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Study of Consumer Spending on Individual Antiviral Drugs During Peak Periods of Seasonal Infectious Diseases

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ABSTRACT

The article analyzes the expenditures of consumers for individual antiviral drugs during peak periods of seasonal infectious diseases. The reason for addressing this topic and its relevance lies in the fact that the volume of consumer spending on pharmaceutical products has certain trends that directly depend on a number of factors: the spread of infectious diseases, an increase in the level of advertising of a particular drug, an increase in the number of pharmacies in a particular network in residential areas and places of the greatest concentration of consumers, etc. However, in our opinion, the first factor is the most important when considering the dynamics of consumer expenditures for pharmaceutical products. In this regard, the most interesting is the dynamics of costs for the purchase of a particular group of drugs and the reasons for its increase.

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INTRODUCTION

In the modern period, consumers are forced to keep their budget taking into account the costs of various antiviral drugs due not only to the suppression of seasonal spread of influenza viruses, but also for the treatment and prevention of the spread of coronavirus infection. Despite the fact that the coronavirus has been spreading in waves around the world for almost two full years now, influenza viruses still remain relevant, largely virulent, which cannot but predetermine the need to control them.[1]

It is known that modern antiviral drugs have various cost, at the same time, the specified cost can be formed on the basis of both the cost of the components of the antiviral drug, and taking into account the marketing policy of pharmaceutical companies, when people overpay more for the brand. For this reason, it is interesting to study the consumer expenditures for individual antiviral drugs during peak periods of seasonal infectious diseases.

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MATERIALS AND METHODS

When writing the study, data concerning the sale of antiviral drugs for a certain period of time were taken for analysis. These data were tabulated, analyzed, and appropriate conclusion was drawn based on the results of the analysis. When working with information obtained from various sources, analytical and comparative research methods were used.

RESULTS

A virus is a microscopic organism that cannot reproduce by itself outside the host organism. Viruses carry either ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) as genetic material, which can be single-stranded or double-stranded.

Infection of people with viruses has led to millions of deaths worldwide and is the cause of human diseases such as HIV/AIDS, hepatitis, influenza, herpes simplex, colds, etc. The infectious process varies depending on the type of virus; however, they follow certain common steps when infecting host animals.[2]

Typical stages of viral infection include:

- Attachment and penetration: initially, glycoproteins on the virus envelope attach to receptor/coreceptor molecules on the membrane of the host cell, which facilitates the penetration of the virus into the host cell through endocytosis;
- Removal of the virus envelope: the capsid of the internalized virus is cleaved by the enzymes of the host cell, and the viral components (genetic material and proteins) are released into the host cytosol;
- Replication and transcription of the viral genome: a viral genome containing DNA or RNA is transported to the nucleus, where it is replicated and transcribed to form multiple copies of genome molecules and matrix RNA (mRNA), respectively.
- The mechanism of replication varies depending on the type of genome, such as DNA/RNA, single-stranded/double-stranded, etc. The RNA genome can replicate in the cytoplasm itself;
- Protein synthesis: viral mRNAs are translated into structural and regulatory proteins in the cytoplasm using the mechanism of protein synthesis of the host cell;
- Compound: successful replication and expression of the viral genome produce components necessary for the survival of the offspring of the virus after release from the host cell. Thus, all the necessary components are packaged together to produce new viruses.;
- Rrelease: offspring viruses are released into the extracellular fluid by lysis of the host cell or budding. The lysis process causes the death of the host cell, whereas budding may not occur.[3]

The infectious nature of viruses has forced the scientific community to develop antiviral drug molecules to limit the survival and spread of viruses by blocking any one or a combination of the above stages of the virus life cycle.

An antiviral drug is an agent (small or large molecules, synthetic or natural) that can reduce an infectious disease caused by a virus. In 1963, the U.S. Food and Drug Administration (FDA) approved the first antiviral drug idoxuridine for the treatment of infection caused by the herpes simplex virus.

The surge in chronic viral infections such as HIV, VHC, HBV, etc., and the emergence of new viruses such as severe acute respiratory syndrome (SARS) coronaviruses highlight the growing need for new strategies for the development of antiviral agents. In particular, the emergence of the human immunodeficiency virus (HIV) epidemic associated with acquired immunodeficiency syndrome (AIDS) worldwide in the 1980s improved efforts leading to advances in therapeutic innovations as well as in basic science. This led to the development of antiviral inhibitors not only of HIV, but also of other viruses.

