DOI:10.1111/irv.12085
www.influenzajournal.com

Antivirals for influenza: a summary of a systematic review and meta-analysis of observational studies

Jonathan Hsu,[a,*,†] Nancy Santesso,[a,*,†] Reem Mustafa,[a] Jan Brozek,[a] Yao Long Chen,[b] Jessica P. Hopkins,[a,c] Adrienne Cheung,[a] Gayane Hovhannisyan,[a] Liudmila Ivanova,[a] Signe A. Flottorp,[d,e] Ingvil Sæterdal,[d] Arthur D. Wong,[f] Jinhui Tian,[b] Timothy M. Uyeki,[g] Elie A. Akl,[a,h] Pablo Alonso-Coello,[i] Fiona Smaill,[j] Holger J. Schünemann[a,k]

[a]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada. [b]Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Gansu, China. [c]Niagara Region Public Health, Thorold, ON, Canada. [d]Norwegian Knowledge Centre for the Health Services, Oslo, Norway. [e]Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway. [f]Michael G. DeGroote School of Medicine, McMaster University, Hamilton, ON, Canada. [g]Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, USA. [h]Department of Medicine, State University of New York, Buffalo, NY, USA. [i]Iberoamerican Cochrane Centre, CIBERESP-IIB Sant Pau, Barcelona, Spain. [j]Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada. [k]Department of Medicine, McMaster University, Hamilton, ON, Canada.

Correspondence: Holger J. Schünemann, MD, PhD, MSc, FRCPC, Chair, Department of Clinical Epidemiology & Biostatistics, Michael Gent Chair in Healthcare Research, Professor of Clinical Epidemiology, Biostatistics and Medicine. Department of Clinical Epidemiology & Biostatistics, McMaster University Health Sciences Centre, Room 2C10B, 1200 Main Street West, Hamilton, ON L8N 3Z5, Canada. E-mail: schuneh@mcmaster.ca

*Contributed equally to this work.

†Prepared this summary of the original work which was published in the Annals of Internal Medicine (Hsu J, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. Ann Intern Med 2012; 156:512–524.) Reproduced with permission from the Annals of Internal Medicine.

Despite the use of antivirals to treat patients with severe influenza, questions remain with respect to effects and safety. Although a recent systematic review has provided some indication of benefit, the analysis is limited by the quality of the available evidence from randomized controlled trials. To supplement the existing information, the authors conducted a systematic review of observational studies of antiviral treatment for influenza. This report summarises the findings of that review. Similar to the randomised trials, the confidence in the estimates of the effects for decision-making is low to very low primarily due to the risk of selection and publication bias in the observational studies. From these observational studies, the summary estimates suggest that oseltamivir may reduce mortality, hospitalisation and duration of symptoms compared with no treatment. Inhaled zanamivir may also reduce symptom duration and hospitalisations, but patients may experience more complications compared with no treatment. Earlier treatment with antivirals is generally associated with better outcomes than later treatment. Further high-quality evidence is needed to inform treatment guidelines because of the overall low to very low quality of evidence.

Keywords antiviral, influenza, M2 ion channel blocker, neuraminidase inhibitor, observational study.

Please cite the original article: Hsu *et al.* Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. Annals of Internal Medicine 2013; 7(Suppl. 2), 76–81.

Introduction

Influenza remains a major global health concern. Most cases of influenza are self-limiting, and prevention through annual influenza vaccination may be an effective strategy. However, antivirals, such as neuraminidase inhibitors (oseltamivir and zanamivir) and M2 ion channel blockers (amantadine and rimantadine), are used to reduce symptoms and prevent hospitalisation or death in patients with severe illness.

Evidence about the effects and safety of antivirals continues to accumulate, and although a recently updated systematic review of randomised control trials (RCTs) offered some indication of treatment benefit,[1] concerns remain over the quality of evidence from published and unpublished randomized trials. The evidence from randomized trials is further limited by the lack of high-quality evidence for patient-important outcomes and lingering questions about the treatment of specific groups such as hospitalised or immunocompromised patients. Observational studies may provide additional information or higher quality evidence than the currently available RCTs for certain elements of antiviral treatment. This report summarises the results of a recently published systematic review of observational studies of antiviral treatment.[2] This review was intended to inform WHO guidelines, and the WHO essential medicine list about the antiretroviral treatment of influenza.

