scientific reports

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Systemic antiviral consumption in Kazakhstan

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There is a lack of studies from low- and middle-income countries on systemic antiviral consumption (SAC). This study aims to fill this gap by providing a comprehensive analysis of nationwide antiviral consumption trends in Kazakhstan over a period of 7 years. The defined daily doses per 1000 inhabitants per day approach was utilized. Time series analyses were applied to analyze historical trends in SAC, evaluate the impact of the coronavirus disease-19 (COVID-19) pandemic, and make future projections until 2030. The total SAC increased over the study period, with an annual growth rate of 10.24%. Overall, the antivirals that exhibited the most substantial increases in consumption after 2020 were anti-herpes, anti-HBV/HCV, and anti-influenza agents. Predictive modeling indicated that future expenditures on antivirals will remain stable in the hospital sector, both in absolute terms and per million population (pmp) rates, but are likely to increase in the community sector, both in absolute terms and pmp rates. The study's findings have important implications for public health policy and resource allocation.

Keywords Antiviral agents, Consumption, Antimicrobial stewardship, Time series, Kazakhstan

Abbreviations

AAPC	Annualized average percent change
AMR	Antimicrobial resistance
AMS	Antimicrobial stewardship
ATC	Anatomical Therapeutic Chemical Classification System
CI	Confidence interval
COVID-19	Coronavirus disease-19
DDD	Defined daily doses
GLASS-AMC	Global Antimicrobial Resistance and Use Surveillance System
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ITSA	Interrupted time series analysis
pmp	Per million population
SAC	Systemic antiviral consumption
SPSS	Statistical Package for Social Sciences
USD	United States dollars

Emergence and circulation of viral infections constitute a major public health challenge today. Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections are among the most significant contributors to this burden. Both viruses lead to chronic diseases that require long-term treatment and management, posing substantial health, social, and economic impacts globally[1]. Influenza and coronavirus disease-19 (COVID-19) viruses also represent significant public health threats, causing seasonal epidemics and global pandemics that strain healthcare systems and disrupt daily life[2]. The group of hemorrhagic fever viruses is another example of viral disorders that can cause severe outbreaks with high mortality rates, such as Ebola and Dengue[3]. Some viral disorders are vaccine-manageable, while others are not. Routine vaccination schedules in many countries around the globe include vaccines against viral diseases, which is a significant achievement of modern public

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health[4]. Unfortunately, vaccine hesitancy has become more prevalent in certain countries, providing a basis for viral outbreaks[5] and making antiviral therapy the only viable option for controlling these infections.

Antivirals belong to a class of antimicrobial agents and play an important role in the prevention and management of viral infections. The advent of antiviral therapies has significantly improved the prognosis and quality of life for individuals affected by viral diseases[6]. While antimicrobial resistance (AMR) is a natural phenomenon most commonly associated with antibacterial agents, resistance also develops against antivirals—potentially to an even greater extent—given the need for triple or quadruple drug combinations to prevent viral escape mutations[7]. Understanding antiviral consumption patterns is important not only for comprehending the emergence of AMR in relation to antivirals but also for optimizing their use in clinical practice. Monitoring and analyzing antiviral consumption helps in identifying trends and potential areas of misuse, guiding public health interventions, and ensuring the sustainability of antiviral therapies[8]. Furthermore, it provides insights into the effectiveness of public health policies and the impact of global events, such as the COVID-19 pandemic, on the use of these critical medications[9].

Globally, most studies investigating the volume of antiviral consumption come from high-income countries. There is a paucity of research coming from low- and middle-income countries, although they constitute a significant portion of antiviral consumption and significantly contribute to the emergence of AMR[10]. The Republic of Kazakhstan (hereafter referred to as Kazakhstan) is an upper-middle-income country located in Central Asia. The country gained independence in 1991, after the dissolution of the Soviet Union, and inherited the Soviet model of the healthcare system[11]. Kazakhstan launched the national action plan for AMR and antimicrobial stewardship (AMS) in 2017[12]. However, strategies directed at mitigating resistance to antibacterial agents received much of the attention, and there is a lack of focus on the rational use of antivirals. This study aims to fill this gap and evaluate the trends in antiviral consumption in Kazakhstan from 2017 to 2023. Specifically, the study aims to analyze data from both community and hospital sectors together and separately, providing a comprehensive overview of how antiviral use has evolved, particularly in response to the COVID-19 pandemic. Understanding these trends will inform public health strategies and policies aimed at optimizing antiviral use in Kazakhstan.

Methods

Study design and data sources

This study utilized a retrospective design and relied on data from the database developed and maintained by the pharmaceutical market research company "Vi-ORTIS". Vi-ORTIS aggregates and analyzes information on pharmaceutical products sold and distributed in Kazakhstan, encompassing both community and hospital sectors. For community pharmacy sales, Vi-ORTIS collects data from pharmaceutical suppliers and community pharmacies, covering more than 90% of these entities nationwide. The community sector encompasses all medications dispensed through community pharmacies, including both prescription and over-the-counter products. These medications are intended for outpatient use and are not administered within hospital facilities. For the hospital sector, data are sourced from "SK-Pharmacia," the national distributor of pharmaceuticals to hospital facilities. Antivirals distributed within the hospital sector are administered during inpatient care and are not intended for outpatient use.

Vi-ORTIS standardizes and validates pharmaceutical procurement and sales data, including returns and transfers between pharmacies and suppliers, through a multi-level validation process. The database is updated monthly and is accessible via a subscription-based web portal[13]. Vi-ORTIS data have been widely used in pharmaceutical market research and policy analysis[14].

For this study, data on antivirals for systemic use (J05 code of the Anatomical Therapeutic Chemical Classification System (ATC)) were extracted for the entire country from January 1, 2017, to December 31, 2023. Data were downloaded on both an annual and quarterly basis to facilitate various statistical analyses. Information on all systemic antivirals was extracted at the ATC level 5 (ATC5), including product name, active ingredient(s), dosage form, active ingredients per unit dose, route of administration, number of tablets/capsules/suspensions/ampoules/vials per package, the number of packages sold, and price.

In addition to the Vi-ORTIS database, this study relied on several other information sources. To evaluate antiviral consumption, data on the population size in Kazakhstan during different time periods were extracted from the annual demographic yearbooks issued by the Bureau of National Statistics[15]. To convert the price of antivirals from the national currency, the Kazakhstani Tenge, to United States dollars (USD), the web portal of the National Bank of Kazakhstan[16] was consulted to retrieve the official exchange rates.

