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EPIDEMIOLOGICAL ASSESSMENT OF ACUTE VIRAL RESPIRATORY INFECTIONS WITH THE IMPROVEMENT OF SURVEILLANCE AND RESPONSE MEASURES

331.01 – EPIDEMIOLOGY

Summary of the PhD thesis in medical sciences

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The thesis was elaborated within the National Agency for Public Health.

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The PhD thesis defense will take place on April 9, 2025, at 12^{00} within „Nicolae Testemitanu” State University of Medicine and Pharmacy, 165 Ștefan cel Mare și Sfânt Bd., office 204, at the meeting of the Commission for Public Defense of PhD thesis, approved by the decision of the Scientific Council of the Consortium no. 51 from December 23, 2024.

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CONCEPTUAL FRAMEWORK OF THE RESEARCH

Relevance of the Topic. Influenza, acute respiratory infections (ARI), and severe acute respiratory infections (SARI) are globally widespread infectious diseases, accounting for up to 95% of infectious diseases in some regions. These infections, characterized by high levels of morbidity and mortality, have a significant impact on public health, and considerable pressure on the healthcare system, resulting in substantial economic losses. [1,2].

Globally, influenza epidemics affect approximately one billion people annually, with three to five million developing severe forms of the disease, and between 290,000 and 650,000 losing their lives [3]. Up to 20% of the general population is infected with influenza annually [4]. A study highlighted that influenza-associated respiratory infections in children under five years old account for 7% of total cases, 5% of hospitalizations, and 4% of deaths globally, with the majority occurring in low- and middle-income countries [5]. Lafond K. et al. demonstrates that influenza viruses are responsible for over five million hospitalizations worldwide annually, including more than two million in Europe [6].

People with lower socioeconomic status are disproportionately affected by influenza due to limited access to healthcare. In low- and middle-income countries, hospitalizations in intensive care units due to influenza are approximately seven times more frequent compared to high-income countries, with case severity increasing with age and the presence of comorbidities [7]. Influenza has severe complications, which increase hospitalization and mortality rates [8].

Influenza viruses frequently undergo mutations and recombinations, influencing the evolution of epidemics and the distribution of cases. Genetic monitoring of influenza viruses is essential for detecting mutations and ensuring effective infection and epidemic management [9,10,11]. Seasonal influenza epidemics typically occur during the winter months [12,13].

Antiviral resistance complicates the treatment and control of epidemics, and continuous surveillance of resistance is crucial for adjusting therapeutic strategies [14]. In 2019, the World Health Organization (WHO) identified influenza as a major global threat and established partnerships to ensure equitable access to diagnostics, vaccines, and antivirals, particularly for developing countries [15]. The WHO is implementing the *Global Influenza Strategy* (2019-2030) to optimize surveillance and promote research and innovation in this field.

The study conducted by Kiseleva I. et al. in 2022 reveals that ARIs are among the most common infections globally. Although they are generally mild and self-limiting, their behavior can vary under pandemic conditions, such as the replacement of influenza viruses by Rhinoviruses and Respiratory Syncytial Virus in some regions [16]. The prevalence of ARIs is influenced by pathogen variability and rapid transmission, especially airborne. Immunity is often incomplete or short-lived, leading to frequent reinfections and temporary immunosuppressive effects [17,18].

The WHO has established criteria for SARI to facilitate the monitoring of influenza-associated hospitalizations, and the definition has been widely adopted for assessing its public health impact [19]. The results of a 2023 study in Tunisia indicate an increase in post-pandemic SARI cases, with influenza A and B strains as the primary causes, highlighting the need for proactive strategies [20]. Another observational study, conducted in 23 countries, reports an overall mortality rate of 9.5%, with the highest rate among individuals over 60 years of age (18.6%) and children under five years old (1%) [21].

Recent studies highlight the significant economic impact of influenza. A 2019 study from Turkey reported an average hospitalization cost of $3,274 for influenza patients, compared to $2,880 for those not confirmed. Influenza vaccination reduced these costs by 4.8 times, with hospitalization costs for vaccinated individuals amounting to $780, compared to $3,762 for those unvaccinated. Community costs exceed $22 million for individuals aged 18-65 and $15 million for those over 65, emphasizing the need for targeted surveillance and prevention [22]. Acute upper respiratory infections generate global costs of approximately 25 billion dollars [1,2]. A study in 20 countries reported average hospitalization costs of €17,804 for adults over 50 and €129 for outpatient care. Costs increase significantly for elderly patients and those with comorbidities [23]. Another 2022 study showed that patients with SARI confirmed with influenza virus had direct medical costs of $700, and total costs amounted to $848 per patient, being three times higher in the elderly [24]. These results underline the economic burden of respiratory infections and the need for effective prevention and control measures to reduce the global economic impact.

Seasonal influenza vaccination is the most effective method for preventing influenza [25,26]. Although these programs have been implemented for decades in high-income countries [27], vaccine uptake remains low in low- and middle-income countries, where mortality and hospitalization rates are higher [28,29,6,30]. In 2022, out of the 194 WHO member states, 128 (66%) had seasonal flu vaccination policies [31]. Low vaccination rates in low- and middle-income countries are influenced by factors such as lack of government involvement and competition for limited health resources. In contrast, high-income countries have higher vaccination rates, associated with a higher socioeconomic status [32]. According to estimates, approximately one in five unvaccinated children and one in ten unvaccinated adult contract seasonal influenza annually [33]. Seasonal influenza vaccination has demonstrated a significant impact in reducing the incidence of influenza, particularly among vulnerable groups, by decreasing severe cases and deaths. Continuous evaluation of program effectiveness is crucial for improving vaccination strategies [34].

Surveillance of viral respiratory infections remains a global challenge due to the unequal capacities of national influenza centers, limited resources, and inefficient monitoring mechanisms [35]. The WHO recommends monitoring influenza, ARIs, and SARI to reduce morbidity and mortality, focusing on geographical spread, epidemic intensity, viral strain prevalence, and antiviral resistance. These require dedicated research projects to improve prevention, surveillance, and response strategies.

Aim of the research: Assessment of the epidemiological and virological characteristics that are associated with the morbidity and mortality caused by influenza, acute respiratory infections (ARI), and severe acute respiratory infections (SARI), depending on the circulating strains of the influenza virus, to improve prevention, surveillance, and response measures at national level.

Research Objectives

1. Analysis of the epidemiological and virological aspects of influenza, ARI, and SARI and their global impact.
2. Evaluation of the epidemiological characteristics associated with influenza, acute and severe viral respiratory infections in the Republic of Moldova.
3. Examination of the virological characteristics of viral respiratory infections in relation to the dominant/codominant strains of influenza A and B viruses.

4. Assessment of the morbidity burden caused by influenza, ARI, and SARI on public health.
5. Improvement of prevention, surveillance, and response measures for viral respiratory infections to mitigate their socioeconomic impact.

Research Hypothesis: The epidemiological and virological characteristics of influenza, ARI, and SARI, influenced by the variability of viral strains, the effectiveness of sentinel-type epidemiological surveillance, and seasonal influenza vaccination, contribute to reducing the socioeconomic impact of these viral respiratory infections and to improving public health measures.

Scientific novelty and originality of the obtained results: The originality of the research is due to its detailed evaluation of the epidemiological and virological characteristics of influenza, ARI, and SARI by analyzing the diversity of influenza strains (genotypic and phenotypic). Sensitivity to antiviral preparations against circulating strains was demonstrated, validating treatment protocols, and phylogenetic studies contributed to the selection of strains for the influenza vaccine cocktail, in line with WHO guidelines. The calculation of the DALY indicator enabled a comprehensive assessment of the impact of viral respiratory infections by combining epidemiological and economic perspectives. This methodology provides essential data for optimizing public health policies, creating a robust foundation for informed decision-making regarding the control and prevention of respiratory infections. For the first time, a post-introduction evaluation of the influenza vaccine (iPIE) was conducted, identifying both strengths and gaps in the implementation of influenza vaccination.

Major applied scientific problem solved: This research identified the epidemiological and virological features of influenza, ARI, and SARI, including an assessment of the genotypic and phenotypic diversity of influenza strains. It demonstrated the influence of these factors on morbidity and mortality rates across different age groups. Through a post-introduction evaluation of the influenza vaccine (iPIE), has been highlighted the effectiveness of the vaccination program while identifying gaps in its implementation. The identification of vulnerabilities in the prevention, surveillance, and control of influenza, ARI, and SARI, including within the sentinel surveillance system and influenza vaccination, provided a clear direction for improving prevention, surveillance, and response strategies. Consequently, a solid foundation was established for optimizing public health measures, contributing to a reduction in morbidity and mortality associated with these infections.

Practical implementation of results: The research findings formed the basis for proposals to update the gradual intersectoral framework plan aimed at mitigating the effects of the novel influenza A(H1N1) pandemic in the Republic of Moldova, including updates to the definitions of suspected, probable, and confirmed cases. These findings also contributed to the revision of Ministry of Health (MH) Disposition 498-d/2014 on the epidemiological surveillance of influenza, ARI, and SARI, as well as the weekly reporting of morbidity associated with these infections by territorial public health centers, focusing on virological monitoring to improve the surveillance system for influenza and acute respiratory infections. This effort included the development and implementation of six normative acts. As part of a collaborative team, the National Clinical Protocol "Influenza in Adults" (PCN-370, 2020) was updated. Annual workshops were organized to prepare for the influenza, ARI, and SARI surveillance season, along with a workshop on prevention measures and promotion of influenza vaccination, approved through ten legislative acts. The post-introduction evaluation of the seasonal influenza vaccine was conducted based on the iPIE study (MoH Disposition no. 616-d of 29.11.2023). The development of the online platform "Information on Influenza, ARI, and SARI" (available at https://gripamd.wordpress.com/) provides the population with up-to-date and verified information on influenza and respiratory infections.