Methods

Electronic databases and grey literature were searched up to 16 November, 2010, using pre-defined eligibility criteria, without restriction on publication language or study type. Observational studies examining the effects of non-intravenous antiviral treatment with oseltamivir, zanamivir, amantadine or rimantadine compared with no treatment, and studies comparing the antivirals with one another or early administration of a particular antiviral (<48 hours) compared with later administration of the same antiviral (>48 hours) were included. Investigators independently screened all citations by title and abstract and by full text (920 articles) for inclusion. Several patient-important outcomes were assessed, including patient death, hospitalisation, duration of signs and symptoms, complications and adverse effects (see original report for full list of outcomes).[2]

Two investigators independently extracted data from the included studies using a pretested electronic form. Established methods to assess the risk of bias were used. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[3] Following GRADE guidelines, confidence in the effect estimates were categorised into four levels from very low to high.

Meta-analyses were conducted by using either the odds ratio (dichotomous outcomes) or mean differences or standardised mean differences (continuous outcomes). Whenever possible, studies were pooled for analysis according to whether or not results were adjusted for confounding. Although greater emphasis should be placed on data from the adjusted meta-analyses, the pooled results from unadjusted studies were also reported to provide a comprehensive view of the available evidence. Studies and other unpublished observational data that could not be pooled were synthesised narratively. When data were available, subgroup analyses were performed by age, risk of complications, laboratory-confirmed influenza versus influenza-like illness as well as other variables.

Results

Twelve thousand one hundred and eighty-eight database citations and 27 articles from the grey literature were identified, and 74 articles met the eligibility criteria. The majority of studies reported comparisons of oral oseltamivir with no antiviral therapy. Table 1 summarises the effects of oseltamivir over no treatment and the quality of evidence for each of the outcomes. Additional tables summarising the effects of the other antivirals are in the original publication.[2]

The evidence suggests that oseltamivir may reduce mortality in high-risk populations, such as hospitalised patients, compared with no antiviral treatment, but this effect is less pronounced when pooling data from unadjusted studies.[4–14] Meta-analyses indicate that oseltamivir may also reduce both hospitalisation in outpatients[15–18] as well as duration of symptoms.[19–24] Data from several studies also suggest that oseltamivir may reduce complications such as pneumonia,[15,17,18] otitis media[15,18] or any recurrent cardiovascular outcome.[25,26] Pre-planned subgroup analyses showed statistically significant effects in children compared with adults for both pneumonia and otitis media.

When comparing zanamivir to no treatment, there was moderate quality evidence that zanamivir reduced the duration of symptoms[24,27,28] (23 hours, CI 95% 17–28 hours; SMD −0·94, CI 95% −1·21 to −0·66); and very low-quality evidence that hospitalisations may be reduced[11,29] (OR 0·66, CI 95% 0·37–1·18). However, patients with influenza-like illness may experience more complications with inhaled zanamivir, including otitis media, respiratory disease or other complications.[29]

In direct comparisons of oseltamivir with zanamivir, inconsistent evidence suggests that zanamivir may have a slight advantage in reducing the duration of symptoms[20,23,28,30,31] (by 7 hours, CI 95% 2–12 hours; SMD 0·26, CI 95% 0·07–0·45). Very low to low-quality evidence showed that the two treatments may not differ with respect to mortality, hospitalisation, ICU admission, critical adverse events or viral shedding (as measured 5 days after treatment).[11,20,24]

Results from studies evaluating the effects of initiating treatment with oral oseltamivir within 48 hours of symptom onset versus initiation of treatment after 48 hours of symptoms suggest that mortality (OR 0·33, CI 95% 0·12–0·86), hospitalisations (OR 0·52, CI 95% 0·33–0·81) and ICU admission (OR 0·22, CI 95% 0·15–0·33) may be reduced when oseltamivir treatment is initiated earlier.[32–39] Similarly, there was low-quality evidence showing a reduction in symptom duration[40] and risk of complications,[41,42] when treatment was initiated earlier rather than later with amantadine or rimantadine, respectively.