Evaluation of antiviral consumption

To evaluate nationwide antiviral consumption rates, the Excel template from the Global Antimicrobial Resistance and Use Surveillance System (GLASS-AMC) was employed. This template facilitates the organization of data on antiviral consumption and the calculation of consumption rates using the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) methodology. All data extracted from the Vi-ORTIS database were entered into this template, allowing the generation of metrics on antiviral consumption. During data entry and analysis, the guidelines from the GLASS Manual on the management of antimicrobial consumption data were followed[17]. DDD per 1,000 inhabitants per day were calculated for each ATC level 5 (ATC5) code of antiviral and for the J05 category overall. All systemic antivirals retrieved from the Vi-ORTIS database fell within the J05A category (direct-acting antivirals). During the period from 2017 to 2023, the following J05A codes were used in Kazakhstan:

- J05AB (nucleosides and nucleotides excluding reverse transcriptase inhibitors).
- J05AC (cyclic amines).

- J05AE (protease inhibitors).
- J05AF (nucleoside and nucleotide reverse-transcriptase inhibitors).
- J05AG (non-nucleoside reverse-transcriptase inhibitors).
- J05AH (neuraminidase inhibitors).
- J05AJ (integrase inhibitors).
- J05AP (antivirals for treatment of HCV infections).
- J05AR (antivirals for treatment of HIV infections, combinations).
- J05AX (other antivirals)[18].

The total consumption, expressed as DDD per 1,000 inhabitants per day[19], was calculated for each pharmacological group, enabling their ranking.

Evaluation of viral disease prevalence

Data on the prevalence of the most common viral diseases in Kazakhstan—namely influenza, HIV, and viral hepatitis B (HBV) and C (HCV)—were extracted from the statistical compilation issued by the Ministry of Health. For HBV, only data corresponding to the ICD-10 code B18.1 (chronic hepatitis B without delta-agent) were included, as this condition is treated with antiviral therapy. Data on the prevalence of COVID-19 were excluded, as it is not officially reported in Kazakhstan[20].

Data analysis

The DDD per 1,000 inhabitants per day for each ATC5 category and each year were entered into IBM SPSS Statistics for Windows, Version 24.0 (Armonk, NY). Given the time series nature of the data, the Forecasting module was utilized for analysis. The annualized average percent change (AAPC) for the period 2017–2023 was calculated and presented as a percentage with a 95% confidence interval (CI), facilitating the evaluation of past trends in antiviral consumption.

The "Expert Modeler" function was employed to perform the forecasting analysis for the four major pharmacological groups of antivirals in terms of consumption rates and for the expenditure on antivirals in both the hospital and community sectors, expressed in absolute numbers and per million population (pmp). This process involved identifying the best-fit epidemiological models for each pharmacological group and projecting total consumption and expenditure for each group up to 2030.

To evaluate the impact of the COVID-19 pandemic on the consumption of the J05 group across total, community, and hospital sectors, as well as each ATC5 code, interrupted time series analysis (ITSA) was utilized with the third quarter (Q3) of 2020 serving as the intervention point. The "Expert Modeler" function was used to identify the best-fit epidemiological model for each antiviral category. A significance level of $p < 0.05$ was used to determine which ATC5 categories to present, with only those reaching statistical significance being included in the final results.

Ethics statement

The study protocol (submission 802/23112023) was reviewed by the Nazarbayev University Institutional Research Ethics Committee (NU-IREC), which granted exempt status on December 1, 2023. Due to the retrospective nature of the study, NU-IREC waived the need of obtaining informed consent. The study was performed in accordance with the Declaration of Helsinki.

Results

The total consumption of antivirals increased from 2017 to 2023, with an annualized average percent change of 10.24%. The highest level of consumption was recorded in 2020, reaching 3.58816 DDD per 1,000 inhabitants per day. The most significant AAPC was observed for famciclovir (77.8%, $p = 0.004$), followed by darunavir (76.23%, $p = 0.023$), and etravirine (56.93%, $p = 0.035$). Conversely, the consumption of several antivirals showed a declining trend, with the most pronounced decrease observed for nevirapine (-62.53%, $p = 0.031$), followed by lopinavir and ritonavir (-40.74%, $p = 0.001$), and abacavir (-24.74%, $p = 0.127$) (Table 1).

The AAPC in the community sector was 15.93%, with antiviral consumption peaking in 2020 at 1.929 DDD per 1,000 inhabitants. Valganciclovir demonstrated the highest annual growth rate (AAPC = 113.78%, $p \leq 0.001$), followed by famciclovir (77.44%, $p = 0.004$) and oseltamivir (59.16%, $p = 0.005$). Overall, the antivirals that exhibited the most substantial increases in consumption after 2020 were anti-herpes, anti-HBV/HCV, and anti-influenza agents. Despite the general upward trend, some antivirals—such as ribavirin—showed a decline in use (AAPC=-28.17%, $p = 0.163$) during the same period (Table 2).

Unlike the community sector, the hospital sector exhibited a more modest growth in antiviral consumption, averaging 6.10% per annum. Hospital consumption peaked earlier, in 2019, reaching 2.21306 DDD per 1,000 inhabitants per day. The most significant growth was seen for tilorone (AAPC = 83.75%, $p \leq 0.001$), followed by darunavir (AAPC = 76.23%, $p = 0.023$) and etravirine (AAPC = 56.98%, $p = 0.035$). Similar to the community sector, the hospital sector also saw a decline in the use of certain antivirals, with nevirapine (AAPC=– 62.53%, $p = 0.031$) and lopinavir and ritonavir (AAPC=– 40.83%, $p = 0.001$) showing the most substantial decreases (Table 3).

Figure 1 illustrates total antiviral consumption, as well as consumption at the community and hospital levels, from 2017 to 2023, disaggregated by quarters. Overall, antiviral consumption fluctuated during this period, with peaks in total and community consumption occurring in the third quarter of 2020, corresponding to the first wave of COVID-19 in the country[21]. Since antiviral consumption in the hospital sector exceeded that in the community sector, total antiviral consumption predominantly mirrored hospital consumption. However, an exception was noted in the third quarter of 2020, when total consumption mirrored community consumption.

