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LIVE ENTEROVIRUS VACCINES FOR EMERGENCY NON-SPECIFIC PREVENTION OF MASS RESPIRATORY DISEASES DURING AUTUMN-WINTER OUTBREAKS OF INFLUENZA AND OTHER ACUTE RESPIRATORY DISEASES

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Influenza and associated respiratory infections cause extensive material loss almost every year and affect many millions of people.

The use of even best manufactures specific influenza vaccines, cannot significantly reduce the mass morbidity during epidemics, since, in addition to the current serotypes of the influenza virus, from 20 to 75% of all other cases of acute respiratory infections (ARI) are caused by other pathogens [4].

Currently, in addition to influenza viruses, 32 serotypes of adenoviruses, three types of parainfluenza viruses, one type of respiratory syncytial virus, more than 60 serotypes of rhinoviruses, some pathogenic enteroviruses from Coxsackie and ECHO groups (more than ten types) are considered to be responsible for ARIs [1, 2, 6, .7]. At least 110 types of viruses are now being associated with ARIs. In addition, acute respiratory infections can be caused by Mycoplasma pneumoniae.

Naturally, with such an etiological variety of diseases during the autumn-winter epidemics of influenza and acute respiratory infections, it is impossible to prevent acute respiratory infections caused by other viruses using specific vaccines, even if they are developed and available.

A completely new principle of prevention during polyetiological outbreaks of diseases that come along with actual flu is required. This principle, based on the use of standard live enterovirus vaccines that stimulate the formation of endogenous interferon in the body, was first developed and proposed in 1965-1966 by Corresponding Member of AMS Prof. M.K. Voroshilova [1]. Her

discovery of the beneficial properties of enteroviral interferon inducers was recently registered with the State Committee for Inventions and Discoveries.

This article analyzes the results of the mass controlled application of the new approach to nonspecific emergency prevention of influenza and other acute respiratory infections with the aid of 2-3-fold vaccinations of standard oral enterovirus vaccines for healthy people in the initial prose of the autumn-winter outbreaks of influenza and other acute respiratory infections.

Materials and methods. Controlled trials of epidemiological efficacy were carried out during three seasonal outbreaks of influenza and other associated acute respiratory infections (1968-1971) in 16 regions of three USSR republics. The surveillance covered about 320 thousand people, 2/3 of whom have received orally from 2 to 3 live enteroviral interferon-inducing vaccine strains (LEV). In addition to the authors, practical medical workers of sanitary-epidemiological stations and some scientific institutes participated in the work on conducting the controlled trials [9].

Throughout the entire period of testing, there was not a single case of any undesirable adverse reactions to the use of LEVs [I, 5–8, 9].

As standard interferon inducers, five types of oral LEVs were selected for testing, including mono-vaccines based on Sabin strains of poliovirus types I, II, III (LPV) and two mono-vaccines (LEV-4 and LEV-7), prepared from non-pathogenic for humans strains of Echovirus 1 and Echovirus 12 serotypes isolated from feces of healthy children in the laboratory of M. K. Voroshilova [2].

Table 1. Efficacy of Sabin live poliovirus vaccine (LPV) against influenza and ARIs.

City, Year, Vaccine name	Individuals under study			% of disease cases		Morbidity reduction, fold	Number of protected individuals
	Control	LPV-1 + LPV-3	All together	control	vaccinated		
Tallinn (1970) LPV-1	2,984	7,560	10,544	26.41	5.81	4.5	1,558
Gorky (1970) LPV-1 + LPV-3	18,880	40,673	59,558	28.9	15.5	1.9	5,451
Balashikha (1970) LPV-1 + LPV-3	2,066	2,744	4,819	20.2	7.0	2.9	363
Vnukovo (1970) LPV-1 + LPV-3	1,994	9,083	11,077	64.9	11.2	5.8	4,878
All together:	25,924	60,965	85,989	-	-	3.8*	12,250

- Mean value of morbidity decrease

LPVs from the three vaccine strains of Sabin are widely used to immunize children and adults against polio. In this and other countries, its safety to humans is proved.

In 1969, two non-pathogenic to humans enterovirus strains LEV-4 (GS strain of Echovirus 1) and LEV-7 (L 0572 MH strain of Echovirus 12) have been approved for nonspecific prevention of enterovirus infections in children and adults in the USSR [3].