Conclusions

The results of this review underscore the need for additional, high-quality studies to inform guidelines about the use of antiviral treatments for influenza. Many of the studies indentified in this review had a high risk of bias resulting from the lack of control for confounding variables and possible selection bias. In addition, meta-analysis was limited by the fact that few studies reported appropriately adjusted effect measures. These limitations make it difficult to draw firm conclusions from the studies, and care must be used when using this information to make healthcare decisions. Based on this evidence, however, oral oseltamivir and inhaled zanamivir may

Table 1. GRADE evidence profile for oral oseltamivir versus no antiviral therapy

Quality assessment		Summary of findings				
		Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up to 30 days	Overall quality of evidence	With no antiviral treatment	With oseltamivir	Relative effect (95% CI)	Risk with no antiviral treatment	Absolute effect with Oseltamivir (95% CI)
Mortality						
681 (three studies)	⊕⊕⊖⊖ LOW*	59/242 (24·4%)	31/439 (7·1%)	Adjusted OR 0·23 (0·13–0·43)	240 deaths per 1000	172 fewer deaths per 1000 (from 120 to 201 fewer)
1557 (nine studies)	⊕⊖⊖⊖ VERY LOW*,** due to risk of bias	61/320 (19·1%)	228/1237 (18·4%)	OR 0·51 (0·23–1·14)***	240 deaths per 1000	101 fewer deaths per 1000 (from 172 fewer to 25 more)
Hospitalisation						
150710 (four studies)	⊕⊕⊖⊖ LOW†	1238/100585 (1·2%)	431/50125 (0·86%)	Adjusted OR 0·75 (0·66–0·89)	12 hospitalisations per 1000	3 fewer hospitalisations per 1000 (from 1 to 4 fewer)
242762 (six studies)	⊕⊖⊖⊖ VERY LOW**,† due to risk of bias	1738/146410 (1·2%)	1086/96352 (1·1%)	OR 0·75 (0·66–0·86)	12 hospitalisations per 1000	3 fewer hospitalisations per 1000 (from 2 to 4 fewer)
ICU admissions/mechanicalventilation/respiratory failure						
1032 (six studies††)	⊕⊖⊖⊖ VERY LOW*,††† due to risk of bias, inconsistency	–	200/1032 (19·4%) Pooled Risk 13·0% (95% CI 11–15%)	–	–	
Duration of hospitalisation (days)						
832 (five studies)	⊕⊖⊖⊖ VERY LOW*,††,††† due to risk of bias, inconsistency	–	832	–	–	The mean duration of hospital stay was 5·16 days (5·02–5·29)
Duration of signs and symptoms (measured from onset of symptoms or treatment) (time to return to normal activity was not measured)						
5842 (six studies)	⊕⊖⊖⊖ VERY LOW*,††† due to inconsistency	449	5393	–	–	The mean time was 0·91 standard deviations lower (1·25–0·57 lower)‡
Complications – Pneumonia						
150466 (three studies)	⊕⊖⊖⊖ VERY LOW†,††† due to inconsistency	2111/100449 (2·1%)	647/50017 (1·3%)	Adjusted OR 0·83 (0·59–1·16)	21 pneumonias per 1000	4 fewer pneumonias per 1000 (from 9 fewer to 3 more)
265276 (six studies)	⊕⊖⊖⊖ VERY LOW**,†,††† due	3244/166256 (2%)	1273/99020 (1·3%)	OR 0·64 (0·46–0·88)	20 pneumonias per 1000	7 fewer pneumonias per 1000 (from 2 to 10 fewer)

Table 1. (*Continued*)

