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CONSUMPTION DETAILS OF SYSTEMICALLY ACTING ANTIVIRAL AND ANTIMICROBIAL PREPARATIONS IN PERIOD OF NOVEL CORONAVIRUS INFECTION SPREAD IN RETAIL SECTOR OF SAMARA REGION PHARMACEUTICAL MARKET

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An analysis of the medicinal preparation consumption structure in the period of the COVID-19 pandemic in the pharmacy network reflects the existing outpatient practice and makes it possible to draw generalized conclusions about its compliance with the pharmacotherapy standards.

The aim. Comparative analysis of population consumption of antimicrobial and antiviral medicines sold in the retail pharmacies of the Samara region in 2015–2021.

Materials and methods. The study was conducted in the retail sector of the Samara region pharmaceutical market. The material of the study was the information on the list of items and dispensing volumes of antibacterial and individual antiviral drugs during the novel coronavirus infection spread (in 2020) in the network of the Samara region pharmacies. The data are compared with the indicators of the drug sales in 2015–2019. Methods of retrospective, comparative, graphical, methodological, content analyzes and statistical methods of analyses were used.

Results. The authors have established a significant distortion in the consumption of systemic antimicrobial preparations in the Samara region pharmacy segment in the period of 2015–2019 with the predominance of the ATC (Anatomical Therapeutic Chemical Classification System) J01D group, primarily cephalosporins (38%), mainly by the parenteral administration route. The share of macrolides (J01F) consumption in volume terms was 14.9%, of fluoroquinolones (J01M) – 11.3%, beta-lactam antibiotics with beta-lactamase inhibitors – 10.7%, beta-lactam antibiotics penicillins (J01C) – 8.1%. Compared to 2019, in 2020, under the conditions of the COVID-19 pandemic, the total consumption of AMPs increased by 2.1 times. In the "Other beta-lactam antibiotics" group with a predominant proportion of cephalosporins, there was an increase by 3.2 times, in the "Macrolides and lincosamides" group – by 3.5 times, in "Quinolone derivatives" – by 2.6 times. The noted facts should be assessed as the phenomenon that can have a direct impact on the growth of an antibiotic resistance on a population scale. Among antivirals, the largest consumption increase was noted for oseltamivir and rimantadine. In absolute terms, the volume of antiviral preparations consumption in 2020 increased by 2.4 times, which was accompanied by an increase in the cost of one package by 55.8%.

Conclusion. In the period of spreading a novel coronavirus infection, a significant increase in the consumption of antimicrobial and antiviral preparations (up to 20 times for certain pharmacotherapeutic groups and names) was notified, which may negatively affect the growth of the antibiotic resistance in the population.

Keywords: systemic antimicrobial preparations; antiviral drugs; pharmacy segment; consumption; COVID-19 pandemic

Abbreviations: AMPs – antimicrobial preparations; MP – medicinal preparations; DDD – Defined Daily Dose; INN – international non-proprietary name; ATC – Anatomical Therapeutic Chemical Classification System; ARVI – acute respiratory viral infection; RNA – ribonucleic acid.

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ОСОБЕННОСТИ ПОТРЕБЛЕНИЯ ПРОТИВОВИРУСНЫХ И АНТИМИКРОБНЫХ ПРЕПАРАТОВ СИСТЕМНОГО ДЕЙСТВИЯ В ПЕРИОД РАСПРОСТРАНЕНИЯ НОВОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИИ В РОЗНИЧНОМ СЕКТОРЕ ФАРМАЦЕВТИЧЕСКОГО РЫНКА САМАРСКОЙ ОБЛАСТИ

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Анализ структуры потребления лекарственных препаратов в период пандемии COVID-19 в аптечной сети отражает существующую амбулаторную практику и позволяет сделать обобщенные выводы о соответствии ее стандартам фармакотерапии.

Цель. Сравнительный анализ популяционного потребления антимикробных и противовирусных лекарственных препаратов, реализованных в розничном секторе фармацевтического рынка Самарской области в 2015–2021 гг.

Материалы и методы. Исследование проведено в розничном секторе фармацевтического рынка Самарской области. В качестве материала исследования использовали сведения о номенклатуре и объемах отпуска антибактериальных и отдельных противовирусных лекарственных препаратов в период распространения новой коронавирусной инфекции (в 2020 г.) в сети аптек Самарской области. Данные сопоставлены с показателями реализации лекарственных препаратов в 2015–2019 гг. Использованы методы ретроспективного, сравнительного, графического, методологического, контент-анализ и статистические методы анализа.

Результаты. Авторами установлена значительная деформация потребления антимикробных препаратов системного действия в аптечном сегменте Самарской области в период 2015–2019 гг. с преобладанием группы АТХ J01D с доминированием цефалоспоринов (38%) преимущественно парентерального пути введения. Доля потребления в натуральном выражении макролидов (J01F) составила 14,9%, фторхинолонов (J01M) – 11,3%, бета-лактамных антибиотиков с ингибиторами бета-лактамаз – 10,7%, бета-лактамных антибиотиков-пенициллинов (J01C) – 8,1%. В сравнении с 2019 г., в 2020 г. в условиях пандемии COVID-19 общее потребление АМП увеличилось в 2,1 раз. В группе «Другие бета-лактамные антибиотики» с преимущественной долей цефалоспоринов произошло увеличение в 3,2 раза, «Макролиды и линкозамиды» – в 3,5 раз, «Производные хинолона» – в 2,6 раза. Отмеченные факты следует оценивать как фактор, который может оказать непосредственное влияние на рост антибиотикорезистентности в популяционном масштабе. Среди противовирусных препаратов наибольший рост потребления отмечен для осельтамивира и римантадина. В абсолютном выражении объем потребления противовирусных лекарственных препаратов в 2020 г. увеличился в 2,4 раза, что сопровождалось увеличением стоимости одной упаковки на 55,8%.

Заключение. В период распространения новой коронавирусной инфекции отмечен значительный рост потребления антимикробных и противовирусных лекарственных препаратов (по отдельным фармакотерапевтическим группам и наименованиям – до 20 раз), что может негативным образом отразиться на росте антибиотикорезистентности у населения.

Ключевые слова: антимикробные препараты системного действия; противовирусные препараты; аптечный сегмент; потребление; пандемия COVID-19

Список сокращений: АМП – антимикробные препараты; ЛП – лекарственные препараты; DDD – суточная поддерживающая доза; МНН – международное непатентованное наименование; АТХ – анатомо-терапевтическо-химическая классификация; ОРВИ – острая респираторная вирусная инфекция; РНК – рибонуклеиновая кислота.

INTRODUCTION

A new coronavirus infection has become an unprecedented challenge for the health care system of the Russian Federation (RF), the pharmaceutical industry, and the regional drug supply system [1–3]. The greatest difficulty is the search for the effective methods of etiotropic treatment. In the absence of new medicinal preparations (MPs) that effectively suppress the SARS-Cov-2 replication, screening of the known antiviral agents seems relevant. Obtaining reliable data on the clinical benefit of drugs has proved to be very problematic in the current situation and has led to the fact that the preference of physicians and patients has become a criterion for benefit [4–8].