Approval of results: The research methodology and study design were evaluated and approved by the Research Ethics Committee of the 'Nicolae Testemițanu' State University of Medicine and Pharmacy, no. 109 from 23.06.2017, and the methodology and design of the post-introduction evaluation study of the influenza vaccine (iPIE) – by the National Clinical Study Ethics Expertise Committee, no. 1565 from 27.09.2023. The study was conducted within the Epidemiological Surveillance of Influenza and Acute Respiratory Viral Infections Department and the Virology Laboratory of the National Agency for Public Health (NAPH), in collaboration with Public Health Center Divisions. The thesis was discussed and approved at the meeting of the Scientific Council (minutes no. 6 from 17.09.2024), at the joint meeting of the doctoral supervisor, the Advisory Committee, and the primary research unit (minutes from 28.10.2024), and at the meeting of the Scientific Seminar of Profile 331.01. Epidemiology, 331.02. Hygiene, 333.01. Occupational Hygiene (minutes from 22.11.2024). The thesis was recommended for public defense by the decision of the Scientific Council of the Consortium on 23.12.2024 (no. 51).

Presentation of research results: Based on the thesis materials, **49** works were published:
7 articles in ISI and SCOPUS-indexed journals (including 4 articles in journals with impact factors (IF: 21.286; IF: 6.454; IF: 4.4; IF: 3.143)), ***3 single-author articles*** (SCOPUS, in international scientific journals and national category B scientific journals), ***3 articles*** in national category B scientific journals, ***10 abstracts*** in national and international scientific conference proceedings**,** ***2 monographs***, ***13 materials*** presented at invention fairs, and ***7 active participations*** with presentations/posters at national and international scientific conferences and congresses, ***1 innovator certificate***, ***2 scientific works*** with copyright, ***1 national clinical protocol***, and ***5 practical implementation acts*** of the research results.

Volume and structure of the thesis: The thesis materials are presented in Romanian, spanning 118 pages, structured according to the Doctoral Thesis and Summary Writing Guide approved by the Senate of "Nicolae Testemițanu" State University of Medicine and Pharmacy, decision no. 6/2 of 21.09.2017. The thesis includes the following sections: *title page*, *copyright page*, *table of contents*, *list of tables and figures*, *introduction*, *five chapters*, *discussions*, *general conclusions*, *recommendations*, 200 bibliographic references, and 40 appendices. The iconographic material includes 30 tables and 40 figures.

Keywords: *influenza, viruses, genotype, phenotype, surveillance, morbidity, mortality, antivirals, costs, vaccination*.

THESIS CONTENT

1. EPIDEMIOLOGICAL AND VIROLOGICAL ASPECTS OF INFLUENZA, ACUTE AND SEVERE RESPIRATORY INFECTIONS, AND THEIR GLOBAL IMPACT

This chapter provides a comprehensive synthesis of data from the scientific literature regarding the prevalence of influenza, ARI, and SARI at global and regional levels, highlighting epidemiological trends observed in Europe and worldwide. It analyzes the epidemiological and virological characteristics of these infections, with a focus on contemporary perspectives. A detailed description of the phenotypic and genotypic characteristics of influenza viruses globally is also provided. The essential role of seasonal influenza vaccination programs is analyzed, emphasizing the current situation and existing challenges on a global scale. Additionally, the economic and social consequences of acute respiratory infections are evaluated, highlighting their significant impact on public health and the need for effective prevention, surveillance, and response measures. The chapter explores addressing these challenges through the latest scientific approaches.

2. MATERIALS AND METHODS

The research was conducted within the National Agency for Public Health through the national routine and sentinel surveillance system for influenza, ARI, and SARI, approved by the WHO according to the standards of the Global Influenza Surveillance Program [36]. The research project, carried out between the 2014/2015 and 2022/2023 seasons, included 6 distinct stages. The flu season begins in week 40 of the year and ends in week 20 of the following year. The research was structured into six stages, each corresponding to a distinct study, in accordance with the established objectives.

The first stage involved collecting data on morbidity and mortality associated with influenza, ARI, and SARI from all administrative territories, according to Annex no. 2 of MoH Disposition 498-d/2014, to conduct comprehensive cross-sectional descriptive observational study.

In ***the second stage***, the virological characteristics of influenza, ARI, and SARI were evaluated through a selective cross-sectional descriptive observational study, using accompanying reports as specified in Annex No. 4 of MoH Disposition 498-d/2014.

The calculation of the representative sample was performed using Cochran's formula:
$n=d[\tilde{\pi}(1-\tilde{\pi})]*(z\alpha/w)^2$, where: d - design effect = 12 (age, gender, place of residence, influenza season, presumptive diagnosis, vaccination status, laboratory result, virus type, surveillance system type, patient status, administered antivirals, clinical manifestations); $\tilde{\pi} = 0.50$; $z\alpha = 1.96$; w – the study was conducted based on frequency evaluation and results presentation through relative values, thus a 95.0% confidence interval was chosen, ES=0.05.

$n = 12*[0.50*0.50]*(1.96/0.05)^2 = 4\,610$ samples

Adjusting the sample with a 10% non-response rate, the minimum sample size calculated for the study was 5 071 samples. As part of the research, 17 194 samples from patients with a presumptive diagnosis of influenza, ARI, or SARI were analyzed (table 1).

Table 1. **Planned and conducted Sample Size**

Cases	% of the total	Absolute frequency from the planned sample	Absolute frequency from the conducted sample
Influenza	0.5%	25	1 706
ARI	92.5%	4 691	13 215
SARI	7.0%	355	2 273
Total	100%	5 071	17 194

The third stage focused on determining the phenotypic and genotypic characteristics of influenza A and B viruses collected in the territory of the Republic of Moldova and on evaluating the resistance of these strains to antiviral agents, in collaboration with the Francis Crick Institute in London – WHO Reference Laboratory.

The fourth stage included conducting an economic study to evaluate the costs associated with illnesses caused by influenza, ARI, and SARI, as well as calculating the DALY indicator (disability-adjusted life years) to quantify the morbidity burden caused by these respiratory infections. Thus, the full economic impact (Ied) resulting from influenza, ARI, and SARI illnesses in the sentinel points during the study period was calculated using the formula: $Ied = Cvmf + Csamu + Cct + Czp + Ccm + Cms + Cdps$, where: *Cvmf* – cost of family doctor visits; *Csamu* – cost of emergency medical assistance requests; *Cct* – cost of treated cases; *Czp* – cost per day/bed of hospitalized cases; *Ccm* – cost of medical leave; *Cms* – cost of specific medications; *Cdps* – cost in the form of damages to the state.

The cost of family doctor visits was set at 200 MDL [37]. The cost of emergency services with a doctor was set at 1 400 MDL [37]. The average cost of treating an influenza case, according to 2022 data, was 3 146 MDL for adults and 2 074 MDL for children, as per the tariff approved by Order MS and CNAM no. 1221/344-A/2021. The cost of a hospitalization day in an infectious disease unit was set at 960 MDL [37]. The cost of medical leave was calculated at 75% of the gross average monthly salary, which was 12 355 MDL in 2023 [38]. The cost of specific medications ranges from 154.74 to 231.28 MDL [39].

The cost associated with death due to influenza infection, referred to as the cost in the form of damages to the state (*Cdps*) was calculated using the formula: $Cdps = Pibpc \times Ani$, where: *Pibpc* – gross domestic product per capita; *Ani* – years of life lost due to death, calculated in relation to life expectancy at birth.

To calculate the burden of diseases using the DALY indicator, the formula recommended by the WHO [40]: $DALY = YLD + YLL$, where: YLD - years lived with disability; YLL - years of life lost. $YLD = I \times D \times DW$, where: I – number of cases; D – average duration of a case until recovery or death, expressed in years [41]; DW - disability weight [42]. $YLL = N \times L$, where: N – number of deaths; L – life expectancy at the age of death, expressed in years [43].

In ***the fifth stage***, a cross-sectional study was conducted to evaluate the sentinel surveillance system for influenza, ARI, and SARI. The sample was structured to ensure institutional diversity and representativeness, including all 9 sentinel sites, thus providing complete coverage of the sentinel surveillance system. The survey was conducted with medical staff directly involved in surveillance and reporting activities for influenza, ARI, and SARI cases, ensuring the relevance and accuracy of the collected data. Additionally, all accompanying reports for biological samples intended for investigating the presence of influenza viruses within the sentinel surveillance system were evaluated for the period 2014-2023—a total of 7 315 lab forms.