Among the antiviral compounds approved by the FDA, most are small molecules with diverse roles in clinical use. Large molecules approved as antiviral drugs include proteins (interferons, monoclonal antibodies), peptides and oligonucleotides. Most of these FDA-approved antiviral drugs target the cellular mechanism of the virus, on the other hand, very few of them target host cells/cellular mechanisms.[4]

Antiviral drugs are prescribed in the form of mono- and combination therapy. In monotherapy, antiviral agents target either the virus or host systems, whereas in the case of combination therapy, although most therapies are aimed at viral proteins, few are aimed at both viral proteins and host proteins. Drug molecules approved by the FDA have various mechanisms of antiviral activity and, based on their structure and/or function, can be grouped into structural analogues (nucleoside analogues, non-nucleoside pyrophosphate analogues, 5-substituted 2'-deoxyuridine analogues, acyclic nucleoside phosphonate analogues, acyclic guanosine analogues), penetration inhibitors, integrase inhibitors, nucleoside reverse reaction inhibitors transcriptases, non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, inhibitors, specific for some viruses (influenza virus inhibitors, NS5A and NS5B protein of hepatitis C virus). polymerase inhibitors), as well as interferons, immunomodulators, antimitotic inhibitors and oligonucleotides.

Over the past decades, effective antiviral drugs have been developed aimed at reducing the activity and suppression of various groups of viruses. The most common of them are respiratory syncytial viruses.

Respiratory syncytial virus (RSV) belongs to the Paramyxoviridae family, containing a linear single-stranded RNA genome with a negative meaning, with two antigenic subtypes: A and B.[5]

The FDA approved RSV-IGIV (RespiGam), a human immunoglobulin for the treatment of RSV in 1996. These antibodies prevent RSV particles from binding to host cells by inhibiting the surface glycoproteins G and F of the virus. However, it has been stopped from clinical use due to the high cost and strict rules of use. Later, in 1998, the cost-effective monoclonal antibody palivizumab (Synagis) was licensed for the treatment of infants at risk of infecting severe RSV infections. Palivizumab is aimed at the epitope in the antigenic site A of the RSV fusion protein (F) and prevents binding to host cells.

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The FDA approved a broad-spectrum antiviral agent, ribavirin (virazole), in 1985 to affect the activity of viral RNA polymerase by inhibiting inosine-5'-monophosphate (IMP) dehydrogenase, which is necessary for the synthesis of GTP.

Influenza viruses belong to the Orthomyxoviridae family with a linear single-stranded RNA genome with a negative meaning and are divided into three types: A, B and C. Influenza pandemics such as the Spanish flu (1918), Asian flu (1957),

Congo flu (1968) and swine flu (2009) were caused by influenza A viruses.

Until April 2020, the FDA approved nine antiviral drugs for the treatment of influenza infections, which include two matrix 2 (M2) ion channel inhibitors, four neuraminidase inhibitors, two polymerase inhibitors and one endonuclease inhibitor.

Transmembrane M2 proteins form proton channels in the viral envelope to maintain pH through the viral membrane during cell penetration and through the Golgi trans membrane of infected cells during viral maturation. Neuraminidase promotes the stage of maturation of influenza infection by cleaving sialic acids from the receptors of host cells, as well as from hemagglutinin and neuraminidase on the surface of formed virions. This process prevents the aggregation of virions and promotes the release of descendant virions, stopping the reverse binding of the virus to the dying host cell.[6]

Amantadine (Symmetrel) and rimantadine (Flumadine) are aimed at removing the virus envelope inside the endosomes by blocking the passage of H+ ions into viral particles through M2 channels. The prescription of amantadine was discontinued due to the high resistance of viruses to its action.

Viral neuraminidase inhibitors include zanamivir (Relenza), oseltamivir (Tamiflu), laninamivir octanoate (inavir) and peramivir (rapivab). Interestingly, inhaling zanamivir prevents the release of viral particles from host cells by affecting viral neuraminidase. Oseltamivir phosphate is recommended orally for the treatment of acute uncomplicated influenza.