The consumption structure of antimicrobial and antiviral preparations by the population through the pharmacy network, reflecting the outpatient practice in the period preceding the pandemic, as well as the

dynamics of the MPs consumption during the pandemic, seems important in terms of compliance with the directions of modern recommendations[1]. Herewith, the scope of use of antimicrobial and antiviral preparations in the outpatient practice of the Russian Federation regions is not reliably known; such data are rare in the press. At the same time, the problem of the antibiotic resistance may become particularly acute in the near future in case of an irrational increase in the AMPs use [9–15]. The AMPs prescribtion and use should always be justified, since the irrational use of this pharmacotherapeutic group MPs can lead to a noticeable increase in the antibiotic resistance on a population-based study [1, 12, 16]. The dynamics of the antimicrobial and antiviral preparations consumption makes it possible to indirectly assess the optimality of pharmacotherapy for the novel coronavirus infection, as well as to establish compliance with current guidelines. The results of such an analysis can be used to improve the medicinal preparations efficiency and safety at the population level [17–26].

In this regard, marketing research is becoming highly relevant, making it possible to identify trends in the population consumption of antimicrobial and antiviral preparations in the retail sector of the pharmaceutical market.

THE AIM. Comparative analysis of population consumption of antimicrobial and antiviral medicines sold in the retail pharmacies of the Samara region in 2015–2021.

MATERIALS AND METHODS

The study was conducted on the retail sector example of the Samara region pharmaceutical market. According to a number of demographics, medical, social, economic and infrastructural indicators, this region is among the most developed ones of the Volga Federal District and the Russian Federation. The regional pharmaceutical market is highly concentrated with a high degree of competition.

The material of the study was information on the list of items and volumes of antimicrobial and antiviral preparations sale during the spread of the coronavirus infection (in 2020–2021) in the pharmacy network of the Samara region. The analyzed pharmacy network includes 30 pharmacies located in different municipalities of the Samara region. These network pharmacies have a wide range of medicines and other pharmacy products (about 30 thousand items).

The following analytical methods were used: methods of the retrospective analysis (changes in the indicators of the retail sale of medicines to the population during 2015–2021), a comparative analysis (the one of individual groups and intragroup indicators), a graphical analysis (presentation pharmaceutical sales time series), a methodological analysis (the identification of common characteristics for the objects, the analysis relationships between the phenomena), content analysis (the analysis of the text arrays content about the medicinal preparations implementation in the analyzed period) and statistical methods of the analysis. A statistical processing was performed using IBM SPSS Advanced Statistics 24.0 No. 5725-A54 (IBM, USA).

The representativeness assessment of the sample in the conducted studies was carried out by assessing the number of the medicinal preparations purchases of the groups under consideration in the analyzed retail network of the Samara region pharmaceutical market. For this purpose, the following formula was used:

$$m = 2\sqrt{n},$$

where: m is the resulting sample size; n is the size of the general totality.

In the conducted studies, the general totality is understood as the Samara region population (n in 2021 was 3 154 200 people). Therefore, to ensure the representativeness of the sample size, it should be 3 552 purchases of antibacterial medicinal preparations in 2020. In the studied pharmacy chain, in 2015-2021, about 50 thousand purchases were made annually, which confirms the representativeness of the data obtained, i.e. the correspondence of the characteristics of the sample to the characteristics of the general population.

As for the medicinal preparations, the cost of one defined daily dose (DDD) was calculated by dividing the total cost of the medicinal preparations packages with one INN by the total number of DDDs.

RESULTS

Consumption of systemic antimicrobials

For the period of 2015–2021, in the studied retail segment sector of the Samara region pharmaceutical market, about 18 million packages of MPs and other pharmacy products were sold, 2.57% of which were accounted for AMPs. In the total volume of the dispensed packages, the average share of AMPs for the period of 2015–2021 was 3.38%. For comparison, in the Russian pharmaceutical market, the share of AMPs sales by volume was about 11.69%. Herewith, 43.7% of purchases were made at the expense of the population's personal funds. In general, in 2015–2021, the range of AMPs averaged (± standard deviation, SD) 54±3 international non-proprietary names (INN), which corresponds to 138±3 trade names.

[1] Interim guidelines "Prevention, diagnosis and treatment of a new coronavirus infection (COVID-19). Version 3 (03.03.2020). Available from: http://edu.rosminzdrav.ru/fileadmin/user_upload/specialists/COVID-19/Vremennye_MR_COVID-19_03.03.2020__versija_3__6-6_ver1.pdf. Russian

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A noticeable increase in the consumption of antibacterial medicinal preparations in the retail sector of the Samara region pharmaceutical market was notified in 2020 (compared to 2019, the sales in packages increased by 2.12 times), which exceeds the average annual fluctuations in realized demand for this group of MPs in 2015-2019. The dynamics study of the realized demand for individual systemic AMPs subgroups (in accordance with subgroups in the anatomical-chemical-therapeutic [ATC-]classification) revealed a significant increase in the number of dispensed packages in 2020 for the following subgroups: J01D "Other beta-lactam antibacterials", J01F "Macrolides, lincosamides and streptogramins", J01M "Quinolone antibacterials" (Table 1, Fig. 1). In the authors' opinion, this circumstance is due to the influence of the novel coronavirus infection spread and, in some cases, the rush demand for drugs from certain pharmacotherapeutic groups.

Herewith, at the end of 2021, the level of the consumer demand returned to the values of 2015–2019. Possible reasons for this trend may be as follows: the formation of AMPs stocks in home medicine cabinets by the end of 2020; the implementation of programs providing the COVID-19 patients with the MPs prescribed for them at the expense of the federal budget; a change in the algorithm for treating outpatients (in 2021, at the outpatient stage of medical care, AMPs were excluded from pharmacotherapy regimens).

In 2020, against the background of a significant increase in demand for drugs of ATC subgroups J01D "Other beta-lactam antibacterials", J01F "Macrolides, lincosamides and streptogramins", J01M "Quinolone antibacterials", a decrease in the share of the AMPs packages total sales for the drugs of J01A subgroups "Tetracyclines" was notified. Besides, there were J01C "Beta-lactam antibacterials, penicillins", J01G "Aminoglycoside antibacterials", J01X "Other AMPs", and "Beta-lactam antibacterials with beta-lactamase inhibitors". As Fig. 2 shows, in 2021, there was a return to the existing picture of demand for AMPs in 2015–2019, with the exception of aminoglycosides, the number of sold packages decreased in 2019–2021 by an average of 35% annually (Fig. 2).