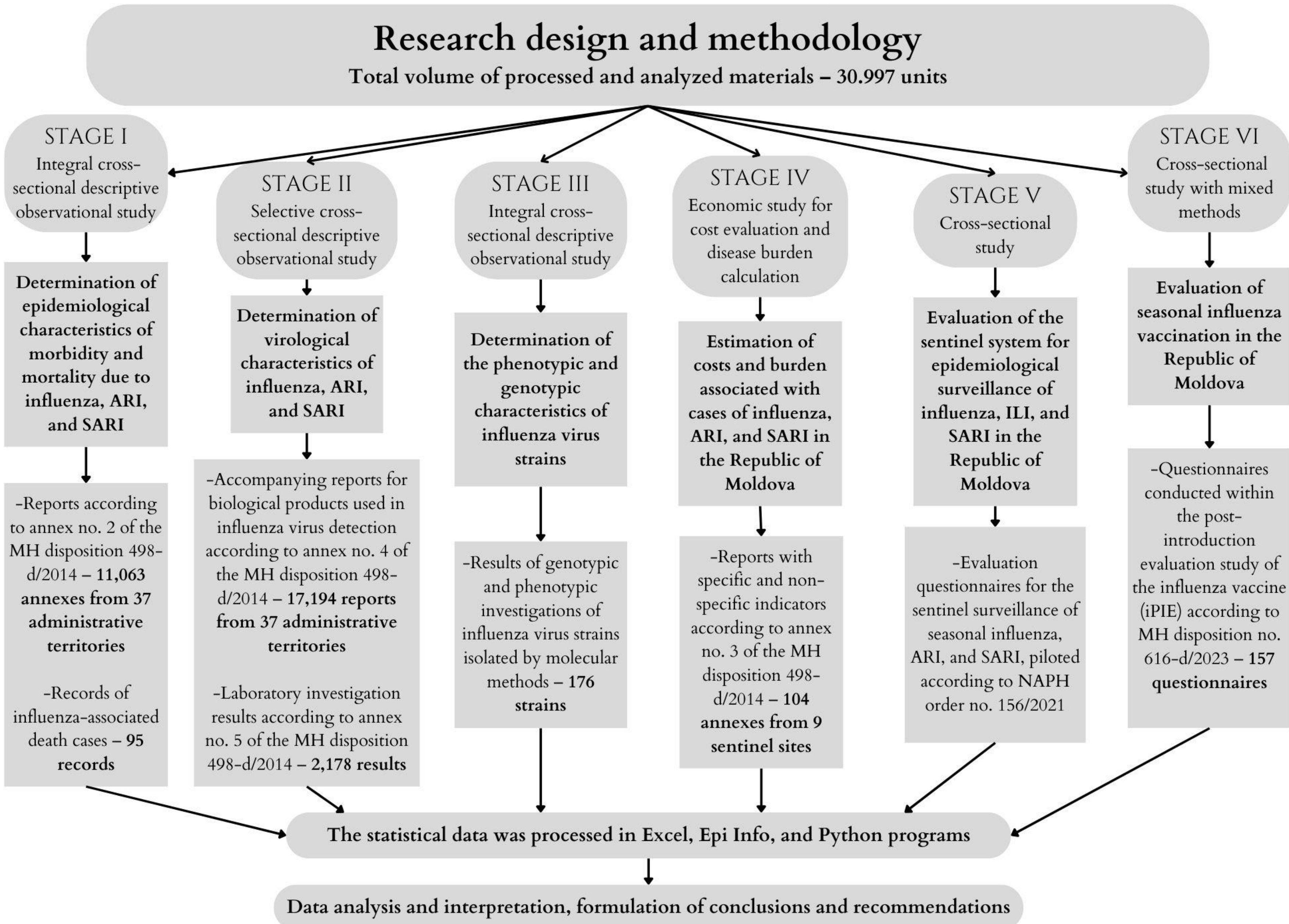
An analysis of the characteristics of the influenza case definition was also performed.

Table 2. **Algorithm for calculating the characteristics of the influenza case definition**

		Laboratory results for the presence of influenza viruses	
		Positive	Negative
Presumptive diagnosis of influenza according to the case definition	Present	a	c
	Absent	b	d

Sensitivity, Specificity, Positive Likelihood Ratio, Negative Likelihood Ratio, Positive Predictive Value, Negative Predictive Value, and Accuracy were calculated.

These indicators are essential for evaluating the effectiveness of the case definition in correctly detecting and excluding influenza cases, considering potential classification errors.


Research design and methodology
Total volume of processed and analyzed materials – 30.997 units
STAGE I
Integral cross-sectional descriptive observational study
Determination of epidemiological characteristics of morbidity and mortality due to influenza, ARI, and SARI
-Reports according to annex no. 2 of the MH disposition 498-d/2014 – 11,063 annexes from 37 administrative territories
-Records of influenza-associated death cases – 95 records
STAGE II
Selective cross-sectional descriptive observational study
Determination of virological characteristics of influenza, ARI, and SARI
-Accompanying reports for biological products used in influenza virus detection according to annex no. 4 of the MH disposition 498-d/2014 – 17,194 reports from 37 administrative territories
-Laboratory investigation results according to annex no. 5 of the MH disposition 498-d/2014 – 2,178 results
STAGE III
Integral cross-sectional descriptive observational study
Determination of the phenotypic and genotypic characteristics of influenza virus strains
-Results of genotypic and phenotypic investigations of influenza virus strains isolated by molecular methods – 176 strains
STAGE IV
Economic study for cost evaluation and disease burden calculation
Estimation of costs and burden associated with cases of influenza, ARI, and SARI in the Republic of Moldova
-Reports with specific and non-specific indicators according to annex no. 3 of the MH disposition 498-d/2014 – 104 annexes from 9 sentinel sites
STAGE V
Cross-sectional study
Evaluation of the sentinel system for epidemiological surveillance of influenza, ILI, and SARI in the Republic of Moldova
-Evaluation questionnaires for the sentinel surveillance of seasonal influenza, ARI, and SARI, piloted according to NAPH order no. 156/2021
STAGE VI
Cross-sectional study with mixed methods
Evaluation of seasonal influenza vaccination in the Republic of Moldova
-Questionnaires conducted within the post-introduction evaluation study of the influenza vaccine (iPIE) according to MH disposition no. 616-d/2023 – 157 questionnaires
The statistical data was processed in Excel, Epi Info, and Python programs
Data analysis and interpretation, formulation of conclusions and recommendations

The sixth stage implied the evaluation of influenza vaccination in the Republic of Moldova, using the WHO tool [44] post-introduction evaluation for the influenza vaccine (iPIE), with support from The Task Force for Global Health (TFGH) and experts from TFGH and CDC.

The administrative territories were selected from all three regions of the country (north, center, and south). In each district, influenza vaccination coverage for the 2022/2023 season was calculated one month after the start of the vaccination campaign. The list of districts was sorted by vaccination coverage in ascending order. From each region, two districts were selected: one with a high level of vaccination coverage and one with a low level. A total of six administrative territories were selected. All family doctor centers and health centers within these territories were similarly sorted. In each territory, three medical institutions were selected: one with the highest coverage, one with average coverage, and one with the lowest coverage. In total, 18 medical facilities were selected.

Data were collected through structured questionnaires, including open and closed questions about influenza vaccination, using the Open Data Kit Collect software. The questionnaires were pre-programmed with logical checks and constraints to ensure data quality and facilitate the interview process. According to the WHO tool, a minimum of 103 questionnaires were planned, but 157 questionnaires were completed.

Statistical Analysis of Data. For data analysis, after processing the data, descriptive statistical tests (univariate and multivariate) and mathematical analyses were applied to calculate proportions, percentages, adjusted rates, and frequency distributions using indicators such as the mean, median, deciles, quartiles, and percentiles. Clopper-Pearson confidence intervals (95% CI) and interquartile ranges (IQR) were calculated for precise estimation.

Data comparison was conducted using statistical tests such as ANOVA F, the Kruskal-Wallis test, and Pearson's Chi-square test, along with p-values to assess statistical significance. In the analysis of the case definition for seasonal influenza, sensitivity, specificity, likelihood ratios (positive and negative), predictive values (positive and negative), and accuracy were calculated.

Various graphical representations were used for data visualization, including Time Series Plots, Clustered Bar Graphs, Area Plots, Filled Maps, Radar Diagrams, Clustered Column Graphs, Stacked Column Graphs, 100% Stacked Bar Graphs, Box Plots, and Heat Maps. The analysis and interpretation of results facilitated the formulation of hypotheses and conclusions relevant to achieving the research aim and objectives. The data were processed using Microsoft Excel 365, Epi Info™ 7.2, and Python 3.10.12.

3. EPIDEMIOLOGICAL AND VIROLOGICAL CHARACTERISTICS OF INFLUENZA, ACUTE AND SEVERE VIRAL RESPIRATORY INFECTIONS WITH INFLUENZA A AND B VIRUSES IN THE REPUBLIC OF MOLDOVA, SEASONS 2014/2015-2022/2023

3.1. Epidemiological characteristics of influenza, ARI, and SARI in the Republic of Moldova in the 2014/2015-2022/2023 seasons

During the 2014/2015-2022/2023 seasons, 13 074 cases of seasonal influenza were recorded. The 2019/2020 season had the highest proportion, at 24.9% (*95%CI 24.2-25.7*), followed by the 2018/2019 season with 16.8% (*95%CI 16.1-17.4*), the 2014/2015 season with 15.3% (*95%CI 14.7-15.9*), and the 2022/2023 season with 15.1% (*95%CI 14.5-15.8*). In the 2020/2021 season, no influenza cases were reported. Epidemic threshold calculation began in the 2018/2019 season at

2.1$^{o}/_{oooo}$, rising to 5,7$^{o}/_{oooo}$ starting from the 2020/2021 season. The 2019/2020 season exceeded the average epidemic threshold (14.2$^{o}/_{oooo}$), reaching the highest incidence of 16.5$^{o}/_{oooo}$ (figure 1).

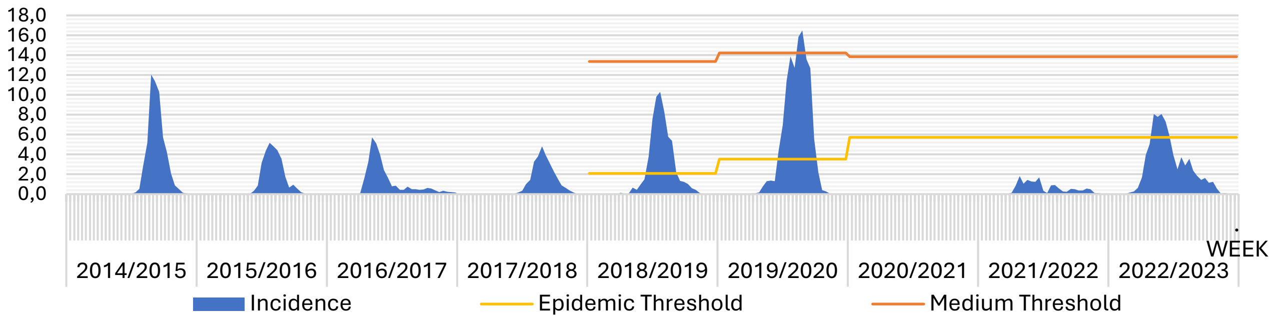


Figure 1. **Evolution of Influenza morbidity in 2014/2015-2022/2023 seasons (100 000 population)**

In two seasons (2016/2017 and 2022/2023), the highest weekly incidence was recorded at the beginning of December, in week 51, with 5.1$^{o}/_{oooo}$ and 8.1$^{o}/_{oooo}$ cases, respectively. In the 2020/2021 and 2021/2022 seasons, the evolution of influenza remained below the epidemic threshold, while in other seasons, the highest incidence was recorded in weeks 06-09 (February). During the seasons analyzed, a total of 9 924 influenza cases requiring hospitalization were recorded, representing 75.9% (*95%CI 75.2-76.6*) of all cases, with the lowest percentage in 2021/2022 (43.0%) and the highest percentage in 2017/2018 (86.6%).