ATC5* code	Substance	Year							Annualized average percent change (95% CI**, *p*-value)
		2017	2018	2019	2020	2021	2022	2023	
J05AF06	Abacavir	0.01886	0.02599	0.00857	0.00229	0.00199	0.00128	0.01610	− 24.74% (− 57.33; 32.72%, $p = 0.127$)
J05AB01	Aciclovir	0.19082	0.22818	0.23125	0.31082	0.30750	0.29021	0.28757	7.39% (1.54; 13.57%, $p = 0.011$)
J05AF08	Adefovir dipivoxil	0.00000	0.00000	0.00000	0.00000	0.00055	0.00120	0.00175	–
J05AP07	Daclatasvir	0.00000	0.00000	0.00000	0.00250	0.00265	0.00000	0.00038	–
J05AE10	Darunavir	0.00073	0.02221	0.03788	0.04927	0.05041	0.05857	0.06909	76.23% (1.86; 204.90%, $p = 0.023$)
J05AJ03	Dolutegravir	0.00028	0.06394	0.11835	0.11962	0.20521	0.01021	0.00930	30.39% (− 60.54; 330.85%, $p = 0.236$)
J05AG03	Efavirenz	0.14320	0.10080	0.43755	0.47723	0.55845	0.50774	0.53605	30.42% (4.50; 62.78%, $p = 0.014$)
J05AF09	Emtricitabine	0.00000	0.00000	0.01417	0.02615	0.04063	0.03945	0.04066	28.65% (− 1.16; 67.46%, $p = 0.028$)
J05AX17	Enisamium iodide	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AF10	Entecavir	0.00000	0.00000	0.00085	0.00636	0.00721	0.00500	0.00843	54.36% (− 26.37; 223.63%, $p = 0.080$)
J05AG04	Etravirine	0.00052	0.01213	0.01497	0.02001	0.02035	0.02225	0.02105	56.93% (− 5.15; 159.64%, $p = 0.035$)
J05AB09	Famciclovir	0.00012	0.00042	0.00294	0.00165	0.00286	0.00470	0.00511	77.8% (26.05; 150.81%, $p = 0.004$)
J05AX27	Favipiravir	0.00000	0.00000	0.00000	0.01628	0.00180	0.00037	0.00000	–
J05AB06	Ganciclovir	0.00000	0.00000	0.00000	0.00000	0.00001	0.00000	0.00023	–
J05AX05	Inosine pranobex	0.15745	0.20471	0.22664	0.35325	0.45387	0.52484	0.49095	23.85% (15.71; 32.56%, $p \leq 0.001$)
J05AF05	Lamivudine	0.12673	0.18645	0.36270	0.16190	0.16187	0.11048	0.05745	− 14.01% (− 32.48; 9.51%, $p = 0.085$)
J05AR10	Lopinavir and ritonavir	0.12534	0.10421	0.10672	0.07498	0.02501	0.01455	0.00572	− 40.74% (− 51.93; − 26.94%, $p = 0.001$)
J05AG01	Nevirapine	0.08525	0.04412	0.04047	0.02313	0.00087	0.00000	0.00000	− 62.53% (− 87.23; 9.96%, $p = 0.031$)
J05AH02	Oseltamivir	0.03929	0.04910	0.05836	0.25356	0.14488	0.26774	0.19978	38.80% (11.45; 72.87%, $p = 0.006$)
J05AX21	Pentanedioic acid imidazolyl ethanamide	0.12011	0.12670	0.10313	0.46081	0.39410	0.36580	0.31659	25.54% (0.35; 57.05%, $p = 0.024$)
J05AB16	Remdesivir	0.00000	0.00000	0.00000	0.00439	0.05272	0.00904	0.00420	− 17.29% (− 94.49; 1140.61%, $p = 0.396$)
J05AP01	Ribavirin	0.00525	0.01006	0.01345	0.01031	0.00789	0.00559	0.00561	− 5.25% (− 21.34; 14.12%, $p = 0.245$)
J05AC02	Rimantadine	0.20470	0.18193	0.19395	0.36079	0.25624	0.22892	0.13421	− 1.87% (− 16.54; 15.38%, $p = 0.388$)
J05AE03	Ritonavir	0.00085	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AP08	Sofosbuvir	0.00000	0.06891	0.22921	0.11222	0.10978	0.08594	0.13582	1.23% (− 25.45; 37.46%, $p = 0.459$)
J05AF11	Telbivudine	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AF13	Tenofovir alafenamide	0.00000	0.00000	0.00000	0.00000	0.00006	0.00187	0.00385	–
J05AF07	Tenofovir disoproxil	0.36537	0.73266	0.70480	0.42679	0.43065	0.54189	0.93042	6.29% (− 10.23; 25.85%, $p = 0.198$)
J05AX19	Tilorone	0.06382	0.07371	0.05954	0.11228	0.05471	0.05505	0.06601	− 2.01% (− 13.98; 11.64%, $p = 0.353$)
J05AX13	Umifenovir	0.07156	0.07323	0.04281	0.14440	0.15417	0.14656	0.12581	16.86% (− 3.42; 41.39%, $p = 0.045$)
J05AB11	Valaciclovir	0.01192	0.01604	0.01781	0.01955	0.02255	0.08333	0.03234	26.25% (2.71; 55.18%, $p = 0.017$)
J05AB14	Valganciclovir	0.00838	0.00032	0.00090	0.00170	0.00395	0.00707	0.01111	35.48% (− 25.89; 147.66%, $p = 0.126$)
J05AF01	Zidovudine	0.15266	0.07562	0.07547	0.03592	0.03895	0.05744	0.03003	− 19.55% (− 31.75; − 5.17%, $p = 0.010$)
Total		1.89322	2.40145	3.10249	3.58816	3.51194	3.44710	3.54564	10.24% (2.90; 18.10%, $p = 0.007$)

Table 1. Total consumption of antivirals in defined daily doses (DDD) per 1,000 inhabitants per day. *Anatomical Therapeutic Chemical Classification, level 5. **95% confidence interval.

According to the ITSA, total antiviral consumption increased by 0.977 defined daily doses (DDD) per 1,000 inhabitants beginning in the third quarter of 2020, compared to the period from 2017 to the second quarter of 2020. This increase was more pronounced in the community sector, which saw a rise of 0.834 DDD per 1,000 inhabitants, compared to a more modest increase of 0.250 DDD per 1,000 inhabitants in the hospital sector. The most substantial change in antiviral consumption was observed for valganciclovir, which increased by 0.585 DDD per 1,000 inhabitants, followed by pentanedioic acid imidazolyl ethanamide and oseltamivir, with increases of 0.264 and 0.255 DDD per 1,000 inhabitants, respectively. In contrast, beginning in the third quarter of 2020, the consumption of certain antivirals—notably lamivudine and nevirapine—declined significantly, by 0.120 and 0.040 DDD per 1,000 inhabitants, respectively (Table 4).

Based on DDD per 1,000 inhabitants per day, four pharmacological groups of antivirals had the highest levels of total consumption over the period from 2017 to 2023: nucleosides and nucleotides excluding reverse transcriptase inhibitors, nucleoside and nucleotide reverse-transcriptase inhibitors, non-nucleoside reverse-transcriptase inhibitors, and other antivirals. Predictive modeling extending to 2030 indicates that the total consumption of nucleosides and nucleotides excluding reverse transcriptase inhibitors is projected to decline. In contrast, the consumption of nucleoside and nucleotide reverse-transcriptase inhibitors is expected to remain unchanged, while the use of non-nucleoside reverse-transcriptase inhibitors and other antivirals is anticipated to increase (Table 5).