In 2015–2021, the maximum share of the total volume of the realized demand was accounted for the ATCs subgroup J01D "Other beta-lactam antibiotics" (Fig. 3). The average value of the share (± SD) of the volume of the realized demand in real terms for this ATCs subgroup was 38.5±5.6%.

In 2020, against the background of the beginning of a novel coronavirus infection pandemic, an increase in the proportion of the medicines of this ATCs subgroup to 47.6% was notified. In 2021, the value of the share of J01D MPs in the total volume of the realized demand returned to the previous average annual values (39.0%) (Table 1, Fig. 1). Over the past two years, an extraordinary demand for these drugs was notified in October, although in 2021 it was less pronounced compared to 2020 (Fig. 4).

In 2020, as in the previous period (2015–2019), in the "Other beta-lactam antibacterials" group, ceftriaxone preparations had the largest volumes of consumption in volume terms (median 72.2%), ranging from 63.5 % in 2020 to 76.8% in 2017 of the total realized demand for drugs from this ATC subgroup. At the same time, in 2020, in the overall structure of the dispensed drugs packs of the ATC J01D subgroup, there was a sharp increase in the share and number of the dispensed packs for the drugs of cefazolin, cefditoren and meropenem, which returned to their previous values in 2021. The greatest demand in the outpatient practice is for parenteral preparations from the group of cephalosporins "Other β-lactam antibacterials", including ceftriaxone, as well as cefazolin (8.3–12.9%) and cefotaxime (7.7–5.4%). In accordance with the current recommendations, amoxicillin and its combination with clavulanic acid (β-lactam antibiotics and β-lactam penicillins with β-lactamase inhibitors) should be the basic treatment for the vast majority of bacterial infections in the outpatient practice. However, the frequency of amoxicillin sales from 2015 to 2021 decreased from 14.1% to 6.1% (Table 1). In combination with β-lactamase inhibitors, where the main share of MPs is accounted for amoxicillin (96.9–81.6%), the frequency of this antibacterial sales does not exceed 10% in total in 2020 (Table 1).

According to the literature data, in outpatient practice, the first-line MPs of choice is amoxicillin, administered orally for pneumonia, exacerbation of chronic obstructive pulmonary disease, acute rhinosinusitis, bronchitis, acute tonsillitis, and uncomplicated skin and soft tissue infection [8, 15, 17]. At the same time, a high consumer demand for β-lactam antibiotics was notified in the retail sector of the Samara Region pharmaceutical market.

In 2015–2021, a significant share in the structure of consumption volume in physical terms was also occupied by medicines of J01F ATC subgroups "Macrolides, lincosamides and streptogramins" (15.0%) and J01M "Quinolone antibacterials" (11.4%) (Table 1, Fig. 1). In 2020, for the group "Macrolides, lincosamides and streptogramins", an increase in the share was notified (in the total structure of the dispensed packages – up to 19.9%). In 2021, this share decreased compared to 2020, but continued to be high compared to the average annual data for the period of 2015–2019 (14.4%). When analyzing the demand by months, it was found out that in 2020 and 2021, the demand for these AMPs, as in the case of the ATC subgroup J01D "Other beta-lactam antibacterials", peaked in October (Fig. 5).

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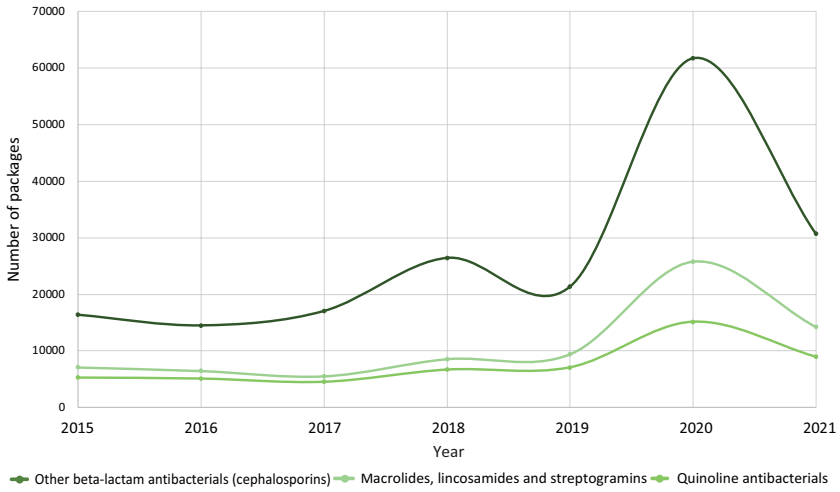

Figure 1 – Dynamics of realized demand for some groups of antibacterial medicinal preparations, pandemic sales of which increased

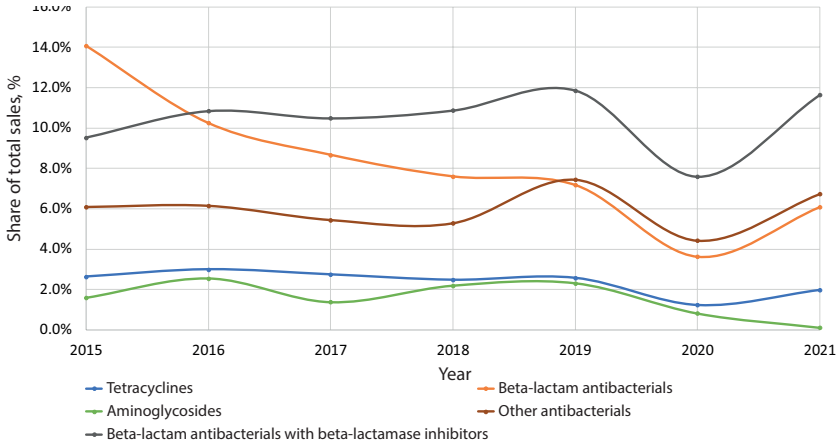

Figure 2 – Dynamics of realized demand for some groups of antibacterials, sales of which decreased or did not change during pandemic

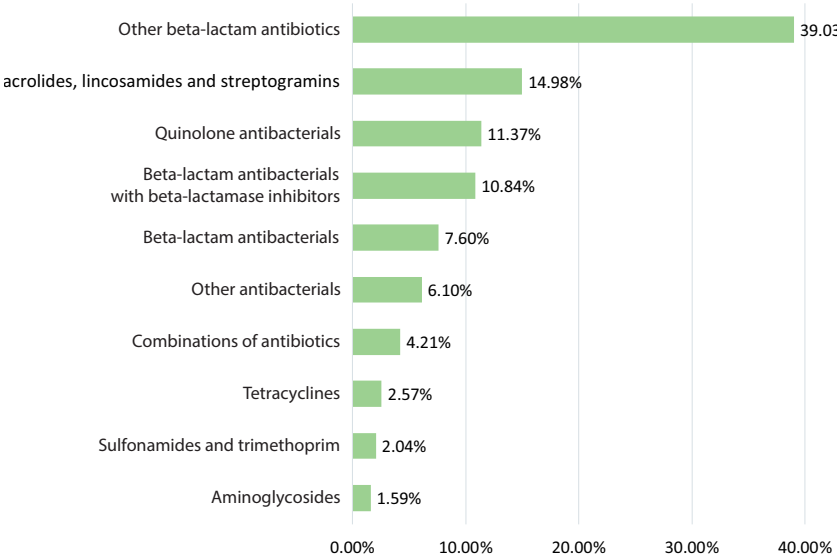

Figure 3 – Median shares of realized demand volume for antibacterial MPs in 2015–2021