On average, the proportion of hospitalized cases was highest in the 65+ age group (85.7%), followed by the 0–4 years (78.3%) and 15–29 years (78.0%) age groups. In five of the analyzed seasons, influenza predominantly affected children aged 0–14 years, with proportions ranging from 54.4% to 64.4%. The 2014/2015 influenza season was the only one in which the 30 – 64 years age group accounted for 44.1%. The fewest cases were recorded in the 65+ age group – 3.3% in the 2019/2020 season and 8.9% in the 2014/2015 season.

The Chi-square test revealed a significant difference between age group and season distributions ($\chi^2=921.0$, $df=21$, $p<0.0001$), indicating a non-uniform distribution of cases. In the 2019/2020, 2021/2022, and 2022/2023 seasons, the incidence of influenza in children under 14 years was 6.5-8.0 times higher than in individuals aged 15 and over.

In the Republic of Moldova, over the 9 analyzed seasons, 2,120,942 cases of acute respiratory infections were recorded, ranging from 6.8% (*95%CI 6.7-6.8*) in the 2020/2021 season to 13.7% (*95%CI 13.6-13.7*) in the 2018/2019 season. The highest weekly incidence of ARI was recorded in week 51 in two seasons, while in 2020/2021, the trend remained below the epidemic threshold. A very high intensity level was recorded in the 2022/2023 season, with 636.3$^{o}/_{oooo}$ cases of ARI in week 51 (figure 2). Of the total ARI cases, 78 622 required hospitalizations, representing 3.7% (*95%CI 3.7-3.7*), with the lowest percentage in 2022/2023 (2.9%) and the highest in 2020/2021 (6.9%).

The highest proportion of hospitalizations was recorded in the 0–4 years age group (6.0%), followed by the 65+ age group (4.2%). In the 5–14 years, 15–29 years, and 30–64 years age groups, the proportion of hospitalized ARI cases was 2.4%, 2.7%, and 2.3%, respectively. Statistical analysis using the Chi-square test revealed a significant difference in the distribution of cases across age groups and seasons ($\chi^2=33,055.3$, $df=24$, $p<0.0001$).

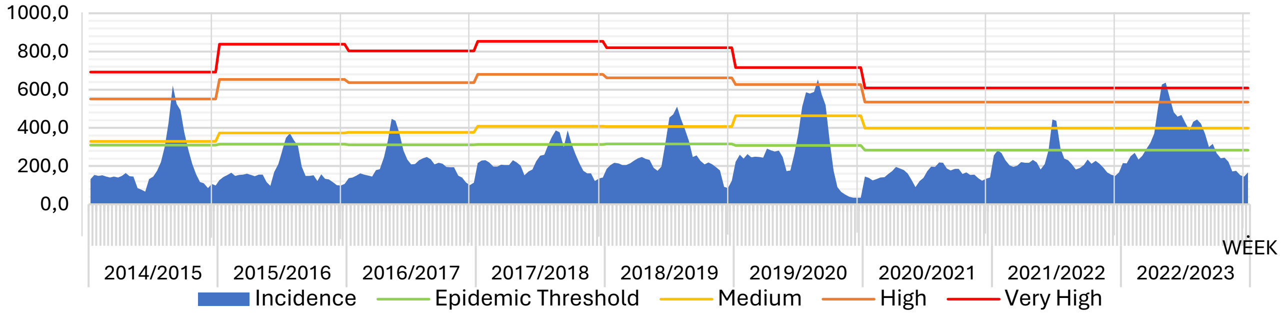


Figure 2. **Evolution of ARI morbidity in 2014/2015-2022/2023 seasons (100 000 population)**

Like influenza, the incidence of ARI was significantly higher among children (0-14 years), reaching a peak in the 2016/2017 season, when the incidence in children was 10.1 times higher than in individuals aged ≥15 years.

During the 2014/2015-2022/2023 seasons, 157 441 cases of severe acute respiratory infections were recorded. The 2016/2017 season had the highest proportion, at 17.9% (*95%CI 17.7-18.1*), followed by 2015/2016 with 16.8% (*95%CI 16.6-16.9*), while the lowest proportion was recorded in 2019/2020 with 6.2% (*95%CI 6.1-6.3*). In the 2020/2021 season, a peak of $40.2^{o}/_{oooo}$ SARI cases was reached in week 08/2021, while the previous season had the lowest rate, with $2.6^{o}/_{oooo}$ cases in week 18/2020.

Throughout all seasons included in the study, the most cases of SARI were registered among children aged 0–4 years, except for the 2020/2021 season, when adults aged 30–64 years were the most impacted. The percentage of cases in the 0-4 age group ranged from 39.7% (2022/2023) to 59.3% (2015/2016), while in the 2020/2021 and 2021/2022 seasons, the 30-64 age group recorded maximum proportions of 49.3% and 29.9%, respectively. Cases in the 65+ age group increased significantly in the last three seasons, from 11.6% to 31.8% (figure 3).

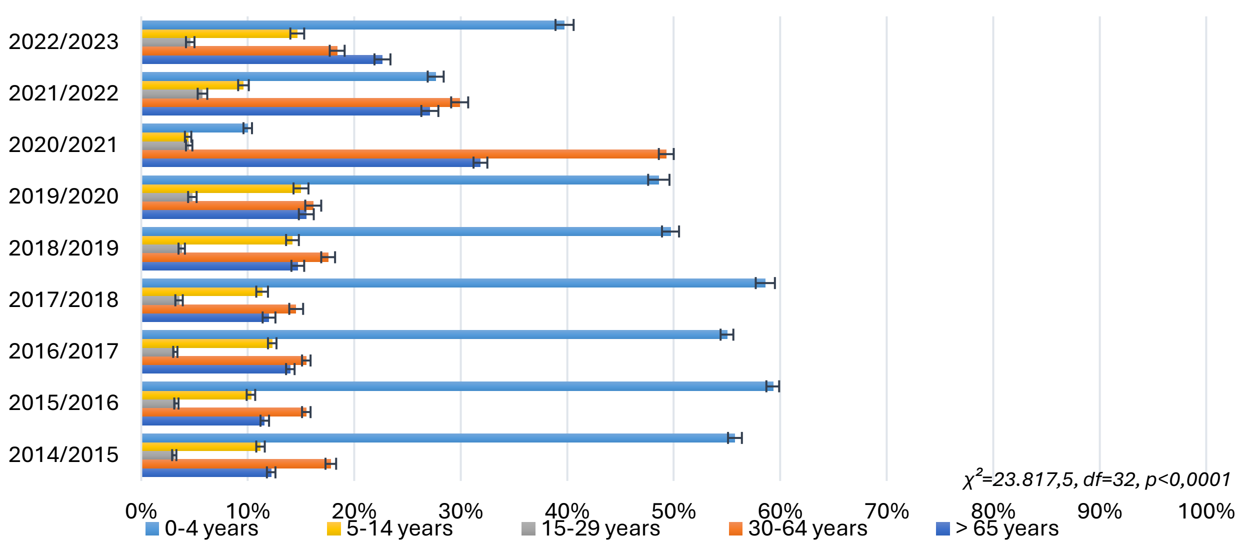


Figure 3. **Proportion of SARI cases by age groups in the 2014/2015-2022/2023 seasons**

Analysis of SARI cases by age groups and seasons, using the Chi-square test, showed significant differences ($\chi^2=23.817,51$, $df=32$, $p<0,0001$), indicating a non-uniform distribution among age groups and seasons. In the 2020/2021 season, a reversal of the usual trend was observed, with the incidence in individuals aged 15 and over being 1.3 times higher than in children aged 0-14 years. In subsequent seasons, a return to normal patterns was observed, with the incidence of SARI in children aged 0-14 being 2.6 times higher in 2021/2022 and 5.4 times higher in 2022/2023 compared to adults.

During the 2014/2015-2022/2023 seasons, the average incidence of influenza was highest in Chișinău (135.6$^{o}/_{oooo}$), followed by Bălți municipality (102.7$^{o}/_{oooo}$). The lowest incidences were recorded in Cantemir (2.8$^{o}/_{oooo}$) and Drochia (2.2$^{o}/_{oooo}$) districts. The average incidence of ARI was highest in Anenii Noi district (19,706.6$^{o}/_{oooo}$) and Bălți municipality (18,154.8$^{o}/_{oooo}$), and lowest in Rezina (1,691.9$^{o}/_{oooo}$) and Florești (1,480.2$^{o}/_{oooo}$) districts. For SARI, the highest incidences were recorded in Glodeni district (1,716.3$^{o}/_{oooo}$) and Chișinău municipality (1,212.5$^{o}/_{oooo}$), with the lowest incidences in Strășeni (203.6$^{o}/_{oooo}$) and Râșcani (61.6$^{o}/_{oooo}$) districts (figure 4).

