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PHARMACOECONOMIC AND EPIDEMIOLOGICAL BASES OF OPTIMAL ROTAVIRUS VACCINE SUPPLY FOR UKRAINIAN POPULATION

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ABSTRACT

Introduction: Several studies has shown that rotaviruses play a leading role in the structure of acute intestinal infections (AII) of viral etiology in children. In the National vaccination calendar of Ukraine, vaccination against rotavirus infection (RVI) is classified as recommended, with the expected goal of reducing the number of severe RVI cases among under five-year-old children. Nevertheless, despite the positive epidemiological and clinical effects of vaccination against RVI, it remains unclear how appropriate the introduction of rotavirus vaccines is in terms of potential costs and benefits, as well as determining the optimal level of subsidy required to cover part of the costs of voluntary vaccination of the population.

The aim: Study of optimal subsidy level of rotavirus vaccine in Ukraine using epidemiological and pharmacoeconomic modeling.

Materials and methods: The retrospective epidemiological data of the monthly RVI incidence in Ukraine as well as the population number from 2010 to 2016 formed the information basis for determining the transmission parameter of the viral agent. The scenario of RVI epidemic process as an acute intestinal infection from the point of view of mathematical epidemiology is best described by developed mathematical model. Cost-benefit of rotavirus vaccination was studied with the use of developed pharmacoeconomic criteria.

Results and conclusions: Prediction of possible implications of RVI vaccination and finding optimal level of vaccine supply involves a comprehensive study of the epidemic process peculiarities of this infection with development of an adequate epidemiological model. We have proposed a model of RVI epidemiological process in Ukraine, determining its main parameters with the use of available retrospective data of anual number of RVI cases for the period from 2010 to 2016. The developed model was used as an analytical tool for analyzing influence of different levels of vaccine supply on vaccination cost-benefit. The results of research showed that the use of epidemiological modeling in pharmacoeconomic analysis of rotavirus vaccination made it possible to determine analytically optimal level of vaccination subsidy level.

KEY WORDS: rotavirus infection, epidemiological model, vaccination, pharmacoeconomic modeling, subsidy

INTRODUCTION

The problem of acute intestinal infections (AII) global spread is currently relevant [1-3], since they play one of the leading role among infectious diseases after the influenza and acute respiratory diseases [4, 5]. The spectrum of agents causing AII is diverse and includes pathogenic and potentially pathogenic bacteria, protozoa, and viruses [6-8]. Several studies have shown that viruses cause from 25 to 60% of AII cases, among which rotaviruses play a leading role in the structure of children's AII of viral etiology [4, 9, 10]. According to the Global Disease Burden in 2015, rotavirus infection (RVI) remains the leading cause of morbidity and mortality in children aged under five years of age, despite a decrease in the number of admission cases associated with diarrhea and death [11, 12]. Despite the fact that the number of deaths caused by rotavirus gastroenteritis declined from 528,000 in 2000 to 215,000 in 2013, of which over 80% were recorded in Asian and African countries, RVI continues to cause significant damage of public health across the world regardless of the economic development level, causing direct and indirect economic loses, estimated at hundreds of billions of dollars per year [13, 14].

Since 1973 and to date, most authors associate RVI with children, attributing it to the section of pediatric problems. As a result, often adults in the world are not examined for the rotavirus in case of AII. This fact is of fundamental importance, as it leads to a large number of non-detected RVI cases among different age groups [15]. However, despite the active role of adults in rotavirus spread, children aged under 5 years play a dominant role in its clinical structure.