Peramivir, which is administered intravenously, demonstrates the same effectiveness as oseltamivir, and is prescribed as a therapy for severe seasonal influenza. On the other hand, laninamivir octanoate inhalation has shown high efficacy in the treatment of seasonal influenza, even in adult patients resistant to oseltamivir.

The triphosphate form of ribavirin (virazole) and favipiravir (avigan) effectively inhibits the activity of influenza RNA polymerase. Favipiravir has been approved in Japan for the treatment of infections caused by influenza A, B and C viruses because it can inhibit RNA polymerases of various influenza viruses, including highly pathogenic H5N1 viruses; and several other positive/negative RNA viruses. In addition, baloxavir marboxil (Xoflusa), approved in October 2018, selectively inhibits the cap-dependent endonuclease of viruses, which, in turn, prevents the activity of influenza virus RNA polymerase and replication of its mRNA.[7]

Currently, one of the seasonal infections in the future may be a new coronavirus infection, which the whole world has been controlling for almost two years.

The practice of treating coronavirus diseases, SARS and MERS included the repurposing of some safe antiviral drugs, such as remdesivir, lopinavir-ritonavir, interferons. Remdesivir (GS-5734), a nucleoside analog that inhibits viral RNA polymerase, has shown antiviral activity against various virus families such as *Filoviridae, Pneumoviridae, Paramyxoviridae* and *Coronaviridae*. Studies using human respiratory tract epithelial cell cultures (HAE) have shown that remdesivir can reduce the growth of SARS-CoV and MERS-CoV because it reduces viral titers and viral RNA in in vitro models.[8]

In addition, remdesivir had similar effects against other various CoVs, including HCoV-NL63 and mouse hepatitis virus (MHV). In addition, treatment of mice infected with MA15 SARS-CoV with remdesivir showed an improvement in the signs of the disease (weight loss, virus titers in the lungs). These results support the use of remdesivir as a therapeutic drug against coronaviruses.

An HIV-1 protease inhibitor, lopinavir-ritonavir (Kaletra), has shown inhibitory activity against 3CL ^{pro} SARS-CoV. Lopinavir-ritonavir in combination with ribavirin reduced viral load and clinical manifestations of death in patients with acute respiratory viral infections. Oral administration of lopinavir-ritonavir in a model of MERS-CoV infection in marmosets improved the condition of the disease. Based on in vitro and in vivo studies, a clinical trial (MIRACLE trial) is currently being conducted to study the effectiveness of combination therapy with lopinavir/ritonavir and recombinant interferon-β1b in hospitalized patients with MERS with a laboratory-confirmed diagnosis.[9]

Studies using monoclonal antibodies (mAbs) as therapeutics have shown the need to target multiple conservative viral epitopes using multiple mAbs, as mutations help the virus escape.

Host proteases such as furin, cathepsins, and TMPRSS2 process S-glycoproteins on the surface of the virus to facilitate its entry into host cells. Inhibition of the activity of these host proteins blocked the penetration of SARS-CoV and MERS-CoV into host cells. However, since different coronaviruses differ in S-glycoprotein, they require different host proteases to penetrate into host cells.[10]

Thus, treatment regimens should include a combination of host protease inhibitors, in particular, to counteract the emergence of new coronaviruses. In addition, immunomodulatory interferons (IFNs) are used to treat coronavirus infection. Treatment with type I interferons against SARS-CoV and MERS-CoV proved to be effective in in vitro and in vivo on primates. Interferons are often administered as part of combination therapy together with ribavirin and lopinavir-ritonavir.

Various strategies have been used to develop potential SARS-CoV-2 inhibitors, but there is no drug approved worldwide for the treatment of SARS-CoV-2 infection. The host binding S-glycoprotein SARS-CoV-2, which has a high homology with the glycoprotein SARS-CoV, proved to be a powerful therapeutic target for inhibition by CR3022, an antibody against SARS-CoV. However, >85% of variations in the receptor-binding domain (RBD) epitopes of S-glycoprotein indicate the need to develop new monoclonal antibodies against SARS-CoV-2.