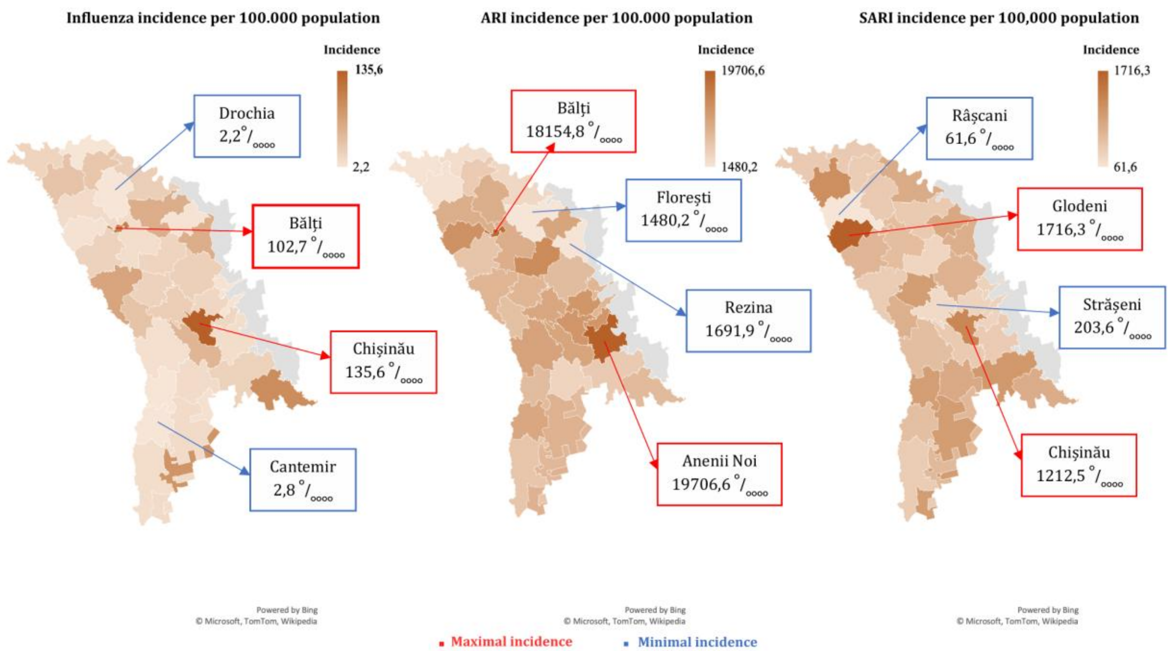


Figure 4. **Average incidence of influenza, ARI, and SARI in administrative territories during the 2014/2015-2022/2023 seasons**

In the Republic of Moldova, influenza tends to emerge between weeks 49 and 15 (December-April), with a similar seasonality observed for ARI. However, SARI does not show a clear seasonality. Analysis of influenza cases by gender, using the Chi-square test, showed a significant difference between males and females ($\chi^2=21.78$, $df=7$, $p=0.0028$), with females representing 50.3% of cases. For ARI, the prevalence in females was 52.5% ($\chi^2=211.89$, $df=8$, $p<0.0001$), while SARI had a prevalence of 49.0% among females ($\chi^2=661.04$, $df=8$, $p<0.0001$).

3.2. Virological characteristics of influenza, ARI, and SARI caused by dominant/codominant influenza viruses in the 2014/2015-2022/2023 seasons

Over the 9 seasons, 17,194 biological samples were analyzed, of which 55.3% (*95%CI 54.5-56.0*) were from females and 44.7% (*95%CI 44.0-45.5*) from males. Regarding the surveillance system, 42.9% (*95%CI 42.1-43.6*) of samples were collected through sentinel surveillance, and 57.1%

(*95%CI 56.4-57.9*) through routine surveillance. Of the total samples examined, 9.8% presented the presumptive diagnosis of influenza, in 77.0% – IACRS and for 13.2% – SARI.

Of the total samples investigated, 12.6% (95%CI 12.1-13.1) were positive for influenza viruses: unsubtyped A 4.7%, A(H1N1)pdm09 41.7%, A(H3N2) 27.9%, and type B 24.8%. The highest positivity was recorded between December and February, with significant seasonal variations. In three seasons, the positivity peak was in January, in another three seasons in February, while in the 2016/2017 and 2017/2018 seasons, the peaks were in December and March, respectively. In the 2020/2021 season, although 682 samples were analyzed, no influenza virus was detected (figure 5).

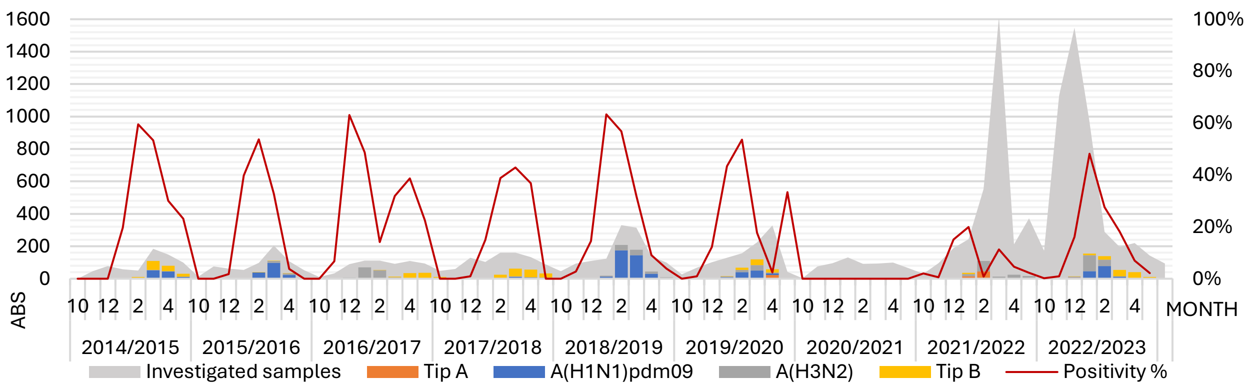


Figure 5. **Monthly distribution of investigated and influenza-positive samples by type and subtype in the 2014/2015-2022/2023 seasons**

Upon examining the laboratory results based on the presence of influenza viruses, it was observed that during the first six seasons, the percentage of negative results fluctuated between 62.5% and 80.0%; however, in the 2021/2022 and 2022/2023 seasons, following the absence of influenza virus detection in the 2020/2021 season, the prevalence of negative results increased to 96.8% and 91.2%, respectively. The detection rate of the influenza virus A(H1N1)pdm09 reached its peak in the 2018/2019 (29.9%) and 2015/2016 (23.9%) seasons, while the A(H3N2) virus showed its highest detection rate in the 2016/2017 season (20.2%). For influenza type B virus, peak detection rates were recorded in the 2017/2018 and 2014/2015 seasons, both at 16.3%.

When assessing the dominance and codominance of influenza virus strains during the analyzed period, it was observed that in three seasons (2014/2015, 2019/2020, and 2022/2023), codominant states existed, where two-three types of viruses were present in relatively equal proportions. In the 2014/2015 season, codominance was observed between A(H1N1)pdm09 (47.0%) and type B (47.8%) viruses. In 2019/2020, the A(H1N1)pdm09 (38.9%), type B (26.8%), and A(H3N2) (21.9%) viruses were relatively balanced, while in the 2022/2023 season, codominance was seen between A(H3N2) (34.6%), A(H1N1)pdm09 (31.5%), and type B (30.3%). The A(H1N1)pdm09 strain dominated in the 2015/2016 (85.0%) and 2018/2019 (79.7%) seasons, while type B was dominant only in the 2017/2018 season (81.3%). The A(H3N2) strain predominated in the 2016/2017 (61.8%) and 2021/2022 (63.6%) seasons.

When distributing positive influenza virus samples by age group, it was observed that 45.1% of all positive samples for A(H1N1)pdm09 were recorded in the 30–64 years age group, while A(H3N2) and type B viruses had the highest proportions in the 5–14 years age group (27.0% and 33.3%, respectively) (figure 6). Regarding the presumptive diagnosis, 81.6% of samples negative for influenza viruses had an ARI diagnosis, while 45.0% of positive samples were associated with this diagnosis, indicating incorrect use of the influenza case definition.

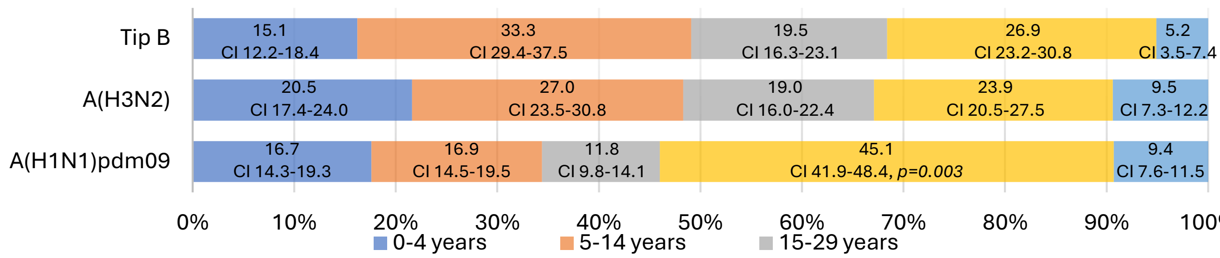


Figure 6. **Distribution of positive samples for influenza viruses by age groups in the 2014/2015-2022/2023 seasons**

Of the 17 194 samples investigated, 1 706 (9.8%) had a presumptive diagnosis of influenza, of which 44.7% were positive for influenza A and/or B viruses. In the first five seasons, the positivity rate was higher, ranging between 47.0% and 64.2%, but it decreased in the last four seasons, with a maximum of 39.5% and a minimum of 15.7%. In total, 13 215 samples (77.0%) had a presumptive diagnosis of ARI, of which 7.4% were positive for influenza viruses. The A(H3N2), A(H1N1)pdm09, and type B strains were identified in 2.6%, 2.2%, and 2.0% of samples, respectively. Of the 2 273 samples collected from patients with SARI, 19.2% were positive for influenza viruses, with the A(H1N1)pdm09 strain present in 10.0% of samples, A(H3N2) in 4.7%, and type B in 4.3%.

3.3. Epidemiological characteristics of mortality associated with influenza infection in the Republic of Moldova in the 2014/2015-2022/2023 seasons

During the 2014/2015-2022/2023 influenza seasons, 95 deaths associated with influenza infection were recorded. Most were recorded in the 2018/2019 season, with 30 cases (31.6% (*95%CI 22.4-41.9*)), followed by the 2014/2015 and 2015/2016 seasons, each with 21 cases (22.1% (*95%CI 14.2-31.8*)). In the remaining seasons, between three and ten cases were recorded, except for the 2020/2021 and 2021/2022 seasons, when no deaths were reported. The fatality rate for influenza was 0.7% (*95%CI 0.6-0.9*), with maximum rates of 1.9% (2015/2016) and 1.4% (2018/2019). The lowest fatality rate was 0.2% (2022/2023).