WHO recommends rotavirus vaccination into the national immunization programs in countries with infant deaths of diarrhea > 10%, such vaccination introduced since 2006 in 20 countries in Latin America, the United States, Australia, South Africa, Belgium, Luxembourg,
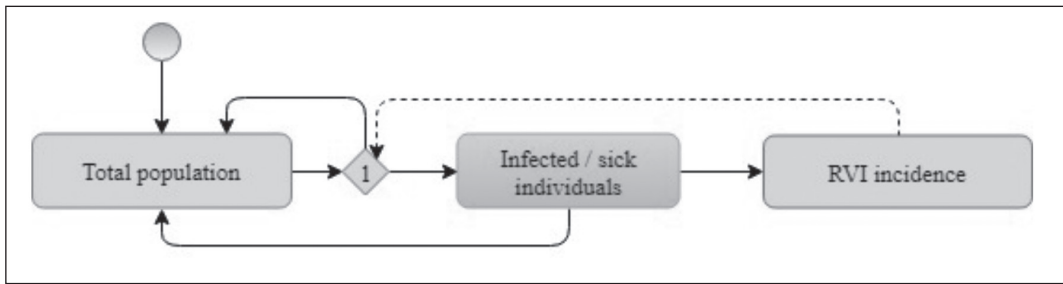
Fig. 1. RVI epidemiological model considering recurrent infection cases.
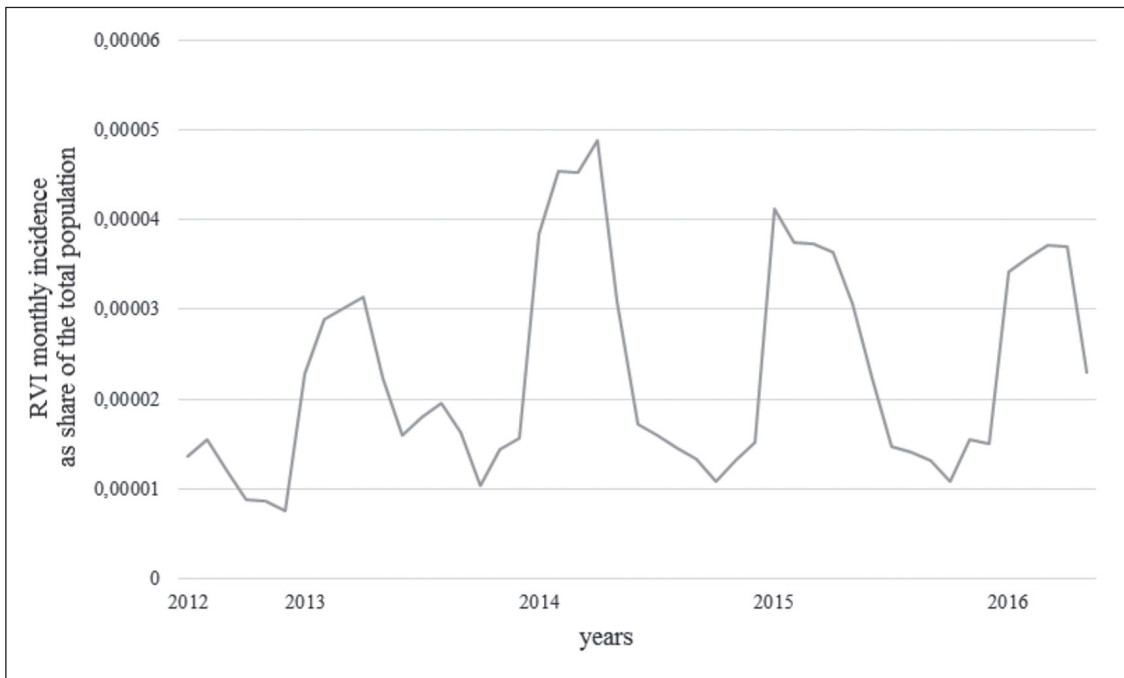

Fig. 2. Monthly RVI incidence during the observational time period.