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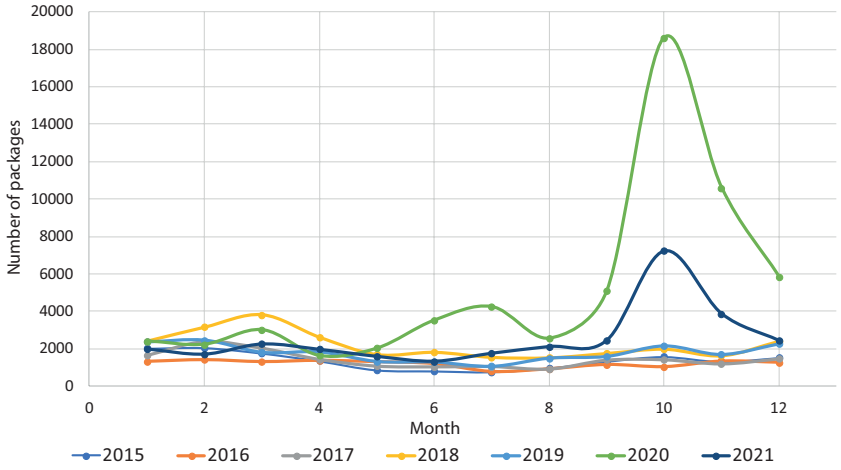

Figure 4 – Dynamics of demand for ATC subgroup medicinal preparations – J01D "Other beta-lactam antibacterials" in 2015–2021 (by months)

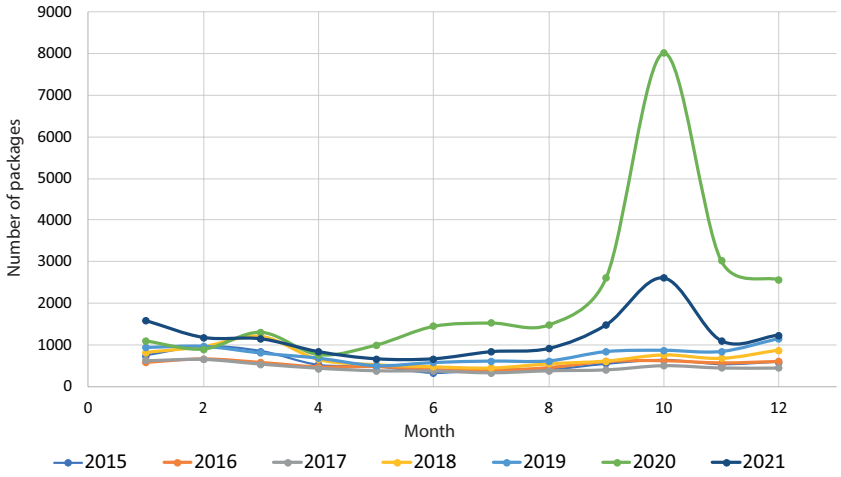

Figure 5 – Dynamics of demand for ATC subgroup medicinal preparations – J01F "Macrolides, lincosamides and streptogramins" in 2015–2021 (by months)

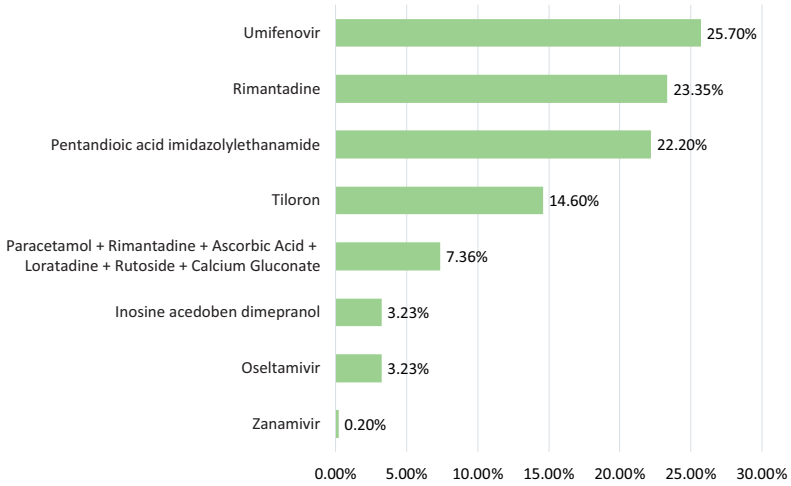

Figure 6 – Median volume shares of realized demand for antiviral medicinal preparations in 2015–2020

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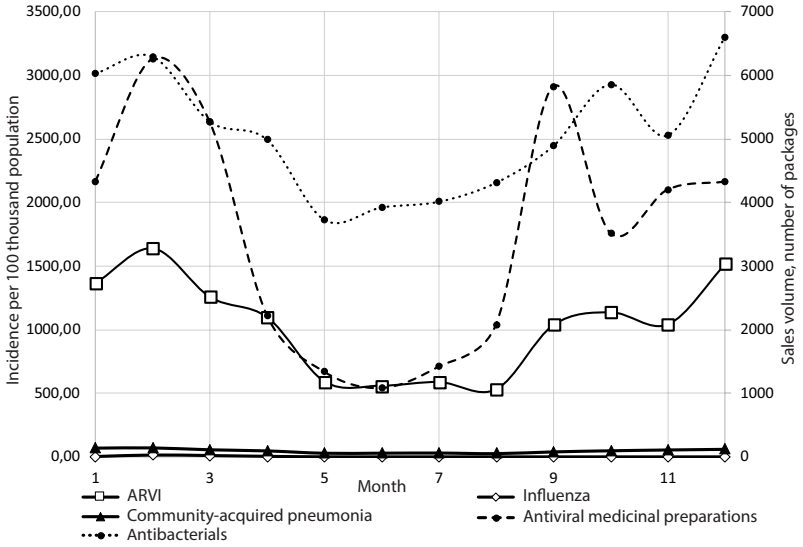

Figure 7 – Incidence of acute respiratory viral infections, influenza, COVID-19, community-acquired pneumonia in 2019 (according to Samara region Rospotrebnadzor), volumes of realized antiviral MPs and AMPs packages