Quality assessment		Summary of findings				
		Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up to 30 days	Overall quality of evidence	With no antiviral treatment	With oseltamivir	Relative effect (95% CI)	Risk with no antiviral treatment	Absolute effect with Oseltamivir (95% CI)
	to risk of bias, inconsistency					
Complications – Otitis media						
78407 (two studies)	⊕⊕⊖⊖ LOW†	546/40022 (1·4%)	285/38385 (0·74%)	Adjusted OR 0·75 (0·64–0·87)	14 otitis media per 1000	3 fewer otitis media per 1000 (from 2 to 5 fewer)
193105 (four studies)	⊕⊖⊖⊖ VERY LOW**,†,††† due to risk of bias, inconsistency	2053/105758 (1·9%)	1381/87347 (1·6%)	OR 0·77 (0·63–0·94)	19 otitis media per 1000	4 fewer otitis media per 1000 (from 1 to 7 fewer)
Complications – Cardiovascular outcomes						
100830 (two studies)	⊕⊕⊖⊖ LOW†	62385	38445	Adjusted OR 0·58 (0·31–1·1)	200 cardiac events per 1000	73 fewer cardiac events per 1000 (from 128 fewer to 16 more)
60678 (two studies)	⊕⊖⊖⊖ VERY LOW**,†,††† due to risk of bias, inconsistency	6814/50696 (13·4%)	606/9982 (6·1%)	OR 0·45 (0·25–0·81)	110 cardiac events per 1000	57 fewer cardiac events per 1000 (from 19 to 80 fewer)
Critical Adverse Events						
104930 (five studies)	⊕⊕⊖⊖ LOW†	60817	44113	Rate Ratio 0·76 (0·7–0·81)	420 adverse events per 1000 patient years	101 fewer adverse events per 1000 patient years (from 80 to 126 fewer)

*Although we did not downgrade, publication bias cannot be excluded.
**Studies not adjusted for potential confounding factors.
***Significant differences in effect for pandemic versus seasonal influenza (see subgroup analyses table).
†Publication bias a concern because large studies had for-profit funding and weighed heavily in analyses.
††No independent comparison group.
†††High heterogeneity among studies.
‡This translates to reduced symptom duration of approximately 33 hours (95% CI 21–45 hours). Despite the large effect, we did not upgrade because there was important inconsistency across studies.
Note: Information linking specific studies to each of the analyses above may be found in the original publication.

provide net benefit over no treatment, although treatment with zanamivir may result in more complications than no treatment. In direct comparisons, zanamivir may be slightly more effective in reducing the duration of symptoms than oseltamivir. The evidence further suggests that administering antivirals within 48 hours of symptoms may be of greater benefit than initiating treatment at a later time.

Although the overall confidence in the effect estimates is low to very low, this review has nevertheless provided important evidence supporting a role for antivirals in the treatment of influenza and must be viewed in the context of the information available from RCTs and the substantial burden of influenza worldwide. There remains a need for high-quality evidence from RCTs that address patient-important outcomes and include hospitalised patients with influenza. Observational studies can continue to supplement this evidence by contributing data about special populations, adverse effects and rare harms.

Acknowledgements

The authors thank Rasha Khatib and Meg Fukuzawa for translation of Japanese articles, Wojtek Wiercioch for help with reference management, DianeHeels-Ansdell for statistical support, Glaxo Smith Kline and James Smith (Roche) for responding to our requests to identify studies, and Dr. Tom Jefferson for his help in interpreting the recent Cochrane reviews that he authored summarising the RCTs on this topic. This article is a summary from Hsu J, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. Ann Intern Med 2012; 156:512–524.

Conflict of interest

Ms. Santesso; Drs. Mustafa, Brozek, Hopkins, Flottorp, and Schünemann; Mr. Chen; Ms. Cheung; Mr. Wong; and Mr. Tian report the following: Grant (money to institution): World Health Organization.

Funding

World Health Organization and McMaster University.

References

1 Jefferson T, Jones M, Doshi P, Del Mar C, Dooley L, Foxlee R. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database Syst Rev 2012; 1:CD008965.

2 Hsu J, *et al.* Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. Ann Intern Med 2012; 156:512–524.

3 Guyatt GH, *et al.* Rating quality of evidence and strength of recommendations GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336:924–926.

4 Chemaly RF, Torres HA, Aguilera EA, *et al.* Neuraminidase inhibitors improve outcome of patients with leukemia and influenza: an observational study. Clin Infect Dis 2007; 44:964–967.

5 Estenssoro E, Rios FG, Apezteguia C, *et al.* Pandemic 2009 influenza A in Argentina: a study of 337 patients on mechanical ventilation. Am J Respir Crit Care Med 2010; 182:41–48.