Austria and Finland, has significantly reduced RVI incidence in these countries [16, 17]. In 2009, WHO recommended to include rotavirus into the list of vaccines for the Expanded Program on Immunization [18]. As of today, two live attenuated peroral rotavirus vaccines are available [19-23]. In the preventive vaccination calendar (MOH Ukraine Order No. 947 dated May 18, 2018), rotavirus vaccination is attributed to recommended vaccinations, wich expected goal of to reduce the number of severe RVI cases among five-year-old children.

Nevertheless, despite the positive epidemiological and clinical effects of vaccination against RVI, it remains unclear how appropriate the introduction of rotavirus vaccines is in terms of potential costs and benefits, as well as determining the optimal level of subsidy required to cover part of the costs of voluntary vaccination of the population.

THE AIM

The aim of research was the study of optimal subsidy level of rotavirus vaccine in Ukraine using epidemiological and pharmacoeconomic modeling.

MATERIALS AND METHODS

The scenario of RVI epidemic process as an acute intestinal infection from the point of view of mathematical epidemiology is best described by the model proposed by W. Kermak and A. Mackendrick in 1927 [24, 25]. According to this model, individuals in the population can be divided into *susceptible* (S) that were not previously exposed to the agent, *infected* (I), that are carriers of infectious agents with manifestation of clinical symptoms or without them, and those *recovered* (R), with acquired specific immunity and subject to the elimination of the pathogen. Since a individual can have RVI several times, especially during the first five years of the child's life, due to the variety of genotypes of circulating rotaviruses and the lack of stable cross-immunity [26], proposed in the literature epidemiological model can be simplified without loss of quality (Fig. 1), given that recovery after infection and elimination of the viral agent is accompanied by an "immediate" return to a group of susceptible individuals and the possibility of a disease re-occurrence caused by rotavirus of another genotype [27]. In this model node (1) denoted probability of RVI, depending on RVI incidence.
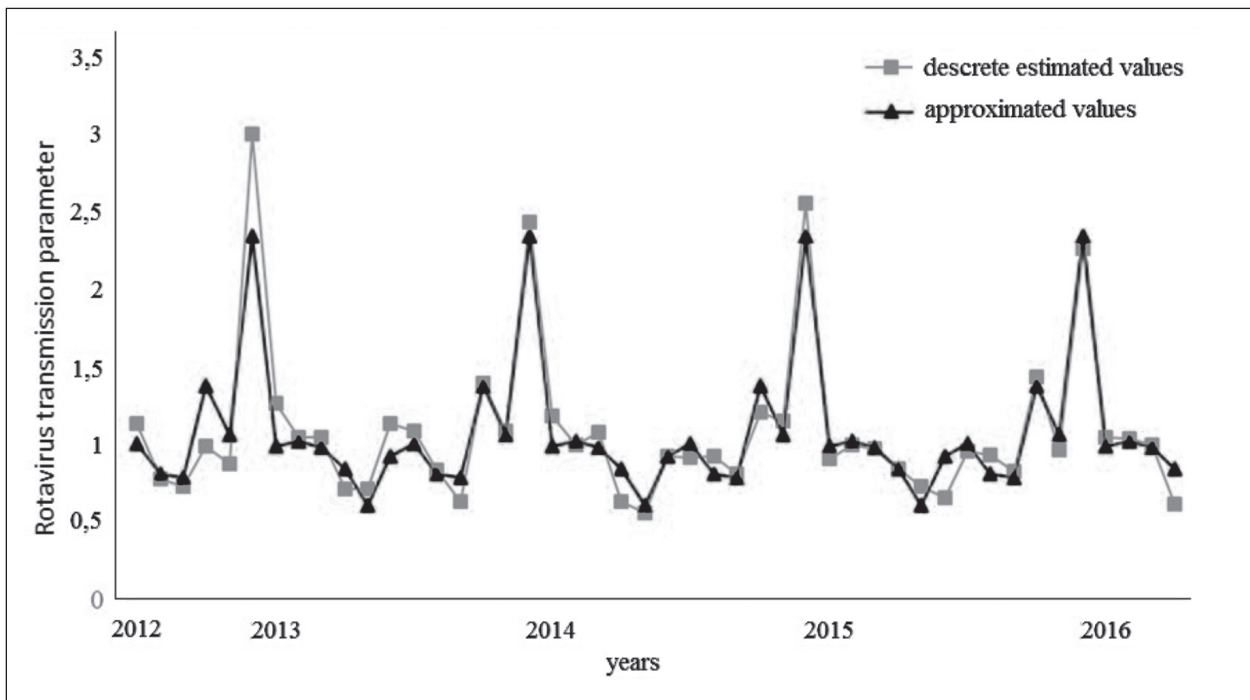
Fig. 3. Rotavirus transmission parameter.