In addition, the development of methods for the treatment of hyperinflammatory conditions in some patients infected with SARS-CoV-2 continues. Although treatment with low doses of corticosteroids in a subset of critically ill patients has shown potential benefits, more research is needed on the use of corticosteroids. Inhibition of interleukin 6 (IL-6), overexpression of which occurs during inflammation, using tocilizumab (an antibody specific to the IL-6 receptor) is under clinical investigation.

Recently, the anti-inflammatory corticosteroid dexamethasone has been shown to reduce the effect of SARS-CoV-2 in critically ill patients. Moreover, a recent study identified 66 human medicinal proteins in SARS-CoV-2 and examined the efficacy of 69 FDA-registered drugs, drugs in clinical trials and/

or preclinical compounds, in the tests for live infection of SARS-CoV-2.[11]

Currently, several other drugs are undergoing clinical trials as monotherapy and combination therapy for the treatment of SARS-CoV-2 infection. In addition, the plasma of convalescents of recovered patients, which serves as a source of specific human antibodies against SARS-CoV-2, is at the stage of clinical studies to determine its efficacy and safety when transfused to patients with SARS-CoV-2.[12]

Accordingly, various drugs play a significant role in preventing the development of seasonal viral diseases and reducing the activity of the virus. It is necessary to assess the demand by consumers of individual drugs included in this group in order to identify consumer preferences in the effectiveness of these drugs.

DISCUSSION

To analyze the volume of consumer spending on antiviral drugs during the period of development of seasonal infections, a study of the pricing policy of three online pharmacies was conducted: Apteka.RU ", "Rigla", "36,6", "Tabletochka".

10 antiviral drugs of solid dosage forms were selected for analysis: tablets and capsules.

Table 1 shows the prices of antiviral drugs offered by online pharmacies "Apteka.RU ", "Rigla", "Tabletochka" and "36,6". When analyzing antiviral drugs in online pharmacies, it was revealed that all of them are available for purchasing.

Figure 1 shows the dynamics of the price policy of antiviral drugs presented in the pharmacies under study in 2020.

During the analysis, it was revealed that the pharmacy "Apteka. RU " offers the lowest prices for antiviral drugs , the highest prices are marked in the pharmacy "36,6".

Analyzing the data presented in Table 1, we can say that among the cheapest offers, among antiviral drugs, the drug "Remantadine" can be noted, its cost ranges from 69.50-106 rubles.

The most expensive drug in the group of antiviral drugs under study is Valtrex, its cost ranges from 1380,9 to 1537,0 rubles.

Let's analyze in which periods (quarters) the sale of antiviral drugs increases (the number of sales of packages), Figure 2 is formed for these purposes.

As can be seen from the data presented in Figure 2, the largest sales of antiviral drugs were noted in the 4th quarter of 2020 for all four pharmacies studied, and the lowest sales (number of packages) were noted in the 3rd quarter (July, August, September). The 4th quarter accounts for the peak incidence of colds and acute respiratory infections, as well as during this cold period, viral diseases among consumers worsen.

Let's analyze what expenditures consumers have during the peak incidence of respiratory viral diseases. Figure 3 is formed for this analysis.

As can be seen from Figure 3, the average cost of antiviral drugs in the 1st quarter is 3850 rubles, in the second quarter 2920 rubles, in the 3rd quarter 4290 rubles, in the 4th quarter at the peak of seasonal antiviral diseases, the average cost of purchasing such drugs is 5560 rubles.

Thus, based on the analysis of the pricing policy of antiviral drugs, it can be indicated that the pharmacy "Apteka.RU "

Table 1: Pricing policy of antiviral drugs offered by pharmacies "Apteka.RU ", "Rigla", "Tabletochka" and "36.6" in 2020