Results and discussion. In cities during the year 1970, influenza outbreaks were caused mainly by influenza viruses (H2N2), but also by several other types of viruses. For the nonspecific emergency prevention of the ARIs, we used oral administration of Sabin type I and III vaccine strains. Table 1 demonstrates the efficacy of the oral administration of this vaccine. In total, there were 85,989 individuals under the observation, including 60,065 healthy individuals who received the vaccine during the 1st week of the outbreak, and 25,924 individuals (control) who did not take the vaccine. During the observation, a significant decrease in the disease incidence rate was obtained among the vaccinated individuals. The decrease was 1.9, 2.9, 4.5, and 5.8 fold (an average 3.8 fold), compared with unvaccinated individuals.

Table 2. The efficacy of live enterovirus vaccines for the prevention of influenza and acute respiratory infections.

City, Year, Vaccine name	Individuals under study			% of disease cases		Morbidity reduction, fold	Number of protected individuals
	Control	LEV-4 + LEV-7	All together	control	vaccinated		
Tallinn (1970) LEV-1 + LEV-7	1,344	649	1,993	7.6	3.8	2.0	76
Khabarovsk (1969) LEV-4	12,179	16,454	28,624	6.33	1.45	4.4	802
Khabarovsk (1970) LEV-7 + LEV-4	716	2,733	3,449	50.98	18.23	2.8	892
Khabarovsk (1971) LEV-4 + LEV-7	1,006	942	1,948	17.59	8.7	2.0	105
Khabarovsk (1971) LEV-4 + LEV-7	343	1,243	1,586	18.37	9.89	1.9	105
All together:	15,579	22,021	37,600	-	-	2.62*	2,059

- Mean value of morbidity decrease

Notably, the decrease in the incidence rate during outbreaks of influenza and other ARIs is significantly higher than when after immunization with specific influenza vaccines.

Table. 2 shows the results of nonspecific prevention of influenza and ARIs in several regions during the 1969, 1970, and 1971 outbreaks by using oral or intranasal administration of LEV-4 plus LEV-7. In total, 22 021 individuals received the vaccine within the initial weeks of the

outbreak, and 15 589 initials who did not take the vaccine (control). There was a significant reduction in the incidence rate among the vaccinated individuals, 1.9 to 2.8 - 4.4 fold, on average, 2.6 fold, compared with the unvaccinated ones, which is close to the usual efficacy of specific influenza vaccines. According to these observations, LEV-4 plus LEV-7 prevented 2059 individuals from contracting the flu or ARI.

Table 3. The efficacy of LEV for non-specific emergency prevention of influenza and acute respiratory infections.

City, Year, Vaccine name	Individuals under study			% of disease cases		Morbidity reduction, fold	Number of protected individuals
	Control	LPV-1 + LEV-4 + LEV-7	All together	control	vaccinated		
Tallinn (1970) LEV-4 + LPV-1	2,492	12,566	15,058	28.17	6.1	4.6	2,786
Dzerzhinsk (1971) LPV-1 + LEV-4	6,869	9,604	16,473	4.55	1.9	2.4	255
Khabarovsk (1970) LEV-7 + LPV-1	3,650	5,733	9,383	18.7	5.2	3.6	774
Kiev (1969-1970) LEV-7 + LPV-1	13,082	42,053	55,145	16.8	5.9	2.8	4,576
All together:	26,103	69,966	96,059	-	-	3.35*	8,391

- Mean value of morbidity decrease

A more significant number of observations (Table 3) was used for the nonspecific prevention of influenza and ARIs, with two viruses LEV-4 and LEV-7 in combination with Type 1 LPV. This combination of sequential use of 3 types of live vaccines in 69,956 individuals at the beginning of outbreaks of influenza and ARIs made it possible to reduce the incidence by an average of 3.35 fold compared with the 26,103 control individuals who did not take the vaccines. A total of 8391 individuals were protected from influenza and acute respiratory infections in these observations.

Summary data on the efficacy of combinations of the three enteroviral vaccines are in Table 4. In total, 152,042 individuals were subjected to enterovirus vaccines at the beginning of outbreaks of influenza and ARIs, while 67,606 individuals were not vaccinated. The arithmetic average of the incidence rate reduction among the vaccinated was 3.2.

Table 4. Comparison of the efficacy of different vaccine combinations.