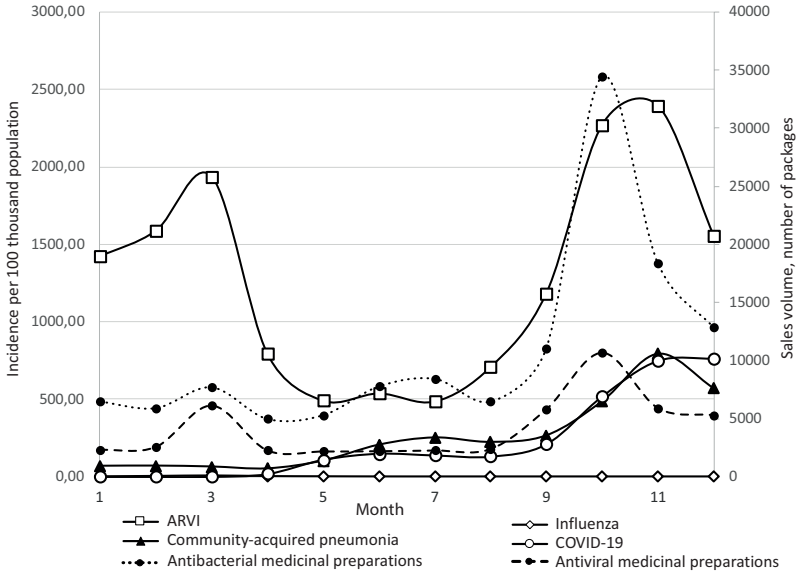

Figure 8 – The incidence of acute respiratory viral infections, influenza, COVID-19, community-acquired pneumonia in 2020 (according to Samara region Rospotrebnadzor), volumes of realized of antiviral MPs and AMPs packages

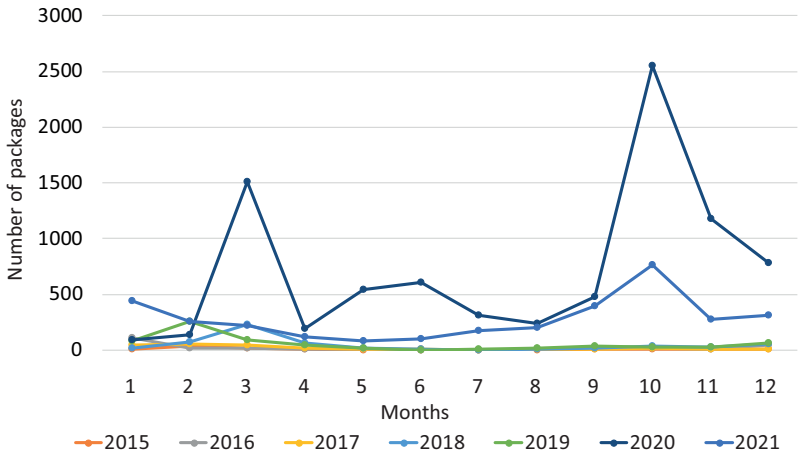

Figure 9 – Dynamics of oseltamivir demand in 2015–2021

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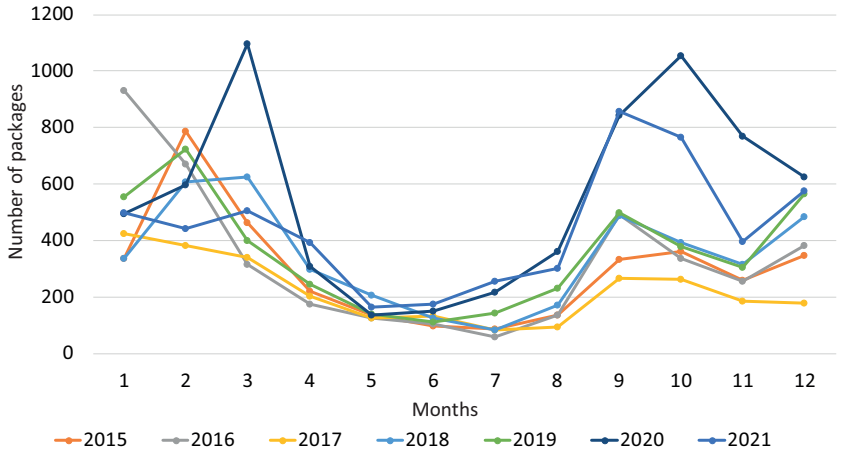