Described epidemiological model can be formalized using next difference equation system:

$$\begin{cases} s_{t+1} = s_t \text{-} \beta_t \cdot i_t \cdot s_t + \gamma_t \cdot i_t \\ i_{t+1} = i_t + \beta_t \cdot i_t \cdot s_t \text{-} \gamma_t \cdot i_t \end{cases}$$

(1)

where s_t – number of susceptible individuals; i_t – number of infected / ill individuals; β_t – rotavirus transmission parameter; γ_t – recovery (infectivity loss) rate.

It was also important to determine the appropriateness of rotavirus vaccination for a certain population group, considering its place in the structure of both susceptible and vaccinated individuals. So, if the proportion of such individuals among the susceptible ones is , and among the infected ones is , then the dynamics of the epidemic process of RVI for such a group will be formally defined making the substitution in eq. 3 for inectious individuals:

$$\frac{i'_{t+1}}{n} = \frac{i'_t}{n} + b_t \cdot i_t \cdot \frac{s'_t}{m} - \gamma_t \cdot \frac{i'_t}{n}$$

(2)

$$i'_{t+1} = i'_t + \frac{n}{m}\beta_t \cdot i_t \cdot s'_t - \gamma_t \cdot i'_t$$

(3)

where it becomes clear that:

$$\beta' = \frac{n}{m} \cdot \beta$$

(4)

In the considered model recovery (infectivity loss) rate is assumed to be equal to one ($\gamma_t = 1$) if the epidemiological observation interval is greater or equal to the average infectious period. The key model parameter is vital agent transmission parameter, which is defined at each time interval as:

$$\beta_t = \frac{I_{t+1} \cdot N_t}{I_t \cdot S_t}$$

(5)

Rotavirus transmission parameter was determined using retrospective monthly RVI incidence epidemiological data in Ukraine (Form 3 of Statistical Report) from 2010 to 2016, provided by the Center for Public Health of the Ministry of Health of Ukraine as share of total population (Fig. 2).

Information on asymptomatic RVI cases was unknown, so it was assumed that it has been already included into parameters of the epidemiological model. According to the WHO recommendations, RVI is considered to be severe if patients have symptoms according to the Vesikari grading scale > = 11 [28].

RESULTS AND DISCUSSION

So, using formula (2) it was found descrete and then approximated (smoothed) rotavirus transmission parameter as key factor in RVI incidence prediction (Fig. 3). It is a characteristic of the infectious agent and is supposed to have a seasonal pattern with peak in winter-spring period, which was confirmed by epidemiological observations.