Laboratory analysis results indicated the presence of the A(H1N1)pdm09 virus in 82 cases of death (86.3% (*95%CI 77.7-92.5*)), while the A(H3N2) virus and type B virus were each detected in 6 cases (6.3% (*95%CI 2.4-13.2*)). One case of co-infection with two influenza virus strains was recorded. Most deaths occurred in weeks 07, 06, and 09 (February-March). There were no deaths associated with influenza infection in weeks 40-49 and 52 (October, November and December) and in weeks 16-20 (April-May) of an influenza season.

Influenza-related deaths were recorded in 31 administrative territories, with the highest proportion in Chișinău Municipality—33 cases, representing 34.7%. Of the 95 death cases, 51 (53.7%) were male. The age group distribution was uneven, with the highest proportion in individuals aged 50-59 years (26.3% (*95%CI 17.8-36.3*)) and 40-49 years (21.1%). The fewest cases were in the 10-19 age group (4.2%).

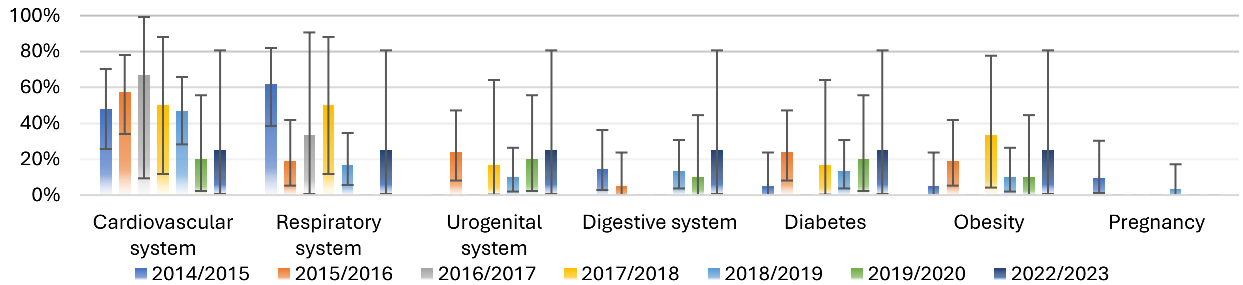


Figure 7. **Structure of mortality based on preexisting pathology and pregnancy in the 2014/2015-2022/2023 seasons.**

The overall analysis of death cases showed that cardiovascular pathologies were associated with mortality in 46.3% of cases, while respiratory pathologies accounted for 28.4%. Diabetes, obesity, and urogenital and digestive system pathologies were also associated with a significant portion of deaths (figure 7). Deaths occurred at various stages of disease progression, with a major proportion in the first 2 weeks after symptom onset – 61.1% (*95%CI 50.5-70.9*).

4. QUANTIFICATION OF THE MORBIDITY BURDEN CAUSED BY VIRAL RESPIRATORY INFECTIONS ON PUBLIC HEALTH

4.1. Costs of influenza, ARI, and SARI cases based on the sentinel epidemiological surveillance system in the 2021/2022-2022/2023 seasons

In the sentinel surveillance system, which covers an estimated population of approximately 981,000 people, emergency pre-hospital healthcare units are also included. During the two influenza seasons included in the study, these units managed a total of 790,346 requests, of which 97,426 (12.3% (95% CI 12.2–12.4)) were related to cases of influenza, IACRS, or SARI. The costs associated with these requests increased from 59.8 million MDL in the 2021/2022 season to 76.6 million MDL in the 2022/2023 season, marking a 28.1% increase.

In the two analyzed seasons, 97 458 cases of respiratory infections were reported, of which 1 394 (1.4%) were cases of influenza, 81 737 (83.9%) were ARI, and 14 327 (14.7%) were SARI. The funds allocated for financing consultations and visits to family doctors increased by 1.34 times, from 8.3 million MDL in the 2021/2022 season to 11.2 million MDL in 2022/2023.

The average cost per treated case was calculated separately for children and adults. In the 2021/2022 season, treatment costs amounted to 105.8 million MDL, of which 48.0 million MDL were allocated for children and 57.9 million MDL for adults. In the 2022/2023 season, these costs increased by 33.3%, reaching 141.0 million MDL.

Regarding hospital care (expressed in bed-days), expenses were 56.4 million MDL in the 2021/2022 season and increased by 19.3% to 67.3 million MDL in the 2022/2023 season. Expenses for sick leave associated with respiratory infections were 15.2 million MDL in 2021/2022 and 17.7 million MDL in 2022/2023, representing 0.0056% and 0.0059% of Moldova's GDP, respectively.

The costs associated with antiviral treatment increased sevenfold in the 2022/2023 season, reaching 235.7 thousand MDL, compared to 33.4 thousand MDL in the previous season. Additionally, four influenza-associated deaths were recorded in the 2022/2023 season, each contributing to a total loss of 104 life years, with an estimated economic impact of 10.5 million MDL.

The price of a dose of quadrivalent influenza vaccine decreased by 10.5% in the 2022/2023 season, costing 127.81 MDL compared to 142.80 MDL in the previous season. The cost of the vaccine is significantly lower than influenza treatment (16.2 times less for children and 24.6 times less for adults) or a day/bed in intensive care (34.4 times less), highlighting the economic efficiency of vaccination.

4.2. Assessment of disease burden for influenza, ARI, and SARI in the Republic of Moldova in the 2014/2015-2022/2023 seasons

To evaluate the impact of respiratory infections, the DALY (disability-adjusted life years) indicator was used, which combines years of life lost due to premature mortality (YLL) and years lived with disability (YLD). One DALY represents one year of healthy life lost due to disease.

For influenza, significant variations between seasons are observed. For example, in the 2018/2019 and 2019/2020 seasons, the highest YLD values were recorded (1.8 and 2.7 years), while no influenza cases were reported in the 2020/2021 season. Overall, 10.8 years were lived with functional impairment due to influenza. For ARI, the 2018/2019 and 2022/2023 seasons recorded high YLD values (34.5 and 34.2 years), and a total of 252.2 years were lived with functional impairment due to ARI. For SARI, the highest YLD values were recorded in the 2015/2016 and 2016/2017 seasons, with a total of 604.9 years lived with functional impairment due to SARI.

Regarding years of life lost due to premature mortality (YLL), the highest losses were recorded among men aged 40-44 years (212.1 years) and women aged 10-14 years (201.6 years). Conversely, the lowest losses were observed in men over 85 years and women aged 80-84 years. Overall, women lost 1 469.6 years due to premature mortality, and men lost 1 336.2 years.

Table 3. **Disability-Adjusted Life Years associated with Influenza by season (in DALYs)**

Season	***Years Lived with Disability (YLD)***	***Years of Life Lost due to Premature Mortality (YLL)***	***Disability-Adjusted Life Years Associated with Influenza (DALY)***
2014/2015	1.7	605.9	607.6
2015/2016	0.9	602.8	603.7
2016/2017	0.9	98.1	99.0
2017/2018	0.8	227.4	228.2
2018/2019	1.8	757.4	759.2
2019/2020	2.7	273.6	276.3
2020/2021	-	-	-
2021/2022	0.3	-	0.3
2022/2023	1.6	131.8	133.4
Total	**10.8**	**2 697.0**	**2 707.8**

The total DALY calculation for influenza over the 9 seasons shows that 2 707.8 disability-adjusted life years were lost, of which 2 697.0 years represent YLL and 10.8 years represent YLD (table 3). The 2018/2019 season had the greatest impact, with 759.2 DALYs, while the 2020/2021 season recorded only 0.3 DALYs.

5. IMPROVEMENT OF PREVENTION, SURVEILLANCE, AND RESPONSE MEASURES FOR INFLUENZA, ARI, AND SARI TO REDUCE THEIR SOCIOECONOMIC IMPACT

5.1. Evaluation of the sentinel epidemiological surveillance system for Influenza, ARI, and SARI in the Republic of Moldova

To evaluate the sentinel surveillance system for influenza, ILI, and SARI, a cross-sectional study was conducted using a questionnaire addressed to 18 medical institutions, representing 58.1% of the total 31 healthcare institutions involved in the surveillance system across the nine sentinel sites. The evaluation results showed that all involved institutions have relevant directive documents regarding the management of respiratory infections and apply them appropriately. Additionally, 100% of the institutions report new influenza cases; however, 6.7% do not fully complete ARI notifications, and 13.3% do not fully report SARI cases.

The majority of respondents (90.0%) confirmed the dissemination of epidemiological data, and 96.7% reported the implementation of control and response measures. Difficulties in completing weekly reports were reported by 56.7% of respondents, with the most common issues being a lack of personnel and limited time for report completion.

Although 100% of participants found the forms clear, 10% mentioned difficulties in completing them. Many respondents (80.0%) have sufficient time to collect data weekly, and 46.7% completed the forms within 2-3 hours.

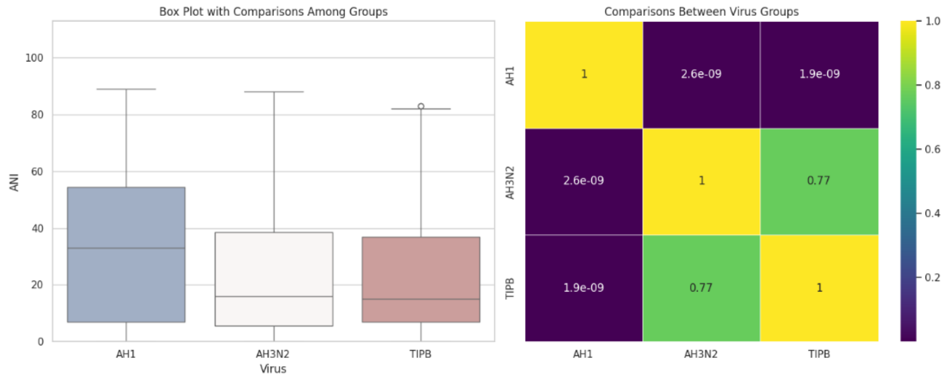
Regarding investigation reports for influenza viruses, 86.7% confirmed the correct verification of information. Internet access is essential, but 43.3% encountered connectivity issues once every few months. The national feedback system operates efficiently, with 90.5% regularly receiving information on test results.