Figure 10 – Dynamics of rimantadine demand in 2015–2020

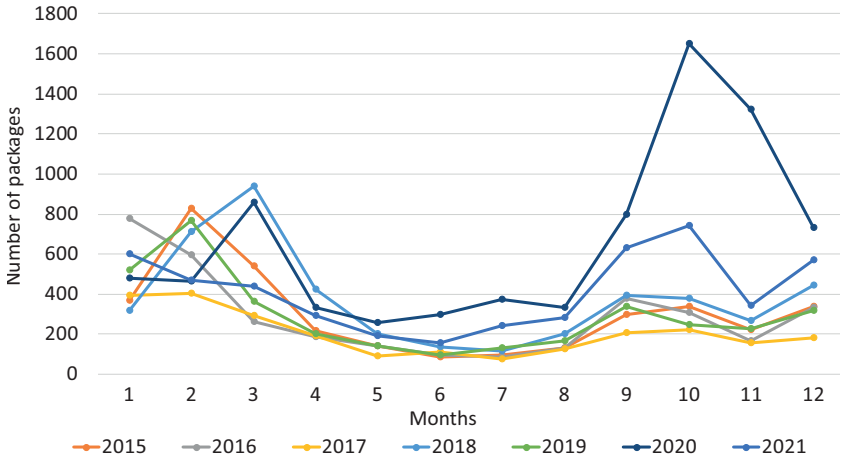

Figure 11 – Dynamics of imidazolylethanamide pentadioic acid demand in 2015–2020

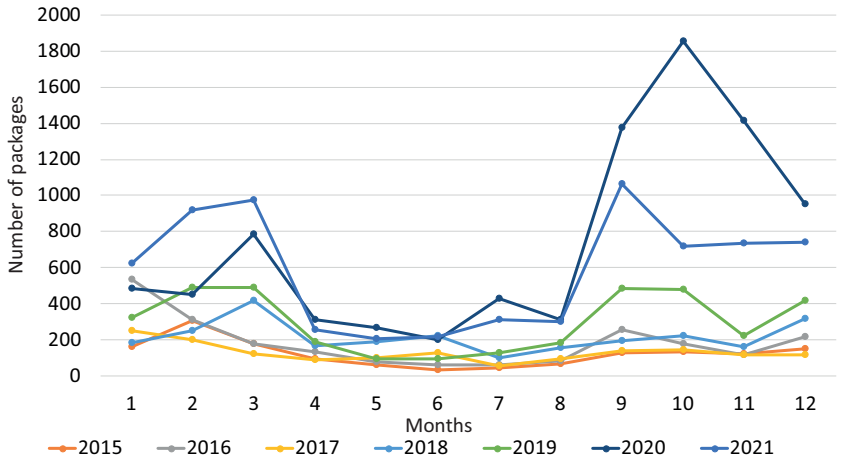

Figure 12 – Dynamics of thyrolon demand in 2015–2020

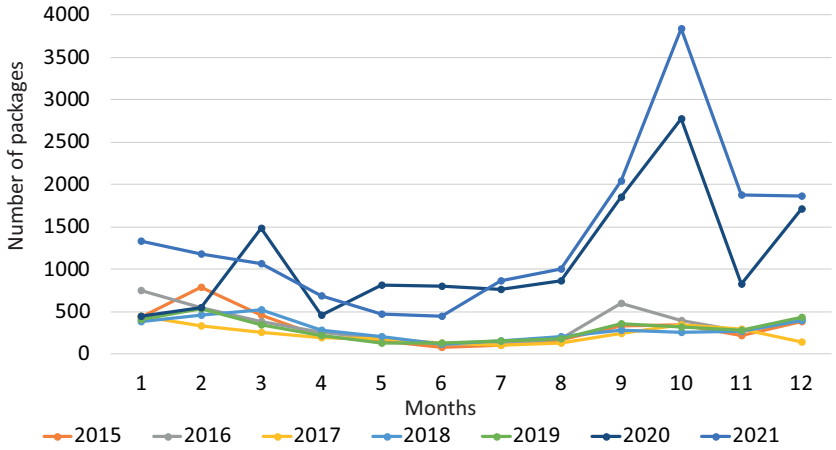

Figure 13 – Dynamics of umifenovir demand in 2015–2020

Table 1 – Consumption structure of antibacterials in retail sector of Samara region pharmaceutical market

ATC-subgroups and medicines (INN)	Share of realized demand volume (in packages), %*							
	Year							Median (minimum-maximum) in 2015–2021
	2015	2016	2017	2018	2019	2020	2021	
J01A Tetracyclines	**2.6**	**3.0**	**2.7**	**2.5**	**2.6**	**1.2**	**2.0**	**2.6 (1.2–3.0)**
Doxycycline	85.5	88.7	85.6	84.3	86.5	80.2	87.7	87.6 (80.2–88.7)
Tetracycline	14.5	11.1	12.8	15.3	13.3	19.1	9.9	13.3 (9.9–19.10)
J01C Beta-lactam penicillins	**14.1**	**10.3**	**8.7**	**7.6**	**7.2**	**3.6**	**6.1**	**7.6 (3.6–14.1)**
Amoxicillin	58.6	81.3	85.4	93.3	91.3	95.5	100.0	91.3 (58.6–100.0)
J01D Other beta-lactam antibacterials	**34.0**	**33.5**	**41.0**	**41.4**	**35.0**	**47.6**	**39.0**	**39.0 (33.5–47.6)**
Ceftriaxone	71.8	65.8	76.8	74.0	72.5	63.5	75.7	72.6 (63.5–76.8)
Cefazolin	8.5	8.3	5.1	4.0	3.5	12.8	4.5	5.1 (3.5–12.8)
Cefotaxime	5.5	7.8	3.1	5.4	5.1	6.3	2.5	5.4 (2.5–7.8)
Cefixime	4.6	5.4	5.9	6.8	8.1	3.9	8.3	5.9 (3.9–8.3)
Cefditoren	0.0	0.4	0.3	1.0	1.8	8.1	2.1	1.0 (0.00–8.1)
Beta-lactam antibacterials with beta-lactamase inhibitors	**9.5**	**10.8**	**10.5**	**10.9**	**11.9**	**7.6**	**11.7**	**10.8 (7.6–11.9)**
Amoxicillin + clavulanic acid	88.2	94.6	95.4	96.9	91.9	81.6	93.3	93.3 (81.6–96.9)
J01E Sulfonamides and trimethoprim	**2.1**	**2.0**	**1.9**	**2.2**	**2.3**	**1.2**	**1.5**	**2.0 (1.2–2.3)**
Co-trimoxazole	85.8	85.7	81.8	85.9	89.6	91.2	98.8	98.9 (81.8–98.8)
Sulfadimethoxine	12.8	12.9	10.6	12.8	9.8	8.4	1.1	10.6 (1.1–12.9)
J01F Macrolides, lincosamides and streptogramins	**14.8**	**15.0**	**13.3**	**13.4**	**15.5**	**19.9**	**18.1**	**15.0 (13.3–19.9)**
Azithromycin	48.2	46.1	44.6	50.4	49.4	79.7	68.7	49.4 (44.6–79.7)
Clarithromycin	23.9	25.3	28.6	27.3	30.2	12.4	20.0	25.3 (12.4–30.2)
Josamycin	8.4	10.4	10.1	7.8	8.2	3.4	5.5	8.2 (3.4–10.4)
Lincomycin	9.0	8.1	8.0	7.4	7.5	2.7	4.2	7.5 (2.7–9.0)
J01G Aminoglycosides	**1.6**	**2.5**	**1.4**	**2.2**	**2.3**	**0.8**	**0.1**	**1.6 (0.1–2.5)**
Gentamicin	19.0	14.1	18.1	13.0	11.1	29.2	72.4	18.1 (11.1–72.4)
Amikacin	51.5	37.9	65.8	86.8	88.5	70.8	27.6	65.8 (27.6–88.5)
J01M Quinolone antibacterials	**10.9**	**11.8**	**10.9**	**10.5**	**11.6**	**11.7**	**11.4**	**11.4 (10.5–11.8)**
Ciprofloxacin	37.1	37.4	37.3	36.1	35.6	21.8	30.4	36.1 (21.8–37.4)
Levofloxacin	25.9	31.1	33.7	37.1	38.1	59.8	49.6	37.1 (25.9–59.8)
Norfloxacin	18.3	17.6	15.4	15.2	15.6	7.8	13.0	15.4 (7.8–18.3)
J01X Other antibacterials	**6.1**	**6.2**	**5.4**	**5.3**	**7.4**	**4.4**	**6.7**	**6.1 (4.4–7.4)**
Metronidazole	96.0	92.8	93.6	91.8	94.8	91.7	92.9	92.9 (91.7–96.0)
Antibiotic combinations	**4.3**	**4.9**	**4.2**	**4.1**	**4.3**	**2.0**	**3.4**	**4.2 (2.0–4.9)**
Benzathine benzylpenicillin + Benzylpenicillin procaine	37.6	35.3	23.9	33.3	21.1	16.3	18.5	23.9 (16.3–37.6)
Benzathine benzylpenicillin + Benzylpenicillin procaine + Benzylpenicillin sodium	18.7	11.7	16.7	13.7	13.3	18.0	13.6	13.7 (11.7–18.7)
Ciprofloxacin + tinidazole	39.8	44.2	51.6	48.2	57.9	63.5	66.5	51.6 (39.8–66.5)

Note: * – indicators of realized demand in packages were used for the analysis. For pharmacotherapeutic groups, the shares of the total volume of realized demand are indicated, for INN it is the share of the volume of realized demand for a particular pharmacotherapeutic group; the table shows INNs with the largest volumes of realized demand within each pharmacotherapeutic group.