Figure 2 visualizes the data presented in Table 5, depicting both observed and projected consumption rates of the major pharmacological groups of antivirals in Kazakhstan through 2030.

ATC5* code	Substance	Year							Annualized average percent change (95% CI**, *p*-value)
		2017	2018	2019	2020	2021	2022	2023	
J05AF06	Abacavir	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AB01	Aciclovir	0.18072	0.21685	0.21960	0.28302	0.28645	0.27975	0.27785	7.66% (2.77; 12.77%, $p=0.005$)
J05AF08	Adefovir dipivoxil	0.00000	0.00000	0.00000	0.00000	0.00055	0.00120	0.00175	–
J05AP07	Daclatasvir	0.00000	0.00000	0.00000	0.00250	0.00265	0.00000	0.00038	–
J05AE10	Darunavir	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AJ03	Dolutegravir	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AG03	Efavirenz	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AF09	Emtricitabine	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AX17	Enisamium iodide	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AF10	Entecavir	0.00000	0.00000	0.00085	0.00636	0.00721	0.00500	0.00842	54.43% (− 26.42; 224.11%, $p=0.080$)
J05AG04	Etravirine	0.00000	0.00006	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AB09	Famciclovir	0.00012	0.00042	0.00294	0.00165	0.00286	0.00470	0.00511	77.44% (26.06; 149.76%, $p=0.004$)
J05AX27	Favipiravir	0.00000	0.00000	0.00000	0.00360	0.00152	0.00037	0.00000	–
J05AB06	Ganciclovir	0.00000	0.00000	0.00000	0.00000	0.00001	0.00000	0.00023	–
J05AX05	Inosine pranobex	0.15712	0.20431	0.22606	0.35101	0.45322	0.52398	0.48981	23.85% (15.73; 32.55%, $p\leq0.001$)
J05AF05	Lamivudine	0.00048	0.00007	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AR10	Lopinavir and ritonavir	0.00000	0.00000	0.00000	0.00027	0.00060	0.00014	0.00000	–
J05AG01	Nevirapine	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AH02	Oseltamivir	0.01458	0.02108	0.02908	0.20493	0.08496	0.22257	0.16213	59.16% (18.54; 113.70%, $p=0.005$)
J05AX21	Pentanedioic acid imidazolyl ethanamide	0.11986	0.12325	0.10264	0.44629	0.39079	0.36386	0.31365	25.63% (0.74; 56.66%, $p=0.023$)
J05AB16	Remdesivir	0.00000	0.00000	0.00000	0.00187	0.00702	0.00028	0.00420	− 7.64% (− 96.59; 2400.17%, $p=0.464$)
J05AP01	Ribavirin	0.00065	0.00009	0.00001	0.00028	0.00026	0.00009	0.00001	− 28.17% (− 67.09; 56.75%, $p=0.163$)
J05AC02	Rimantadine	0.20210	0.18119	0.18977	0.35796	0.25291	0.22305	0.13165	− 2.06% (− 16.78; 15.26%, $p=0.378$)
J05AE03	Ritonavir	0.00008	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AP08	Sofosbuvir	0.00000	0.00000	0.00000	0.00243	0.00371	0.00622	0.00822	51.78% (31.99; 74.54%, $p=0.003$)
J05AF11	Telbivudine	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AF13	Tenofovir alafenamide	0.00000	0.00000	0.00000	0.00000	0.00006	0.00187	0.00384	–
J05AF07	Tenofovir disoproxil	0.00090	0.00336	0.00273	0.00026	0.00041	0.00048	0.00037	− 26.06% (− 50.98; 11.53%, $p=0.059$)
J05AX19	Tilorone	0.06360	0.07317	0.05881	0.11068	0.05171	0.04994	0.05722	− 4.23% (− 16.41; 9.73%, $p=0.226$)
J05AX13	Umifenovir	0.07144	0.07301	0.04227	0.14297	0.15394	0.14631	0.12531	16.88% (− 3.52; 41.60%, $p=0.045$)
J05AB11	Valaciclovir	0.01144	0.01364	0.01443	0.01573	0.01980	0.02231	0.03031	16.28% (12.01; 20.72%, $p\leq0.001$)
J05AB14	Valganciclovir	0.00023	0.00020	0.00024	0.00122	0.00374	0.00661	0.01074	113.78% (65.71; 175.78%, $p\leq0.001$)
J05AF01	Zidovudine	0.00000	0.00001	0.00001	0.00000	0.00000	0.00000	0.00000	–
Total		**0.82335**	**0.91072**	**0.88942**	**1.92943**	**1.72287**	**1.85836**	**1.63120**	**15.93% (3.31; 30.09%, p = 0.011)**

Table 2. Consumption of antivirals in defined daily doses (DDD) per 1,000 inhabitants per day in the community sector. *Anatomical Therapeutic Chemical Classification, level 5. **95% confidence interval.

According to Fig. 3, during the period 2017–2023, the prevalence of HIV and influenza infections remained largely stable, with AAPC of 3.17% and − 2.63%, respectively. In contrast, the prevalence of HBV and HCV increased substantially, with AAPC of 23.29% and 32.98%, respectively.

Hospital sector expenditure on antivirals peaked in 2021, both in absolute and per capita terms, at 31,418,027.2 USD and 1,664,130.0 USD, respectively. In contrast, community sector expenditure on antivirals peaked in 2020, with 24,644,451.0 USD in absolute terms and 1,322,711.0 USD in per capita rates. Reflecting consumption rates, hospital sector expenditure on antivirals exceeded that of the community sector. By 2030, hospital sector expenditure on antivirals is projected to be 21,372,257.6 USD in absolute terms and 1,136,783.4 USD in per capita rates. Meanwhile, community sector expenditure is projected to reach 38,552,192.1 USD in absolute terms and 1,893,584.2 USD in per capita rates, surpassing that of the hospital sector (Table 6).

As illustrated in Fig. 4, the projected expenditure on antivirals in the community sector is expected to grow, both in absolute numbers and per capita terms. In contrast, the expenditure in the hospital sector is projected to remain stable.