Starting from the 2016/2017 season, reporting transitioned from Word format to Excel format, improving the efficiency and accuracy of reports.

The analysis of lab bulletins for samples collected in the sentinel surveillance system included 7,315 samples tested for influenza virus detection. Of these, 52.3% were collected from females and 47.7% from males. In total, 19.2% of the samples were positive for influenza viruses, of which 6.9% were A(H1N1)pdm09, 6.0% A(H3N2), 5.9% type B, and 0.6% unsubtyped.

Approximately 47.9% of positive samples were associated with an ARI diagnosis, indicating incorrect use of the influenza case definition. However, only 30.3% of confirmed influenza samples had influenza as the presumptive diagnosis.

Age group analysis showed that the median age for individuals diagnosed with the A(H1N1)pdm09 virus is 33 years, while for A(H3N2) and type B influenza virus, the medians were 16 and 15 years, respectively (figure 8). Age differences between groups were not statistically significant (*ANOVA F-test: F=37.6345, p=8.8548*).



ANOVA F-test: F = 37.63454859397484, p = 8.854866555274362e-17

Figure 8. **Comparison of positive influenza results according to the age of patients within the sentinel surveillance system.**

The condition of the patients from whom the samples were collected, 7.3% presented mild manifestations, 41.9% - moderate manifestations, 15.9% - severe manifestations and 0.7% manifestations classified as very severe. ARI was the predominant diagnosis in all four severity categories, and the diagnosis of SARI was established in 29.2% of very severe cases.

In the analysis of antiviral treatment, 4.9% of patients were already under treatment at the time of sample collection. Among these, 48.8% were diagnosed with influenza, and antivirals were administered with significantly different frequencies.

The analysis of accompanying bulletins for samples collected for influenza virus detection highlighted various clinical manifestations in tested individuals. Among these, fever was registered in 70.0% of cases, of which 61.1% were associated with an ARI diagnosis. Other commonly encountered symptoms included cough (58.8%), acute onset (55.0%), fatigue (51.4%), and headache (50.7%), each predominantly associated with an ARI diagnosis. SARI diagnosis was most notable in cases of dyspnea, observed in 47.9% of cases. Myalgia, a typical symptom of influenza, was present in 30.9% of cases, but only 19.5% of these were diagnosed as influenza, with the majority diagnosed as ARI (table 4).

Table 4. **Frequency of clinical signs in individuals from whom samples were collected for investigation in the sentinel system**

Symptoms	Symptom Presence		Of these, the presumptive diagnosis was established as:						χ^2	*p*
			Influenza		ARI		SARI			
	%	95% CI	%	95% CI	%	95% CI	%	95% CI		
Fever	70.0	68.9-71.0	14.4	13.4-15.4	61.1	59.7-62.4	24.6	23.4-25.8	90.54	<0.0001
Acute onset	55.0	53.8-56.1	16.5	15.4-17.7	58.2	56.7-59.7	25.3	24.0-26.7	149.36	<0.0001
Fatigue	51.4	50.2-52.5	16.8	15.7-18.1	55.9	54.2-57.5	27.3	25.9-28.8	212.27	<0.0001
Myalgia	**30.9**	29.9-32.0	**19.5**	17.8-21.1	**56.7**	54.7-58.8	**23.8**	22.0-25.6	167.53	<0.0001
Headache	50.7	49.6-51.8	16.7	15.5-17.9	60.0	58.4-61.6	23.3	22.0-24.7	131.34	<0.0001
Cough	58.8	57.7-60.0	14.2	13.1-15.3	58.2	56.7-59.7	27.6	26.3-29.0	172.87	<0.0001
Expectorations	17.3	16.4-18.1	13.9	12.0-15.9	46.7	43.9-49.5	39.5	36.8-42.2	283.18	<0.0001
Dyspnea	23.5	22.5-24.5	12.7	11.2-14.4	39.4	37.1-41.8	47.9	45.5-50.3	786.84	<0.0001
Rhinitis/Coryza	43.0	41.9-44.2	13.8	12.6-15.0	65.1	63.4-66.8	21.2	19.7-22.6	135.12	<0.0001
Pharyngitis	40.3	39.1-41.4	15.3	14.0-16.6	67.1	65.4-68.8	17.6	16.2-19.0	227.70	<0.0001
Otitis	2.4	2.1-2.8	15.9	10.8-22.2	67.6	60.2-74.5	16.5	11.3-22.8	95.78	<0.0001

Note: 18.0% of the lab bulletins did not include information on the presence of signs and symptoms.

When evaluating the characteristics of the use of the influenza case definition in the territory, it was found that its sensitivity is 38.7%, which means that only about 39% of people with influenza are correctly identified. The specificity of 85.5% shows a good ability of the case definition to exclude healthy people. The positive likelihood ratio indicates a 2.7-fold higher probability that patients with influenza will be correctly diagnosed, while the negative likelihood ratio (0.7) shows a good ability to minimize false-negative cases (table 5).

Table 5. **Characteristics of using the Influenza case definition**

Indicators	Value	95% CI
Sensitivity	38.71%	35.81%-41.66%
Specificity	85.54%	84.45%-86.58%
Positive Likelihood Ratio	2.68	2.41-2.97
Negative Likelihood Ratio	0.72	0.68-0.75
Positive Predictive Value	40.79%	38.30%-43.33%
Negative Predictive Value	84.43%	83.78%-85.06%
Accuracy	75.95%	74.78%-77.09%

The positive predictive value indicates that 40.8% of individuals diagnosed with influenza according to the case definition are correctly identified, while the negative predictive value is 84.4%, indicating good efficiency in excluding negative cases. The overall accuracy of the influenza case definition is 75.9%.

5.2. Evaluation of seasonal influenza vaccination in the Republic of Moldova

Seasonal influenza vaccination is a public health priority in the Republic of Moldova, given the increasing incidence of acute respiratory infections, including influenza. The iPIE study, which assessed the impact and efficiency of the influenza vaccination program, highlighted both strengths and challenges in each involved sector, using the WHO tool.

Regulatory Aspects: Influenza vaccines are recommended for high-risk and professional groups. Moldova has a well-established vaccine authorization system, allowing rapid access to licensed vaccines in emergency situations.

Planning and Coordination: The National Immunization Program (NIP) is coordinated by NAPH and is well-managed. Each vaccination campaign is meticulously planned, and human resources are effectively mobilized.

Funding: Vaccines are purchased through National Medical Insurance Company, and the operational costs of influenza vaccination campaigns, estimated at $14,000 to $15,000 annually, are covered by the NIP budget. However, there is no budget dedicated exclusively to influenza vaccination.

Vaccine Administration: Vaccination coverage is monitored through the RVC-19 system, which tracks data in real time. Vaccine utilization rates are high, with minimal waste.

Vaccine Management, Transport, and Logistics: The cold chain is well managed. No medical unit has reported issues with the transport or delivery of influenza vaccines, and the use of pre-filled syringes has reduced waste-related risks.

Knowledge, Training, and Supervision of Healthcare Workers: Among primary healthcare workers surveyed, 100% (*95% CI 89.7-100, p<0.0001*) were vaccinated during the 2022/2023-2023/2024 influenza seasons. Regarding the mandatory influenza vaccination policy, 56% (*95% CI 37.9-72.8, p=0.49*) support this measure for healthcare workers. Annual supervision visits are conducted to identify any issues.

Advocacy, Communication, and Acceptance: Vaccine acceptance varies by target group. Healthcare workers have the highest acceptance rate, while pregnant women and parents of young children show hesitancy (figure 9). Communication about vaccination is carried out through various channels, including media and home visits.

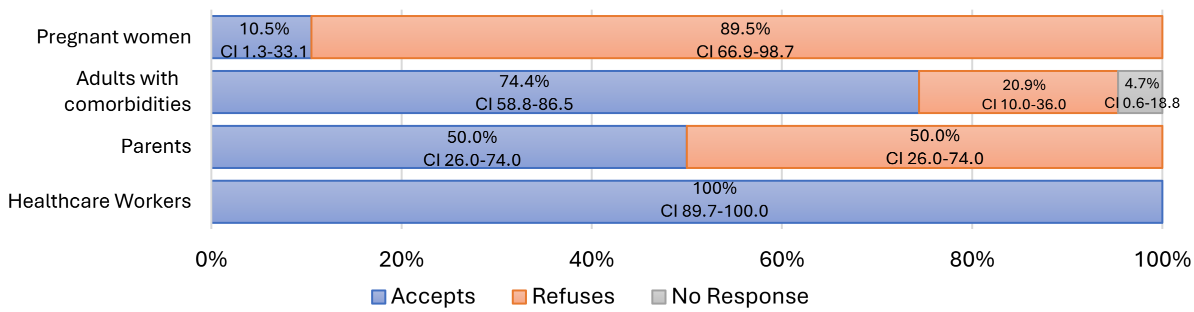


Figure 9. **Attitude towards influenza vaccination of risk groups**

Vaccine Safety: Moldova has an efficient monitoring system for adverse events following immunization (AEFI), which ensures accurate reporting and monitoring of cases. No severe AEFI cases have been reported in the past 5 years.

These findings underline the efficiency of the surveillance and vaccination system but also highlight the need for improvements, particularly in increasing vaccine acceptance among certain vulnerable groups.

5.3. Phenotypic and Genotypic characteristics of Influenza A and B viruses identified in the Republic of Moldova in the 2014/2015-2022/2023 seasons

To deepen the understanding of influenza A and B viruses identified in the Republic of Moldova during the 2014/2015-2022/2023 influenza seasons, a detailed assessment of their phenotypic and genotypic characteristics was carried out. This process facilitated the identification of antigenic and genetic variations that are important for determining the strains that should be included in the composition of the vaccines recommended by WHO. At the same time, the sensitivity of these viruses to antivirals was investigated, in order to assess their response to the drugs used.