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Table 2 – Consumption structure of antiviral medicinal preparations prescribed for treatment of respiratory viral infections in retail sector of Samara region pharmaceutical market

Antiviral medicinal preparations (INN)	Share in realized demand structure, %						
	2015	2016	2017	2018	2019	2020	2021
Zanamivir	0.10	0.40	0.20	0.34	0.23	0.19	0.06
Pentandioic acid imidazolylethanamide	24.97	22.20	22.64	25.63	16.80	15.85	11.96
Inosine acedoben dimepranol	3.49	2.58	2.95	4.63	4.82	2.09	3.23
Oseltamivir	0.71	1.60	2.11	3.23	3.25	17.26	8.04
Rimantadine	24.74	25.55	24.69	23.35	20.35	13.34	12.81
Tiloron	10.26	14.10	14.34	14.60	20.56	17.71	17.00
Umifenovir	25.61	26.97	25.70	19.97	17.13	26.79	40.13
Favipiravir*	–	–	–	–	–	0.44	1.18
Paracetamol + Rimantadine + Ascorbic Acid + Loratadine + Rutoside + Calcium Gluconate	10.11	6.61	7.36	8.23	0.17	6.22	5.52

Note: for the analysis, indicators of realized demand in packages were used; * – Favipiravir preparations were registered in Russia in 2020.

Table 3 – Average cost of treatment for one maintenance daily dose of antiviral MPs in 2019–2020

INN	Median (minimum-maximum) cost of 1 DDD, rub. (2019)	Median (minimum-maximum) cost of 1 DDD, rub. (2020)	Median (minimum-maximum) cost of 1 DDD, rub. (2021)	Median (minimum-maximum) cost of 1 DDD in treatment with original drugs, rub. (as exemplified by 2021)
Zanamivir	234.09 (234.09–234.09)	276.33 (256.33–300.10)	280.32 (280.32–280.32)	280.32 (280.32–280.32)
Pentandioic acid imidazolylethanamide	82.21 (77.34–87.08)	103.38 (85.86–120.70)	102.09 (73.33–122.79)	102.09 (73.33–122.79)
Inosine Acedoben Dimepranol	192.43 (93.19–417.22)	209.75 (115.25–374.58)	216.98 (145.00–312.09)	247.40 (187.88–245.72)
Oseltamivir	174.88 (133.92–291.74)	202.99 (167.22–288.68)	210.53 (126.46–248.71)	245.38 (242.05–248.71)
rimantadine	11.64 (6.87–255.80)	20.65 (11.32–261.82)	16.92 (7.72–157.55)	–
Tiloron	102.09 (41.66–143.53)	102.26 (51.99–151.42)	92.27 (46.29–134.74)	133.43 (132.12–134.74)
Umifenovir	169.06 (97.77–291.56)	188.25 (99.85–335.25)	238.62 (119.60–384.22)	253.10 (246.88–384.22)
Favipiravir	–	2 073.68 (1 795.27–2 073.68)	1 255.79 (1 001.78–2 382.38)	–

In 2020–2021, in the group "Macrolides, lincosamides and streptogramins", there was an increase in the share of azithromycin-containing medicines in the total number of the dispensed packages of this ATC subgroup, which amounted to 79.7% and 68.7%, respectively (compared to the average value of 47.8±2.4% in 2015–2019). The demand for other medicines within this ATC subgroup remained at the same level or slightly decreased. According to the document of the World Health Organization (WHO) and domestic recommendations, macrolides should be considered as second-line drugs in the treatment of respiratory infections [16].

The group of fluoroquinolones is considered as reserve AMPs and is not recommended for the treatment of acute uncomplicated infections in the outpatient practice. In this study, their share of the total number of the dispensed packages remained approximately at the same level and averaged 11.4±0.5%. The drugs of the ATC subgroup "Quinolone antibacterials" were more often applied for. They were the medicines containing the active ingredients ciprofloxacin, levofloxacin or norfloxacin (medians for the period of 2015–2021 – 36.1%, 37.1% and 15.4% of the volume of this group realized demand, respectively). At the same time, in 2020–2021, there was an increase in demand for "respiratory" drugs of this group: levofloxacin and moxifloxacin.

In 2020, for the ATC subgroups "Other beta-lactam antibacterials", the number of the dispensed packages increased by 3.2 times, for "Macrolides, lincosamides and streptogramins" – by 3.5 times, for "Quinolone antibacterials" – by 2.6 times in 2020 (compared to the average values of the dispensed MPs packages of these subgroups in 2015–2019). A similar increase was notified for individual INNs: ceftriaxone – by 2.9 times, cefazolin – by 7.5 times, by cefotaxime – by 3.3 times, cefditoren –

by 33 times, meropenem – by 90 times, azithromycin – by 5.8 times, levofloxacin – by 4.7 times, moxifloxacin – by 7.0 times. Interest in cefditoren is obviously due to the fact that it was included in the domestic clinical guidelines for the treatment of community-acquired pneumonia in 2018. The number of dispensed packages of the remaining drugs was approximately at the level of the previous period, respectively, their share in the total consumption structure in 2020 slightly decreased.

For most of the groups and individual items of the MPs under consideration, there was an increase in the cost of 1 DDD in 2020 compared to 2019. The cost of one package increased by 15%, the median cost of 1 DDD increased by 20%. In 2021, the corresponding values compared to 2020, were 3.5% and 5.0%, respectively.

Antiviral medicinal preparations

The range of antiviral medicinal preparations approved for use in the treatment of acute respiratory viral infections was represented by 8 out of 9 INNs registered in the Russian Federation (except baloxavir carboxyl, registered in September 2020), which corresponded to 35 trade names. At the end of 2021, the share of antiviral medicinal preparations in the total structure of the dispensed packages amounted to 0.92% (for comparison, in 2018 and 2020 – 0.93% and 1.02%, respectively). In absolute terms (in terms of the package quantity), in 2020, the volume of consumption of medicinal preparations increased by 2.38 times, which exceeds the average annual fluctuations in the consumer demand in the period preceding the start of the novel coronavirus infection spread (an average increase by 1.15 times).

Among antiviral medicines, the largest consumption volume in physical terms was accounted for the MPs of imidazolylethanamide pentadioic acid (median 22.2% of the realized demand volume, the range of 15.9% – 25.6%), umifenovir (25.7%, 16.7% – 40.1%) and rimantadine (23.4%, 12.8% – 25.6%) (Table 2, Fig. 6). In 2020–2021, the consumption of rimantadine naturally decreased to 13.3 and 12.8%, respectively, since the indications for its use do not refer to ARVI, SARS-Cov-2 infections, while the incidence of influenza in 2020, compared to 2019, decreased by 25%.