Discussion

This study aimed to evaluate the trends in antiviral consumption in Kazakhstan from 2017 to 2023, both in total and disaggregated by community and hospital sectors. The specific sub-aims included analyzing the impact of the COVID-19 pandemic on antiviral consumption, including separate ATC5 categories, and modeling the projected antiviral consumption rates up to 2030 by major pharmacological groups. Additionally, the study aimed

ATC5* code	Substance	Year							Annualized average percent change (95% CI**, *p*-value)
		2017	2018	2019	2020	2021	2022	2023	
J05AF06	Abacavir	0.01886	0.02599	0.00857	0.00229	0.00199	0.00128	0.01610	− 24.74% (− 57.33; 32.72%, $p = 0.127$)
J05AB01	Aciclovir	0.01010	0.01133	0.01165	0.02780	0.02104	0.01046	0.00972	1.13% (− 18.83; 26.00%, $p = 0.450$)
J05AF08	Adefovir dipivoxil	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AP07	Daclatasvir	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AE10	Darunavir	0.00073	0.02221	0.03788	0.04927	0.05041	0.05857	0.06909	76.23% (1.86; 204.90%, $p = 0.023$)
J05AJ03	Dolutegravir	0.00028	0.06394	0.11835	0.11962	0.20521	0.01021	0.00930	30.39% (− 60.54; 330.85%, $p = 0.296$)
J05AG03	Efavirenz	0.14320	0.10080	0.43755	0.47723	0.55845	0.50774	0.53605	30.42% (4.50; 62.78%, $p = 0.014$)
J05AF09	Emtricitabine	0.00000	0.00000	0.01417	0.02615	0.04063	0.03945	0.04066	28.65% (− 1.16; 67.46%, $p = 0.025$)
J05AX17	Enisamium iodide	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AF10	Entecavir	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AG04	Etravirine	0.00052	0.01207	0.01497	0.02001	0.02035	0.02225	0.02105	56.98% (− 5.08; 159.62%, $p = 0.035$)
J05AB09	Famciclovir	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AX27	Favipiravir	0.00000	0.00000	0.00000	0.01268	0.00028	0.00000	0.00000	–
J05AB06	Ganciclovir	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AX05	Inosine pranobex	0.00033	0.00040	0.00058	0.00224	0.00065	0.00086	0.00115	21.38% (− 7.10; 58.59%, $p = 0.061$)
J05AF05	Lamivudine	0.12625	0.18637	0.36270	0.16190	0.16187	0.11048	0.05745	− 13.97% (− 32.48; 9.60%, $p = 0.086$)
J05AR10	Lopinavir and ritonavir	0.12534	0.10421	0.10672	0.07471	0.02441	0.01441	0.00572	− 40.83% (− 51.98; − 27.09%, $p = 0.001$)
J05AG01	Nevirapine	0.08525	0.04412	0.04047	0.02313	0.00087	0.00000	0.00000	− 62.53% (− 87.23; 9.96%, $p = 0.031$)
J05AH02	Oseltamivir	0.02471	0.02802	0.02927	0.04862	0.05992	0.04517	0.03765	11.05% (− 2.05; 25.91%, $p = 0.042$)
J05AX21	Pentanedioic acid imidazolyl ethanamide	0.00025	0.00346	0.00050	0.01452	0.00331	0.00194	0.00294	33.97% (− 29.07; 153.06%, $p = 0.145$)
J05AB16	Remdesivir	0.00000	0.00000	0.00000	0.00252	0.04570	0.00876	0.00000	–
J05AP01	Ribavirin	0.00460	0.00996	0.01344	0.01004	0.00763	0.00550	0.00559	− 4.08% (− 21.74; 17.57%, $p = 0.311$)
J05AC02	Rimantadine	0.00260	0.00074	0.00418	0.00283	0.00333	0.00588	0.00256	14.82% (− 15.43; 55.89%, $p = 0.149$)
J05AE03	Ritonavir	0.00077	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AP08	Sofosbuvir	0.00000	0.06891	0.22921	0.10979	0.10606	0.07972	0.12760	− 0.35% (− 27.05; 36.13%, $p = 0.488$)
J05AF11	Telbivudine	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	–
J05AF13	Tenofovir alafenamide	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001	–
J05AF07	Tenofovir disoproxil	0.36447	0.72929	0.70208	0.42653	0.43025	0.54141	0.93005	6.35% (− 10.13; 25.86%, $p = 0.195$)
J05AX19	Tilorone	0.00022	0.00054	0.00074	0.00160	0.00300	0.00511	0.00880	83.75% (73.18; 94.96%, $p \leq 0.001$)
J05AX13	Umifenovir	0.00011	0.00022	0.00055	0.00143	0.00024	0.00025	0.00051	15.14% (− 23.41; 73.08%, $p = 0.207$)
J05AB11	Valaciclovir	0.00048	0.00240	0.00338	0.00383	0.00275	0.06101	0.00203	46.01% (− 22.81; 176.19%, $p = 0.094$)
J05AB14	Valganciclovir	0.00815	0.00013	0.00066	0.00048	0.00021	0.00046	0.00037	− 24.49% (− 59.79; 41.80%, $p = 0.152$)
J05AF01	Zidovudine	0.15266	0.07560	0.07546	0.03592	0.03895	0.05744	0.03003	− 19.54% (− 31.74; − 5.16%, $p = 0.010$)
Total		1.06987	1.49073	2.21306	1.64245	1.78726	1.58838	1.91444	6.10% (− 4.07; 17.36%, p = 0.096)

Table 3. Consumption of antivirals in defined daily doses (DDD) per 1,000 inhabitants per day in the hospital sector. *Anatomical Therapeutic Chemical Classification, level 5. **95% confidence interval.

to forecast expenditure rates on antivirals in both hospital and community sectors until 2030. The major finding of this study is that the rate of antiviral consumption, expressed in DDD per 1,000 inhabitants per day, increased over the study period, with a total AAPC of 10.24%. The COVID-19 pandemic had a significant impact on antiviral consumption, with a more pronounced effect in the community sector. Predictive modeling indicated a future decline in the total consumption of nucleosides and nucleotides excluding reverse transcriptase inhibitors, while the consumption of non-nucleoside reverse-transcriptase inhibitors and other antivirals is expected to grow. Furthermore, predictive modeling showed that future expenditures on antivirals will remain stable in the hospital sector, both in absolute terms and pmp rates, but are likely to increase in the community sector, both in absolute terms and pmp rates. The findings of this study warrant a detailed discussion to understand their implications and to inform future health policies and resource allocation strategies in Kazakhstan.

The significant rise in antiviral consumption observed during the COVID-19 pandemic reflects the responsiveness of the healthcare system to the challenges posed by the pandemic. The surge in consumption, especially in 2020, suggests two possibilities: effective mobilization of resources to combat the pandemic and irrational use of antivirals during this viral outbreak. Both options need to be considered.