2014/2015 Influenza Season

The isolated A(H1N1)pdm09 strains showed antigenic similarities to the reference strain A/California/7/2009, used in the vaccine composition for that season. For influenza B viruses of the Victoria lineage, the B/Moldova/049.05/2015 strain was antigenically similar to B/Odessa/3886/2010. Tests indicated that the isolated strains were susceptible to treatments with Oseltamivir and Zanamivir.

2015/2016 Influenza Season

The A(H1N1)pdm09 strains continued to display antigenic similarities to the A/California/7/2009 strain (figure 10). The type B virus of this season, strain B/Moldova/46.03.2016, showed high reactivity to the reference strain B/Brisbane/60/2008. Tests showed that all strains responded positively to neuraminidase inhibition, indicating antiviral sensitivity.

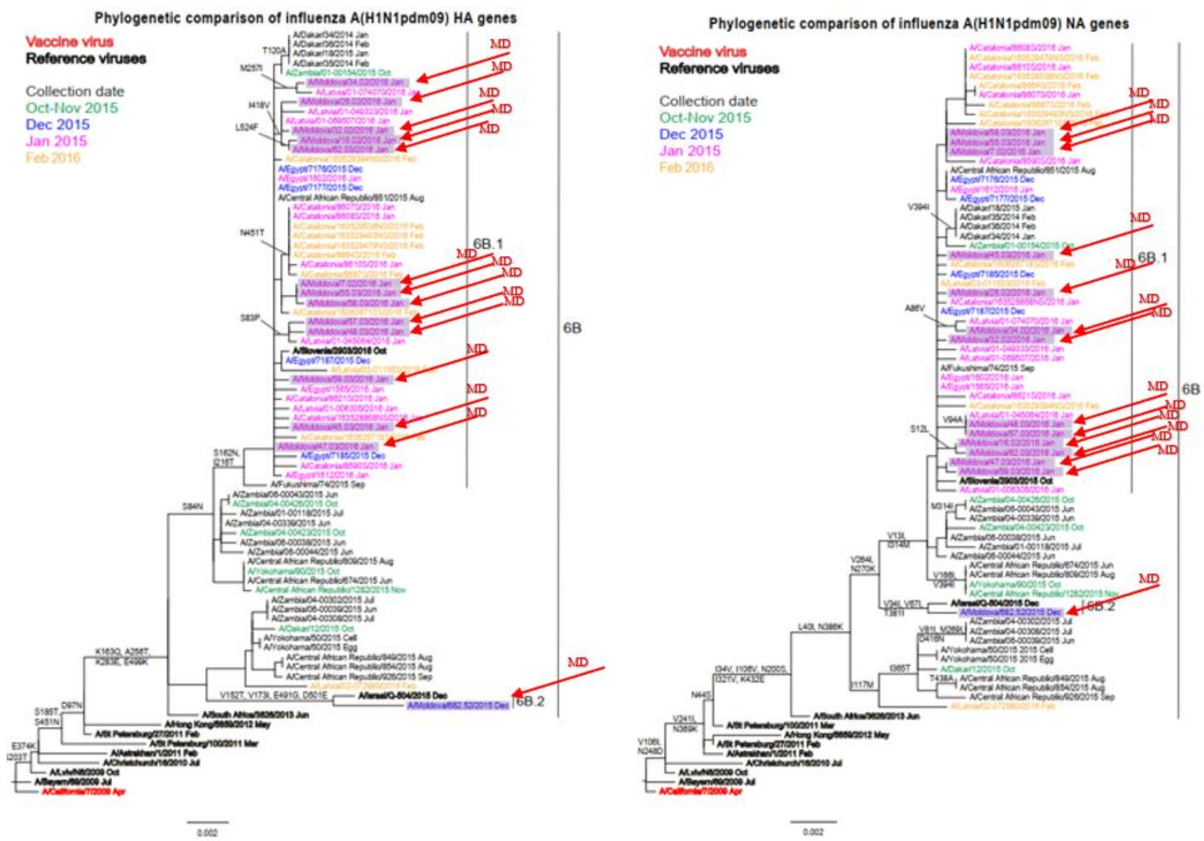


Figure 10. **Phylogenetic comparison of Influenza A(H1N1)pdm09 strains based on HA and NA genes (2015/2016 season)**

2016/2017 Influenza Season

The analysis of A(H1N1)pdm09 strains showed that they fit into genetic groups 6B.1 and 6B.2, antigenically similar to the vaccine strain A/California/7/2009. Influenza B viruses were antigenically similar to the vaccine strain B/Brisbane/60/2008, and antiviral sensitivity was confirmed for all isolated strains.

2017/2018 Influenza Season

The influenza A(H1N1)pdm09 and B (Victoria and Yamagata) viruses were analyzed from an antigenic and genetic perspective, and all strains demonstrated sensitivity to antivirals. The results confirmed that the isolated strains were antigenically similar to those included in the seasonal vaccine.

2018/2019 Influenza Season

The A(H1N1)pdm09 strains fell within the 6B.1A5 subclade and were well recognized by antisera against vaccine strains. The A(H3N2) viruses exhibited reduced recognition by antisera for the new viruses from clade 3C.3a. Sensitivity to Oseltamivir and Zanamivir was confirmed for all viruses.

2019/2020 Influenza Season

The isolated A(H1N1)pdm09 and A(H3N2) viruses fell within specific genetic clades, and genetic analysis showed similarities to vaccine strains. All viruses were sensitive to Oseltamivir and Zanamivir.

2021/2022 Influenza Season

The A(H1N1)pdm09 strains were included in subclade 6B.1A.5a.1, while A(H3N2) viruses had HA genes in subclade 3C.2a1b.2a.2. All viruses demonstrated antiviral sensitivity.

2022/2023 Influenza Season

The A(H1N1)pdm09 strains fell into clade 5a.2a, while A(H3N2) strains were in clades 2a.1b and 2b. Type B viruses (Victoria lineage) were included in clade V1A.3a.2. Sensitivity to Oseltamivir and Zanamivir was confirmed for all analyzed strains.

The genetic analysis of influenza virus strains from all studied seasons confirmed that they fit within the relevant phylogenetic tree for the analyzed period. No significant antigenic differences were observed compared to strains from other regions of the Northern Hemisphere.

The sensitivity of specific influenza antivirals, Oseltamivir and Zanamivir, remained constant. These findings support WHO recommendations on the use of these antivirals in influenza treatment. Phylogenetic studies were essential for understanding the evolution of influenza viruses and for selecting strains used in the influenza vaccine for the Northern Hemisphere, according to WHO guidelines.

GENERAL CONCLUSIONS

1. The study revealed varying intensities for influenza and ARIs: influenza presented with low to moderate levels, while ARI ranged from low to very high, predominantly affecting children aged 0-14 years. ARI were more frequent in females (52.5%), while SARI predominated in males (51.0%). The A(H1N1)pdm09 strain was 2.2 times more common in SARI compared to other strains, without a clear predominance in ARI. Influenza fatality was 0.7%, peaking in February, with deaths occurring within the first 2 weeks after onset.
2. Out of the 17,194 samples tested, 12.6% were positive for influenza viruses, with the A(H1N1)pdm09 strain predominating. The A(H3N2) viruses and type B were more frequently detected in children under 14 years old, while the A(H1N1)pdm09 strain was more common among adults aged 30–64 years.
3. Only 30.3% of influenza virus-confirmed samples matched the presumptive diagnosis of influenza. The accuracy of the case definition for influenza is 75.9%; however, the low sensitivity (38.7%) leads to underdiagnosis of influenza.
4. Molecular biology tests confirmed the inclusion of influenza strains within the regional phylogenetic tree, with no antigenic differences compared to other regions in the Northern Hemisphere. Phylogenetic studies highlighted the diversity of strains monitored by the sentinel surveillance system, contributing to the formulation of the influenza vaccine cocktail in accordance with WHO guidelines. The sensitivity of antivirals Oseltamivir and Zanamivir remains stable, aligning with WHO recommendations.
5. The DALY indicator for influenza over nine seasons showed a loss of 2,707.8 healthy life years due to premature mortality and disabilities, while the YLD for ARI and SARI accounted for a loss of 857.1 years. The economic impact of respiratory infections, calculated for the first time based

on the sentinel surveillance system (~981,000 individuals), amounted to 570.1 million MDL over two seasons, with 43.3% allocated to treatments, 23.9% to emergency medical care, and 21.7% to hospitalizations.

6. A dose of influenza vaccine costs 36.1% less than a medical consultation, 16.2 times less than the treatment of a child, 24.6 times less than that of an adult, and 34.4 times less than a day in intensive care. Vaccination is safe and cost-effective, significantly reducing medical expenses; however, additional efforts are needed to address challenges related to acceptance, logistics, and funding.

RECOMMENDATIONS

At the national level:

1. Strengthening the routine and sentinel surveillance, control, and response systems for influenza, ARI, and SARI, including with qualified medical staff, to efficiently detect seasonal variations and risk groups, aiming to improve prevention and control measures.
2. Developing of a national preparedness and response plan for pandemics caused by respiratory agents with pandemic potential.
3. Monitoring the implementation of regulatory acts regarding diagnosis, treatment, and epidemiological surveillance, ensuring compliance with national and international protocols on acute respiratory infections.
4. Surveilling influenza virus strain variations and epidemiological and virological records from the Republic of Moldova within the EpiPulse system to quantify national and international data, ensuring the sustainability of global seasonal epidemic response efforts.
5. Annually determining the eligible population for influenza vaccination within each risk group.

At the territorial level (Primary Healthcare, Public Health Centers):

1. Ensuring and complying with the collection of biological samples from patients with influenza, ARI, and SARI, according to the WHO and MoH – established algorithm, within the sentinel surveillance system.
2. Training, compliance, and implementation of the standard case definition for seasonal influenza according to WHO and MoH.

SUGGESTIONS FOR FUTURE RESEARCH

1. The research results facilitated the identification of vulnerable points in the public health service regarding epidemiological surveillance of influenza, ARI, and SARI.
2. The study assessed the economic impact of influenza and respiratory infections as an initial step, highlighting the need for further in-depth research.
3. Monitoring through molecular biology tests of the genotype and phenotype of influenza strains for the development of prevention, control, and response measures for respiratory infections.

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