№	*Name of the antiviral drug*	*Price in «Apteka.RU» (rub.)*	*Price in «Rigla» (rub.)*	*Price in «Tabletochka» (rub.)*	*Price in «36,6» (rub.)*
1	Arbidol tab. 100 mg. No. 10	270,60	292,0	269,0	321,0
2	Remantadine tab. 10 mg. No. 20	69,5	73,50	102,0	106,00
3	Ingavirin caps. 90 mg. № 7	532,0	569,0	594,0	620,0
4	Kagocel tab. 0.012 mg. No. 10	287,0	309,0	311,0	313,0
5	Acyclovir tab. 400 mg. No. 20	254,00	262,0	267,0	283,0
6	Ergoferon tab. for races. № 20	449,9	398,0	449,0	775,0
7	Umifenovir, caps, 50 mg No. 10	122,5	134,2	144,9	122,0
8	Famvir tab. 500 mg. No. 3	1693,3	1573,0	1692,0	1856,0
9	Valtrex tab. 500 mg. No. 10	1380,9	1395,0	1380,0	1537,00
10	Ribavirin caps. 200 mg. No. 30	384,0	390,2	392,8	395,80

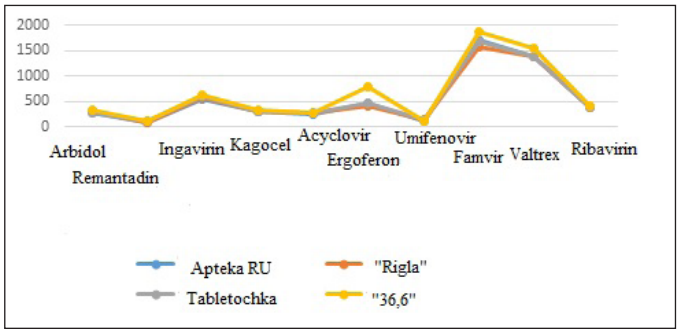

Fig. 1: Pricing policy of antiviral drugs presented in the study group of pharmacies: "Apteka.RU ", "Rigla", "Tabletochka" and "36.6" in 2020.

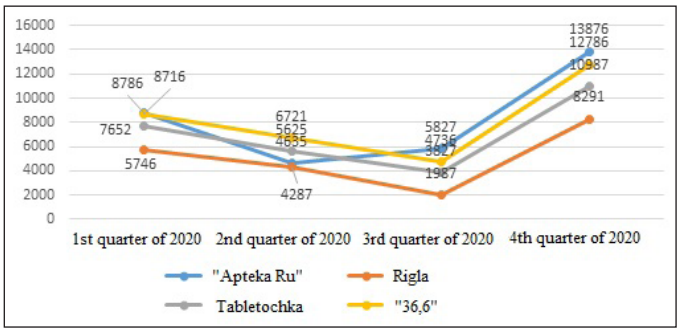

Fig. 2: The volume of sales of antiviral drugs in the pharmacies under study "Apteka.RU ", "Rigla", "Tabletochka" and "36.6" by quarters in 2020.

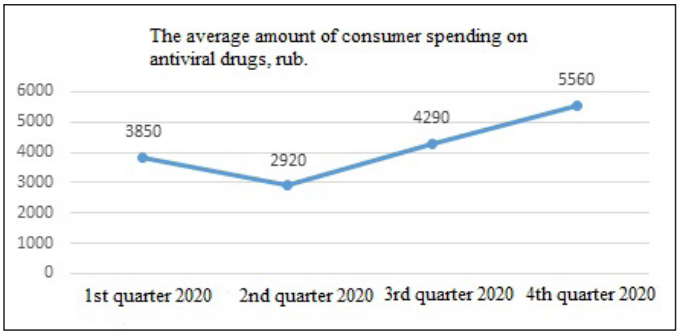

Fig.3: The average amount of consumer spending on antiviral drugs by quarters in 2020.

offers the lowest prices, the highest prices are recorded in the pharmacy "36,6". The largest volumes of sales of antiviral drugs were noted in the 4th quarter of 2020, and consumers in this period (4th quarter) spend the most money on average in the amount of 5,560 rubles, since during this period there is usually a peak of viral and respiratory diseases.

CONCLUSION

Effective antiviral drugs should resist drug resistance that develops in viruses with prolonged use, cope with the effects of embedded viral DNA in the human genome, be able to treat coinfections caused by various viruses, exclude interactions between drugs in combination treatment to prevent side effects, be cost-effective and cause low toxicity in patients. A negative factor noted in the analysis of consumer expenditures for antiviral drugs can be called the increase in prices for antiviral drugs in the season of disease growth - in spring and autumn. This factor affects the growth of consumer expenditures and reduces the possibility of purchasing the most effective medicines.

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