To support the first assumption, several observations can be made. The emergence of COVID-19 in Kazakhstan resulted in the rapid development of national standards of care as early as February 2020, which were revised more than ten times as the outbreak progressed and new scientific evidence emerged. According to these standards, two antivirals (remdesivir and favipiravir) were indicated for the treatment of COVID-19 at the hospital level, and no antiviral was recommended for COVID-19 management at the community level[22]. It

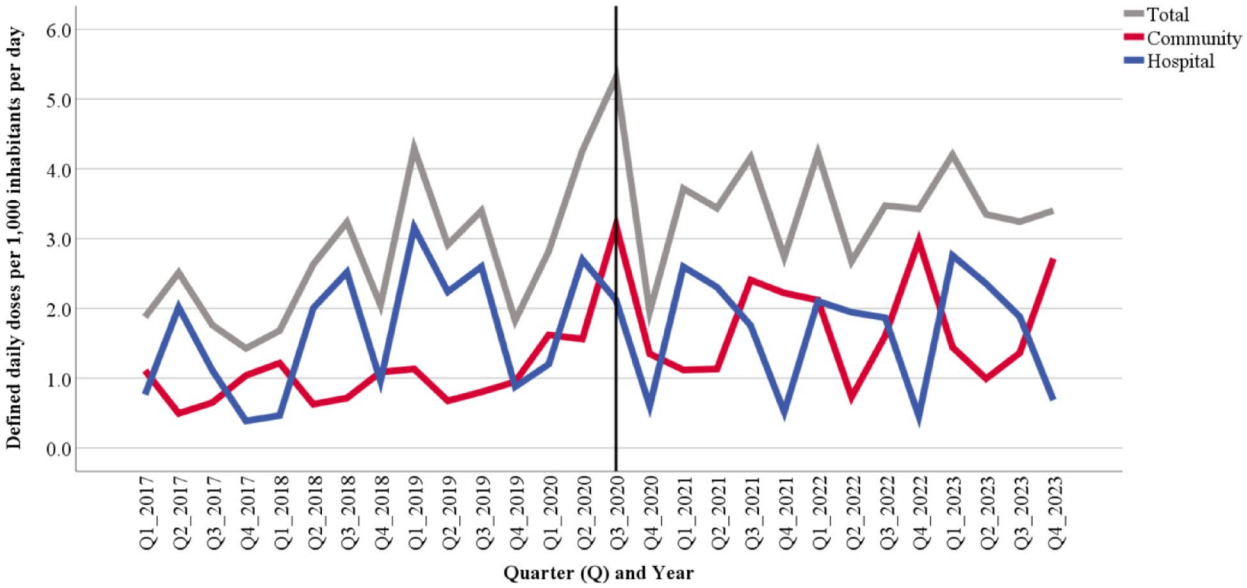

Fig. 1. Antiviral consumption expressed in defined daily doses per 1,000 inhabitants per day, disaggregated by quarter from 2017 to 2023. The black vertical line indicates the intervention point, marking the first wave of COVID-19 in the third quarter of 2020.

Consumption		Model	Estimate	*P*-value
Total		Winter's additive	0.977	≤0.001
Community		ARIMA 0.0.0	0.834	0.001
Hospital		ARIMA 0.0.0	0.250	0.023
Total consumption of selected antivirals				
J05AB09	Famciclovir	Simple	0.003	≤0.001
J05AB11	Valaciclovir	Simple seasonal	0.027	0.002
J05AB14	Valganciclovir	ARIMA 0.1.1	0.585	0.002
J05AE10	Darunavir	ARIMA 0.0.0	0.031	0.030
J05AF05	Lamivudine	ARIMA 0.0.0	− 0.120	0.038
J05AF09	Emtricitabine	ARIMA 0.0.0	0.017	0.013
J05AF10	Entecavir	ARIMA 0.1.0	0.006	0.003
J05AG01	Nevirapine	ARIMA 0.0.1	− 0.040	0.014
J05AG04	Etravirine	Winter's additive	0.012	0.001
J05AH02	Oseltamivir	ARIMA 0.0.0	0.255	≤0.001
J05AP07	Daclatasvir	Simple	0.001	0.025
J05AX21	Pentanedioic acid imidazolyl ethanamide	ARIMA 0.0.0	0.264	0.001

Table 4. Interrupted time series analysis of the impact of the COVID-19 pandemic on antiviral consumption in Kazakhstan, expressed in defined daily doses (DDD) per 1,000 inhabitants per day.

is noteworthy that before 2020, neither remdesivir nor favipiravir was available in the country, and the Ministry of Health took rapid measures to certify them for use against COVID-19[23]. The earlier versions of the national standards of care included the use of lopinavir and ritonavir against COVID-19, which were later excluded as international randomized controlled trials demonstrated their ineffectiveness[24].

ITSA indicated that the consumption of remdesivir, favipiravir, lopinavir, and ritonavir did not significantly increase after the third quarter of 2020. Additionally, the peak of antiviral consumption in the hospital sector occurred in 2019, making the second assumption—that the consumption of antivirals was likely influenced by their irrational use—more plausible. This is further supported by the fact that the peak of community consumption occurred in 2020 and that community consumption of antivirals increased by 0.834 DDD per 1,000 inhabitants per day starting in the third quarter of 2020, which was significant ($p = 0.001$). This observation emphasizes the need for public health campaigns educating healthcare providers and the general public about the appropriate use of antivirals, especially during public health crises[9].

Kazakhstan has ambitious plans for the development of its pharmaceutical industry, aiming to have local pharmaceutical companies manufacture half of all medications consumed in the country by 2025. These plans

Year		Pharmacological group			
		Nucleosides and nucleotides excluding reverse transcriptase inhibitors, DID*	Nucleoside and nucleotide reverse-transcriptase inhibitors, DID*	Non-nucleoside reverse-transcriptase inhibitors, DID*	Other antivirals, DID*
Observed	2017	0.211241	0.663627	0.228974	0.412931
	2018	0.244962	1.020713	0.157051	0.478352
	2019	0.252897	1.166557	0.492996	0.432130
	2020	0.338107	0.659418	0.520373	1.087011
	2021	0.389597	0.681926	0.579673	1.058658
	2022	0.394353	0.758610	0.529991	1.092614
	2023	0.340558	1.088690	0.557105	0.999362
Projected	2024	0.288413	0.888818	0.686917	1.290824
	2025	0.236257	0.888818	0.751807	1.419895
	2026	0.184100	0.888818	0.816697	1.548966
	2027	0.131944	0.888818	0.881587	1.678038
	2028	0.079787	0.888818	0.946477	1.807109
	2029	0.027631	0.888818	1.011367	1.936180
	2030	− 0.024526	0.888818	1.076257	2.065251
	Model parameters	Brown, $p = 0.003$	Simple, $p = 0.373$	Holt, $p = 0.431$	Holt, $p = 0.354$

Table 5. Observed and projected consumption rates of major pharmacological groups of antivirals in Kazakhstan, expressed in defined daily doses (DDD) per 1,000 inhabitants per day, until 2030. *Defined daily doses per 1,000 inhabitants per day