Vaccine name	Individuals under study			Morbidity reduction, fold	Number of protected individuals
	Control	vaccinated	All together		
LPV-1 + LPV-3	25,924	60,063	85,989	3.8	12,250
LEV-4 + LEV-7	15,579	22,021	37,600	2.6	2,059
LPV-1 + LEV-4 + LEV-7	26,103	69,956	96,059	3.3	8,391
All together:	67,606	152,042	219,649	3.2	22,700

The protective mechanism of standard enterovirus interferon-inducing vaccines against influenza and ARIs is probably based on the rapid spread of the enteroviruses in the body and thus interfering with the subsequent infection of cells with respiratory viruses. The detailed mechanism of the interference needs additional studies. However, the nonspecific beneficial effect of enteroviruses against influenza and other respiratory viruses does not raise doubts.

The endogenous interferon, which appears in the blood and the throat swabs within the first days after vaccination of healthy people with enterovirus vaccines, according to L. S. Priymyagi et al. [5], reached the highest values on days 7–9; the interferon titer reduction was observed on days 14 - 16. In the case of revaccination within two weeks, the decrease in interferon titers could be delayed for another 4-6 days [5].

Consequently, a 2–to 3-fold administration of enterovirus vaccines at intervals of 10–14 days can provide short (3–5 weeks) but quite adequate protection against influenza and acute respiratory infections. Such an approach can significantly reduce the total number of disease cases during the winter outbreaks, which usually lasts for no more than two months. It is recommended to alternate the sequential administration of different serotypes of LEV mono-vaccines in order to avoid mitigation of the effects by arising antiviral immunity.

Nonspecific vaccination with LEVs does not work in advance when applied long before the outbreaks, due to the relatively short period of circulation of endogenous interferon in the body.

The interferon-inducing enterovirus vaccines can also be taken intranasally, but oral administration in liquid form, or as jelly beans, is the most convenient. Typically, a dose of vaccine contains between 1 and 2 million culture infection units of the virus. There is no danger of overdose of standard LEVs.

In addition to the preventive effect, the use of standard LEVs at the beginning of outbreaks of influenza and ARIs can also have a therapeutic effect that ameliorated the first symptoms of the disease in the initial stages. As an example, during an influenza outbreak in Moscow, 18 employees of an institution received LEV-4. The vaccine was administered within 2 to 14 hours after the appearance of typical signs of the disease (general malaise, catarrhal symptoms in the nasopharynx, headache, muscle pain, chills, fever). The vaccine was administered in most cases at night and on an empty stomach.

In 12 patients, the symptoms of the disease were completely absent 10-12 hours after taking the vaccine. In 6 individuals, after 10-12 hours, a significant improvement was observed, and after 24 hours, the symptoms of the disease completely disappeared. Meantime, in the same institution, 8 out of 10 individuals who received a sterile Hanks solution, as a placebo, at the beginning of the disease have developed disease with an average of 4 days.

The significant advantages of the method of nonspecific prevention of influenza and ARIs are as follows:

- the possibility of emergency mass prevention of diseases in the context of an upcoming epidemic outbreak of influenza of unknown etiology and ARIs to reduce the incidence;
- lack of adverse effects and safety of standard enterovirus vaccines;
- the simplicity and convenience of oral administration of interferon inducing enterovirus vaccines;
- cost-effectiveness and the availability of the recommended interferon inducing enterovirus vaccines;
- the possibility of the combined use of enterovirus vaccines and some preventive chemotherapy drugs.

As a result of the 3-year long controlled trials of epidemiological efficacy of five serotypes of LEVs for nonspecific emergency prevention during epidemics of influenza and acute respiratory infections, a significant decrease in the total incidence of influenza and ARIs was achieved. The use of enterovirus vaccines in 152,042 individuals allowed to protect at least 22,700 people from influenza and ARIs by reducing the incidence by an average of 3.2 fold compared with the individuals who did not receive LEVs.

These results allow us to recommend the new approach for nonspecific emergency prevention of influenza and other unidentified ARIs within the initial phases of seasonal outbreaks.

Conclusions

1. The efficacy of the new approach to nonspecific emergency prevention of influenza and ARIs using live oral enterovirus vaccines as interferon inducers was evaluated.

2. The use of live enterovirus vaccines in controlled trials reduced the incidence rate 3.2 fold allowing to recommended the use of LEVs for nonspecific emergency prevention of influenza and other ARIs within the initial phases of outbreaks.

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