6 Hien ND, Ha NH, Van NT, *et al.* Human infection with highly pathogenic avian influenza virus (H5N1) in Northern Vietnam, 2004–2005. Emerg Infect Dis 2009; 15:19–23.

7 Huang YC, Li WC, Tsao KC, Huang CG, Chiu CH, Lin TY. Influenza-associated central nervous system dysfunction in Taiwanese children: clinical characteristics and outcomes with and without administration of oseltamivir. Pediatr Infect Dis J 2009; 28:647–648.

8 Li IW, Hung IF, To KK, *et al.* The natural viral load profile of patients with pandemic 2009 influenza A(H1N1) and the effect of oseltamivir treatment. Chest 2010; 137:759–768.

9 Liem NT, Tung CV, Hien ND, *et al.* Clinical features of human influenza a (H5N1) infection in vietnam: 2004–2006. Clin Infect Dis 2009; 48:1639–1646.

10 McGeer A, Green KA, Plevneshi A, *et al.* Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. Clin Infect Dis 2007; 45:1568–1575.

11 Siston AM, Rasmussen SA, Honein MA, *et al.* Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA 2010; 303:1517–1525.

12 Xi X, Xu Y, Jiang L, Li A, Duan J, Du B. Hospitalized adult patients with 2009 influenza A(H1N1) in Beijing, China: risk factors for hospital mortality. BMC Infect Dis 2009; 10:256.

13 Hanshaoworakul W, Simmerman JM, Narueponjirakul U, *et al.* Severe human influenza infections in Thailand: oseltamivir treatment and risk factors for fatal outcome. PLoS ONE 2009; 4:e6051.

14 McGeer A, Green K, Drews S *et al.* Epidemiology of influenza illness requiring intensive care unit admission in Toronto, Canada. 19th European Congress of Clinical Microbiology and Infectious Diseases [conference abstract]. 2009; vol 15:S26.

15 Blumentals WA, Song X. The safety of oseltamivir in patients with influenza: analysis of healthcare claims data from six influenza seasons. MedGenMed 2007; 9:23.

16 Dharan NJ, Gubareva LV, Klimov AI, Fiare AE, Bresee JS, Fry AM. Antiviral treatment of patients with oseltamivir-resistant and oseltamivir-susceptible seasonal influenza A (H1N1) infection during the 2007–2008 influenza season in the United States. Clin Infect Dis [Letter]. 2010; 50:621–622.

17 Nordstrom BL, Sung I, Suter P, Szneke P. Risk of pneumonia and other complications of influenza-like illness in patients treated with oseltamivir. Curr Med Res Opin 2005; 21:761–768.

18 Piedra PA, Schulman KL, Blumentals WA. Effects of oseltamivir on influenza-related complications in children with chronic medical conditions. Pediatrics 2009; 124:170–178.

19 Imamura T, Hosoya M, Oonishi N, *et al.* The study on efficacy of oseltamivir for influenza A in children. Kansenshogaku Zasshi 2003; 77:971–976.

20 Kawai N, Ikematsu H, Iwaki N, *et al.* A comparison of the effectiveness of zanamivir and oseltamivir for the treatment of influenza A and B. J Infect 2008; 56:51–57.

21 Kawai N, Ikematsu H, Iwaki N, *et al.* A comparison of the effectiveness of oseltamivir for the treatment of influenza A and influenza B: a