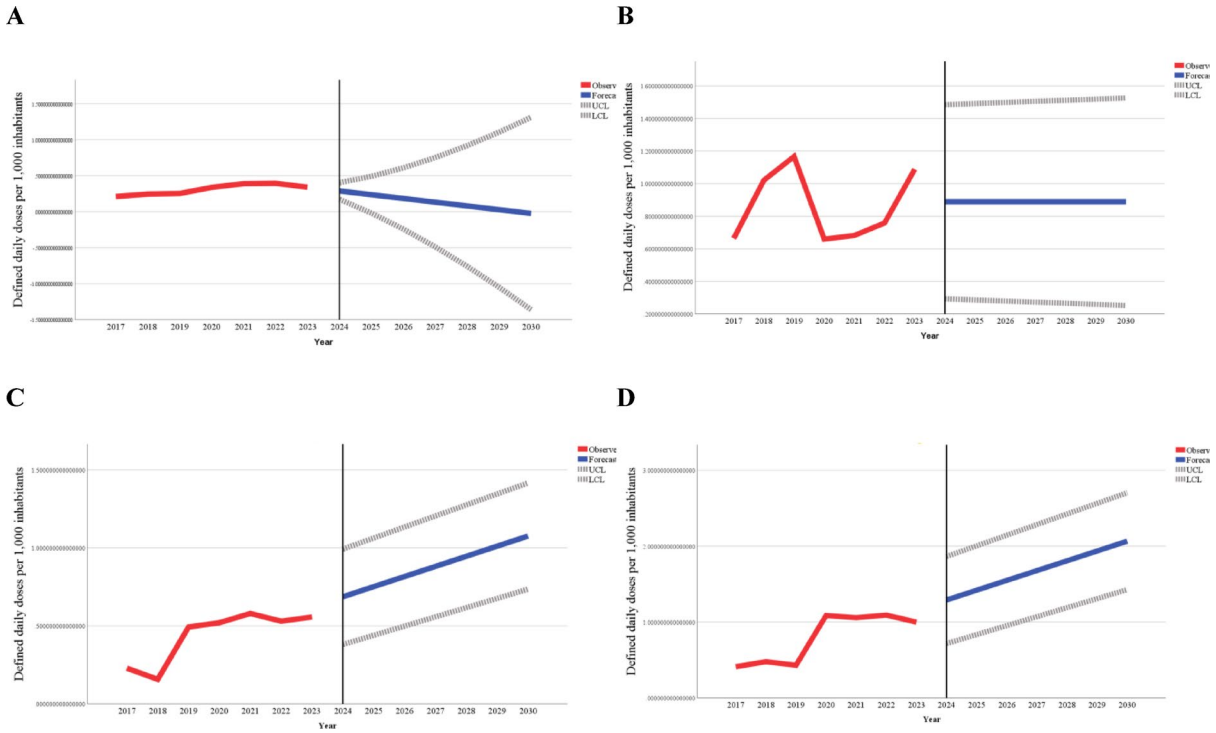

Fig. 2. The observed and projected consumption rates of major pharmacological groups of antivirals in Kazakhstan—nucleosides and nucleotides excluding reverse transcriptase inhibitors (**A**), nucleoside and nucleotide reverse-transcriptase inhibitors (**B**), non-nucleoside reverse-transcriptase inhibitors (**C**), and other antivirals (**D**)—until 2030.

reflect a strategic decision to reduce dependency on international pharmaceutical companies and meet internal market needs through local production[25]. Forecast modeling has provided insights into which classes of antivirals will be increasingly needed in the near future. Generally, our forecasts indicate that the consumption of nucleosides and nucleotides, excluding reverse transcriptase inhibitors, is likely to decrease by 2030. In the Kazakhstani

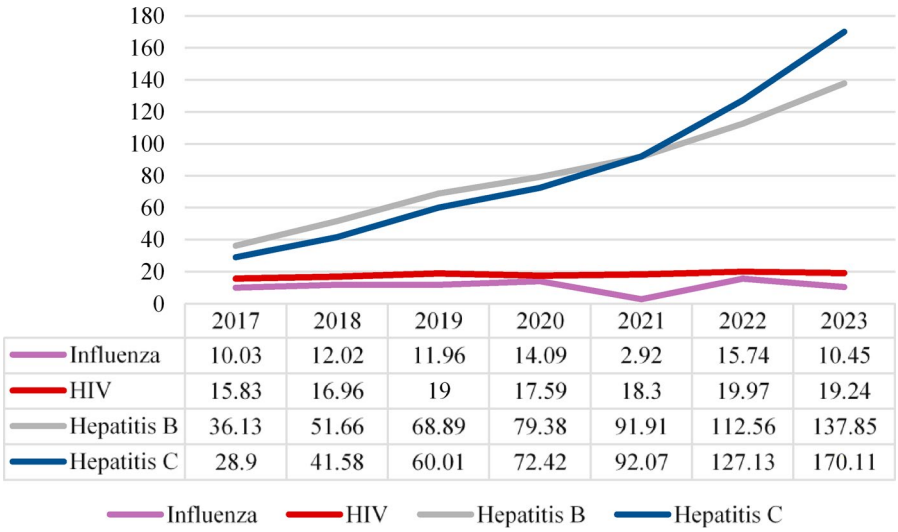

Fig. 3. Prevalence rate of the commonest types of viral infections in Kazakhstan, 2017–2023.

Year		Expenditure			
		Hospital expenditure, absolute number	Hospital expenditure, pmp*	Community expenditure, absolute number	Community expenditure, pmp*
Observed	2017	19,498,024.6	1,088,168.0	13,061,458.0	728,948.6
	2018	16,044,260.5	883,624.1	13,284,625.0	731,639.5
	2019	19,053,892.4	1,035,787.0	10,946,213.0	595,046.2
	2020	17,274,779.2	927,167.5	24,644,451.0	1,322,711.0
	2021	31,418,027.2	1,664,130.0	22,844,151.0	1,209,994.0
	2022	22,585,076.7	1,158,021.0	21,246,560.0	1,089,391.0
	2023	23,731,743.0	1,200,586.0	22,816,890.0	1,154,303.0
Projected	2024	21,372,257.6	1,136,783.4	26,319,207.1	1,335,073.3
	2025	21,372,257.6	1,136,783.4	28,358,038.0	1,428,158.5
	2026	21,372,257.6	1,136,783.4	30,396,868.8	1,521,243.6
	2027	21,372,257.6	1,136,783.4	32,435,699.6	1,771,101.9
	2028	21,372,257.6	1,136,783.4	34,474,530.4	1,707,413.9
	2029	21,372,257.6	1,136,783.4	36,513,361.3	1,800,499.1
	2030	21,372,257.6	1,136,783.4	38,552,192.1	1,893,584.2
Model parameters		ARIMA (0.0.0), $p \leq 0.001$	Holt, $p \leq 0.001$	ARIMA (0.0.0), $p = 0.524$	Holt, $p = 0.543$

Table 6. Observed and projected expenditures on antivirals in the community and hospital sectors, in absolute numbers and per million population rates, expressed in United States dollars. *Per million population.

market, this group includes aciclovir, ganciclovir, famciclovir, valaciclovir, valganciclovir, and remdesivir. These medications are used for the treatment and prevention of herpes simplex virus (HSV), varicella-zoster virus, and cytomegalovirus infections[26], except for remdesivir, which was initially developed for Ebola virus treatment but later repurposed for severe COVID-19[27]. The projected decline in this pharmacological group is likely due to the decreased use of remdesivir, as the consumption of other antivirals in this group increased from 2017 to 2020.

