пронумерованы арабскими цифрами и указаны в тексте в скобках (*например:* таб. 1). Название таблицы должно располагаться над таблицей в центре (*например:* Таблица 1).

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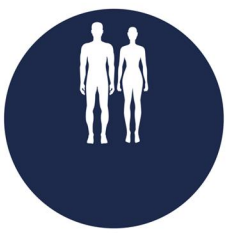
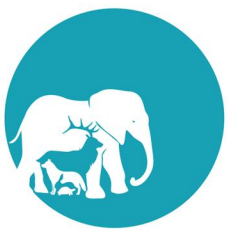
The *One Health* concept

Human health



The WHO defined health in 1946 as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity", with the later addition of "the capacity to lead a socially and economically productive life".

Animal health



The OIE defines animal welfare in 2008: an animal is in good condition if it is healthy, enjoys comfort, is well fed, is safe, is able to display its innate (natural) behavior and does not suffer from unpleasant conditions such as pain, fear and stress.

Plant and environmental health

Environmental health refers to those aspects of human health that include the quality of life determined by physical, biological, socio-economic and psycho-social factors in the environment. The interrelationships of people with the environment concern medicine, when an ecological system is in a state of equilibrium, the health of the population prevails.

Globally, the *One Health* concept is a worldwide strategy to expand interdisciplinary collaborations and communications in all aspects related to the health care of humans, domestic animals or wildlife, which can no longer be approached separately, but only jointly.

One Health addresses not only human and animal disease concerns, but also issues related to lifestyle, diet, exercise, the impact of different types of human-animal relationships, and environmental exposures that can affect both populations. In order to achieve the expected effects, it is also necessary to educate the population to make them aware of the risk factors and benefits of prevention, as well as communication and understanding between patients and healthcare providers.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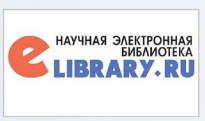
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