In the period of the new coronavirus infection spread (2020), a significant increase in the share of oseltamivir was notified in the overall consumption structure (up to 17.26% compared to 0.71% in 2015, 1.60% in 2016, 2, 11% – in 2017, 3.23% – in 2018 and 3.25% – in 2019), and the number of the dispensed packages (by 23.5 times compared to the average value in 2015–2019). Oseltamivir, a neuraminidase inhibitor approved for the treatment of influenza, has no documented *in vitro* activity against SARS-CoV-2. It seems that understanding of oseltamivir ineffectiveness in the SARS-CoV-2 infection and diagnostics advance led to a decrease in the share of the total oseltamivir demand to 8.0% in 2021.

In addition, in 2020, a number of the dispensed imidazolylethanamide pentanedioic acid, tilorone and umifenovir packages increased by 2.2, 3.9 and 3.8 times, respectively, compared with the average values in 2015–2019). Inosine acedoben dimepranol has been registered in more than 70 countries as an antiviral and immunomodulatory MP that has received a good evidence base since 1971. It has been shown to inhibit the replication of herpes simplex virus, cytomegalovirus and Epstein-Barr virus, human papillomavirus, human immunodeficiency virus, influenza viruses and SARS [22, 24]. Nevertheless, the positive qualities of the medicines did not affect its consumption frequency, which remains one of the lowest in the considered segment of the pharmacy market (Table 2).

Umifenovir has a high sales rating in this study (Table 2, Fig. 6), since it is officially recommended by the Ministry of Health of the Russian Federation to be used in patients with mild COVID-19, as well as in patients with signs of SARS and unconfirmed SARS-Cov-2 [25, 27]. In 2021, umifenovir MPs were accounted for 40.1% of total antiviral MPs sales.

Among the antiviral medicinal preparations used to treat acute respiratory viral infections, the highest cost per 1 DDD was for medicines containing favipiravir, a substance active against the novel coronavirus infection (according to the results of 2021, the median was 1,255.79 rubles, in the range from 1,001.78 to 2,382.38 rub.).

Taking into account the fact that in 2019 the MPs containing favipiravir was not introduced in the retail sector, the increase in the cost of 1 DDD of antiviral MPs in 2020, compared to 2019, occurred by 43.1% (at the same time, the average cost of one package increased by 55.8%). Excluding these medicines, the average cost of 1 DDD increased by 9.4% (the average price of one package increased by 13.7%). In 2021, there were no significant changes in the price level compared to 2020, with the exception of umifenovir MPs, for which the cost of 1 DDD increased by 26.8% (Table 3). In all the cases, the cost of treatment with original MPs exceeded the cost of treatment with generic MPs (if available on the pharmaceutical market).

Fig. 7 and 8 show the incidence of acute respiratory viral infections, influenza, community-acquired pneumonia in 2019 and 2020, as well as COVID-19[2] in 2020. In addition to the well-known dynamics of

[2] [Information materials of the Office of Rospotrebnadzor of the Samara Region on the epidemiological situation of the incidence of SARS and influenza in the Samara Region for the period 2019 and 2020]. Available from: https://www.63.rospotrebnadzor.ru

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a decrease in the incidence in the summer period, an increase in the incidence of the acute respiratory viral infections by 24% in 2020 and a decrease in the incidence of influenza by 25% compared to 2019 should be notified. The sales volumes of antiviral MPs presented in these graphs in volume terms show clearly defined seasonal fluctuations with maximum values in the autumn-winter-spring period, which corresponds to the period of the highest incidence of SARS. As expected, the smallest volumes of antiviral MPs sales during 2015–2020 were recorded in July and August. It should be notified that the volume of AMPs sales is significantly higher than that of antiviral MPs, and this trend is most pronounced in 2020.

Fig. 9–13 show a monthly dynamics of antiviral MPs realization in 2015–2021. Despite different ranges of the MPs, their consumption dynamics is exactly the same. The dynamics of demand for typical anti-influenza MPs, oseltamivir and rimantadine, is absolutely consistent with other antiviral drugs and does not correlate with the incidence of influenza among the Samara region population. In 2020–2021, in all cases, an extraordinary demand for antiviral drugs was observed in the autumn period, however, in 2021 it was lower compared to 2020.

Thus, a significant increase in demand for antibacterial and antiviral MPs was recorded in the autumn period of 2020 against the backdrop of an increase in the incidence of the novel coronavirus infection.

CONCLUSION

There was a 2.12-fold increase in the AMPs consumption in 2020 compared to the average values of the dispensed MD packages of these subgroups in 2015–2019. For the ATC subgroups “Other β-lactam antibacterials”, “Macrolides, lincosamides and streptogramins”, “Quinolone antibacterials” in 2020, this indicator increased by 3.2, 3.5 and 2.6 times, respectively, which has adverse consequences for the bacterial resistance.

In 2020, the dynamics of the SARS, COVID-19 and community-acquired pneumonia incidence have largely a similar pattern, which is probably more due to the difficulty of recognizing these respiratory infection forms, mainly based on the results of the PCR method for detecting SARS-Cov-2 RNA. The AMPs and antiviral MPs consumption is closely related to the incidence of acute respiratory viral infections and has clear maxima in the spring and autumn-winter periods. At the same time, the AMPs consumption is higher than that of antiviral MPs. In 2020, the cumulative influenza incidence was 25% lower than in 2019, which can be explained by the curing effect of sanitary measures during the COVID-19 pandemic.

In absolute terms, in 2020, the volume of antiviral MPs consumption increased by 2.38 times, which was accompanied by an increase in the average cost of one package by 55.8%. In the initial period of the novel coronavirus infection spread (2020), a significant increase in the share of oseltamivir was notified in the overall consumption structure (up to 17.26% compared to 0.71%, 1.60%, 2.11%, 3.23% and 3.25% in 2015–2019, respectively), and the number of the dispensed packages (by 23.5 times compared to the average value in 2015–2019). In 2021, the share of umifenovir MPs in the total volume of the realized demand increased (up to 40.1%).

In the authors’ opinion, the results of the study confirm the need to strengthen control over the implementation of AMPs. Other measures may include timely informing outpatient medical specialists about the new editions appearance of methodological recommendations of the Russian Ministry of Health for the treatment of a novel coronavirus infection. By no means unimportant is the educational work with the population about the inadmissibility of following false algorithms for COVID-19 therapy. They periodically appear in the public domain on the Internet, social networks and instant messengers, and contain information about the need to take two, and sometimes three AMPs at the same time, even with mild course of the novel coronavirus infection.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS’ CONTRIBUTION

IKP, PAL – concept and design of the study, editing, approval of the article final version;
IIS, EPG – collection and processing of material, statistical data processing;
TKR – collection and processing of material, writing a text, compiling a references;
AAG – writing a text, compiling a references.

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