The forecast modeling also indicates that the consumption of non-nucleoside reverse-transcriptase inhibitors is likely to grow by 2030. In Kazakhstan, this group includes nevirapine, efavirenz, and etravirine, which are integral components of antiretroviral therapy[28]. The observed and projected growth in the consumption of this pharmacological group is likely attributed to the increasing prevalence of HIV, projected to rise by 2030[29]. The group of other antivirals in Kazakhstan includes inosine pranobex, umifenovir, enisamium iodide, tilorone, pentanedioic acid imidazolyl ethanamide, and favipiravir. The consumption of this group is also projected to grow. These medications are used for treating various viral disorders, including influenza, acute respiratory viral infections, and HSV infections[30]. The climate of Kazakhstan, with long cold winters in the north and moderately cold rainy winters in the south, contributes to the common circulation of viral respiratory tract infections[31]. This climatic factor helps explain why the consumption of this group of antivirals is likely to grow until 2030.

Forecast modeling also predicted the expected growth of expenditure on antivirals in the community sector, expressed in both absolute numbers and per capita rates. This projected growth likely mirrors the increase in

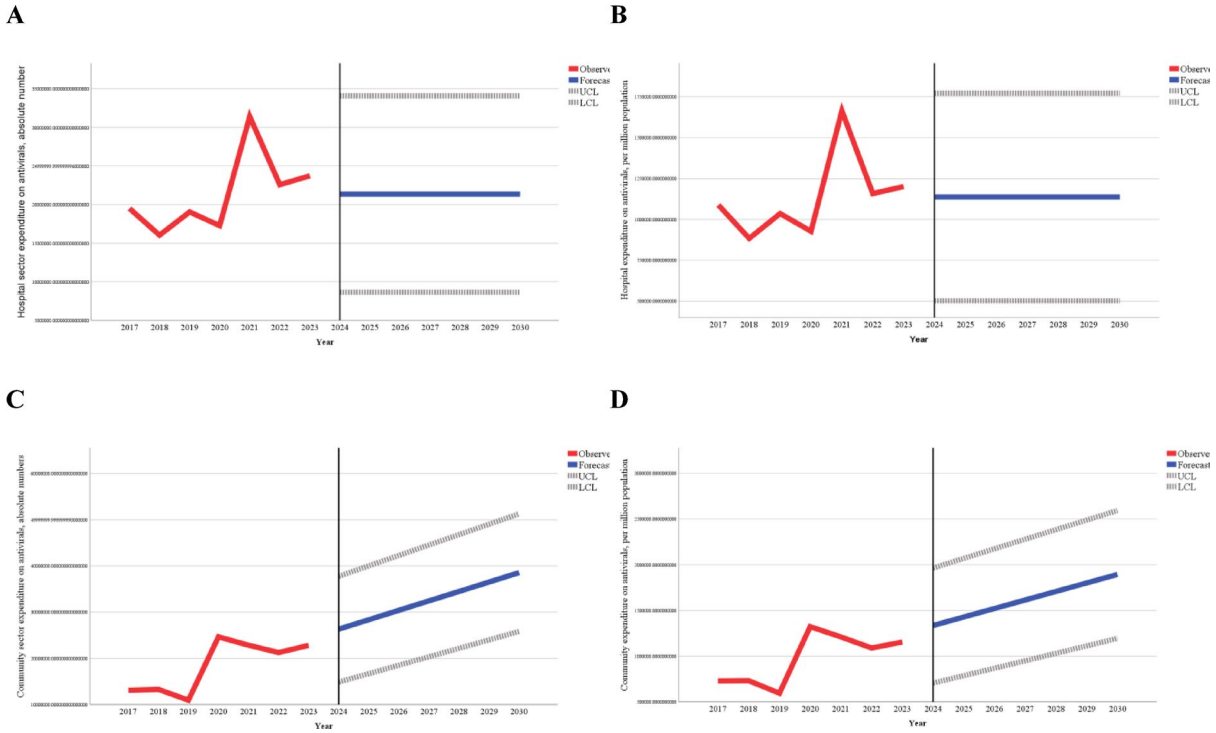

Fig. 4. The observed and projected expenditure rates of antivirals in the hospital sector presented both in absolute numbers (**A**) and per million population rates (**B**), as well as in the community sector in absolute numbers (**C**) and per million population rates (**D**), expressed in United States dollars.

antiviral consumption in the community sector, which has grown more rapidly than in the hospital sector. This change may be a consequence of healthcare reforms implemented in Kazakhstan, aimed at decentralizing healthcare services and increasing access to medications at the community level[11]. As a result, more patients are seeking and obtaining antivirals outside hospital settings, contributing to the observed increase in community sector consumption. However, this also creates favorable conditions for the unwise use of antivirals and calls for the implementation of AMS strategies, including curbing over-the-counter sales of antivirals[32].

The study has several limitations that should be considered when interpreting the results. First, the use of aggregated national data may mask regional variations in antiviral consumption patterns. Second, the impact of the COVID-19 pandemic on healthcare systems and antiviral usage may introduce confounding factors that are difficult to fully account for. Third, the study period may not be sufficient to capture long-term trends and emerging patterns in antiviral consumption, and the assumptions made in predictive modeling may not account for future changes in healthcare policies, practices, or the emergence of new antiviral drugs.

Despite these limitations, the study also has a number of strengths. First, it provides a comprehensive analysis of nationwide antiviral consumption trends over a period of seven years, using robust statistical methods. Second, the inclusion of both hospital and community sectors offers a holistic view of antiviral consumption. Third, the study's findings have important implications for public health policy and resource allocation, providing valuable insights for future planning and the development of targeted interventions to improve antiviral stewardship in Kazakhstan.

Data availability

All data supporting the findings of this study are available within the paper and its Supplementary Information Files.

Received: 29 July 2024; Accepted: 30 May 2025
Published online: 01 July 2025

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Funding

This work was supported by the Nazarbayev University under Collaborative Research Program Grant № 211123CRP1609 "Evidence-based practice and policy to improve antibiotic stewardship and reduce antimicrobial resistance in Central Asia".

Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

The study protocol (submission 802/23112023) was reviewed by the Nazarbayev University Institutional Research Ethics Committee (NU-IREC), which granted exempt status on December 1, 2023.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-05161-3.

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