Japanese multicenter study of the 2003–2004 and 2004–2005 influenza seasons. Clin Infect Dis 2006; 43:439–444.
22 Sato M, Saito R, Sato I, *et al.* Effectiveness of oseltamivir treatment among children with influenza A or B virus infections during four successive winters in Niigata City. Japan. Tohoku J Exp Med 2008; 214:113–120.
23 Sugaya N, Mitamura K, Yamazaki M, *et al.* Lower clinical effectiveness of oseltamivir against influenza B contrasted with influenza A infection in children. Clin Infect Dis 2007; 44:197–202.
24 Sugaya N, Tamura D, Yamazaki M, *et al.* Comparison of the clinical effectiveness of oseltamivir and zanamivir against influenza virus infection in children. Clin Infect Dis 2008; 47:339–345.
25 Casscells SW, Granger E, Kress AM, Linton A, Madjid M, Cottrell L. Use of Oseltamivir after influenza infection is associated with reduced incidence of recurrent adverse cardiovascular outcomes among military health system beneficiaries with prior cardiovascular diseases. Circ Cardiovasc Qual Outcomes 2009; 2:108–115.
26 Peters PH Jr, Moscona A, Schulman KL, Barr CE. Study of the impact of oseltamivir on the risk for pneumonia and other outcomes of influenza, 2000–2005. MedGenMed 2008; 10:131.
27 Machado CM, Vilas Boas LS, Mendes AVA, *et al.* Low mortality rates related to respiratory virus infections after bone marrow transplantation. Bone Marrow Transplant 2003; 31:695–700.
28 Saito R, Sato I, Suzuki Y, *et al.* Reduced effectiveness of oseltamivir in children infected with oseltamivir-resistant influenza A (H1N1) viruses with His275Tyr mutation. Pediatr Infect Dis J 2010; 29:898–904.
29 Cole JA, Loughlin JE, Ajene AN, Rosenberg DM, Cook SF, Walker AM. The effect of zanamivir treatment on influenza complications: a retrospective cohort study. Clin Ther 2002; 24:1824–1839.
30 Kawai N, Ikematsu H, Iwaki N, *et al.* Clinical effectiveness of oseltamivir for influenza A(H1N1) virus with H274Y neuraminidase mutation. J Infect 2009; 59:207–212.
31 Komiya N, Gu Y, Kamiya H *et al.* Clinical features of cases of influenza A (H1N1)v in Osaka prefecture, Japan, May 2009. Euro Surveill. 2009; 14.
32 Chien YS, Su CP, Tsai HT, *et al.* Predictors and outcomes of respiratory failure among hospitalized pneumonia patients with 2009 H1N1 influenza in Taiwan. J Infect 2010; 60:168–174.
33 Hien TT, Boni MF, Bryant JE, *et al.* Early pandemic influenza (2009 H1N1) in Ho Chi Minh city, Vietnam: a clinical virological and epidemiological analysis. PLoS Med 2010; 7:e1000277.
34 Lee N, Chan PKS, Hui DSC, *et al.* Viral loads and duration of viral shedding in adult patients hospitalized with influenza. J Infect Dis 2009; 200:492–500.
35 Ling LM, Chow AL, Lye DC, *et al.* Effects of early oseltamivir therapy on viral shedding in 2009 pandemic influenza A (H1N1) virus infection. Clin Infect Dis 2010; 50:963–969.
36 Centers for Disease Control and Prevention (CDC). Patients hospitalized with 2009 pandemic influenza A (H1N1) – New York City, May 2009. MMWR Morb Mortal Wkly Rep 2009; 2010(58):1436–1440.
37 Lee N, Choi KW, Chan PKS, *et al.* Outcomes of adults hospitalised with severe influenza. Thorax 2010; 65:510–515.
38 Subramony H, Lai FY, Ang LW, Cutter JL, Lim PL, James L. An epidemiological study of 1348 cases of pandemic H1N1 influenza admitted to Singapore Hospitals from July to September 2009. Ann Acad Med Singapore 2010; 39:283–288.
39 Yu H, Liao Q, Yuan Y, *et al.* Effectiveness of oseltamivir on disease progression and viral RNA shedding in patients with mild pandemic 2009 influenza A H1N1: opportunistic retrospective study of medical charts in China. BMJ 2010; 341:c4779.
40 Kawai N, Ikematsu H, Iwaki N, *et al.* Factors influencing the effectiveness of oseltamivir and amantadine for the treatment of influenza: a multicenter study from japan of the 2002–2003 influenza season. Clin Infect Dis 2005; 40:1309–1316.
41 Gagarinova VM, Shadrin AS, Kubar OI, Kustikova IG, Araslanova II. Organization and evaluation of the effectiveness of emergency prophylaxis and early treatment of influenza with remantadine in serevodvinsk. Zh Mikrobiol Epidemiol Immunobiol. 1983;3: 60–63.
42 Shadrin AS, Araslanova II, Dekterev AN, Gagarinova VM, Tamarkina KN. Organization and the results of the early ambulatory treatment of influenza patients. Sov Med 1980; 9:103–104.