Optimal level of voluntary vaccination coverage could be found by modification of above mentioned epidemiological model, adding class of vaccinated individuals (Fig. 4) into above-described epidemiological model (Fig. 1). Here nodes (1-2) denoted share of Vaccination
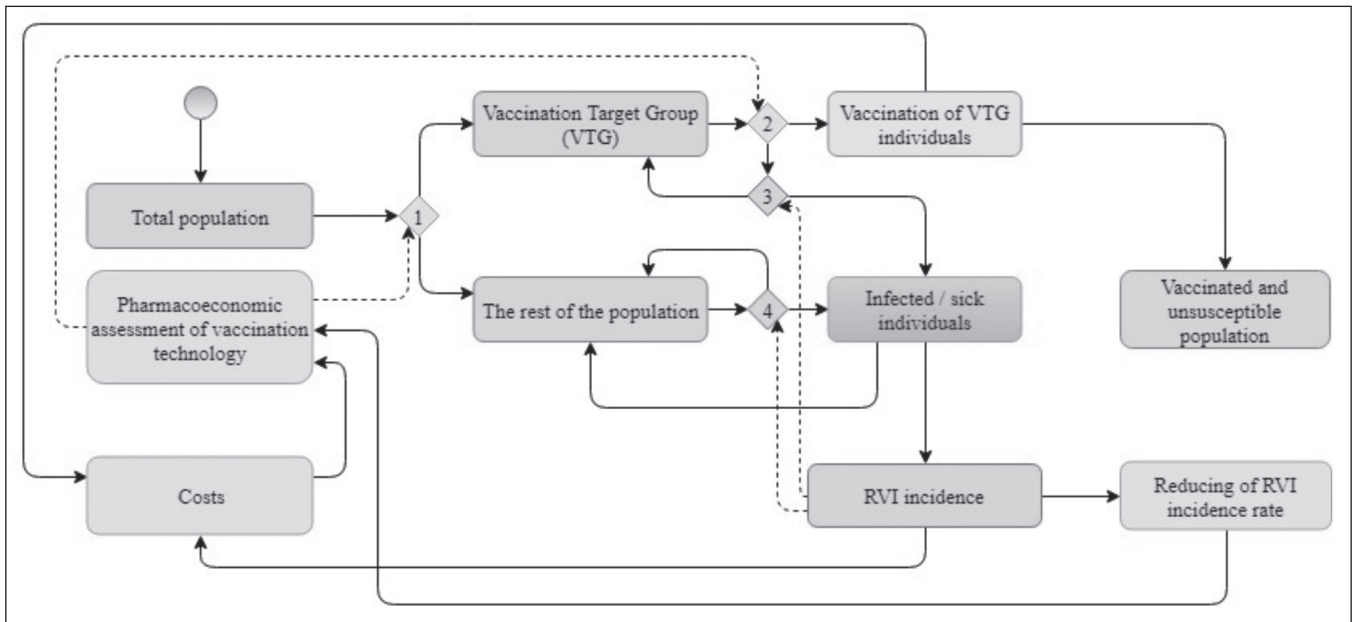
Fig. 4. RVI epidemiological model with vaccination considering recurrent infection cases.

Target Group (VTG) and probability of vaccination in this group respectively. Nodes (3-4) denoted RVI probabilities for VTG and the rest of population, depending on RVI incidence.

Such model was described mathematically using the following system of difference equations:

$$\begin{cases} s_{t+1} = s_t - \beta_t \cdot i_t \cdot s_t + \gamma_t \cdot i_t - v_t \cdot s_t \\ i_{t+1} = i_t + \beta_t \cdot i_t \cdot s_t - \gamma_t \cdot i_t \\ v_{t+1} = v_t + v_t \cdot s_t \end{cases}$$

(6)

where s_t – proportion of susceptible individuals; i_t – proportion of infected / ill individuals; v_t – proportion of vaccinated individuals; β_t – rotavirus transmission parameter; γ_t – recovery (infectivity loss) rate; v_t – level of vaccination coverage.

From epidemiological point of view marginal vaccine benefit population vaccine benefit (PVB) is determined as a ratio of the total number of prevented RVI cases to the total number of vaccinated individuals was taken as epidemiological effectiveness criteria of vaccine supply:

$$PVB = \frac{\sum_t i_t - \sum_t i_t^v}{\sum_t v_t}$$

(7)

where i_t – number of infected / ill individuals *without introduction of* vaccination *at time t*; i_t^v – number of infected
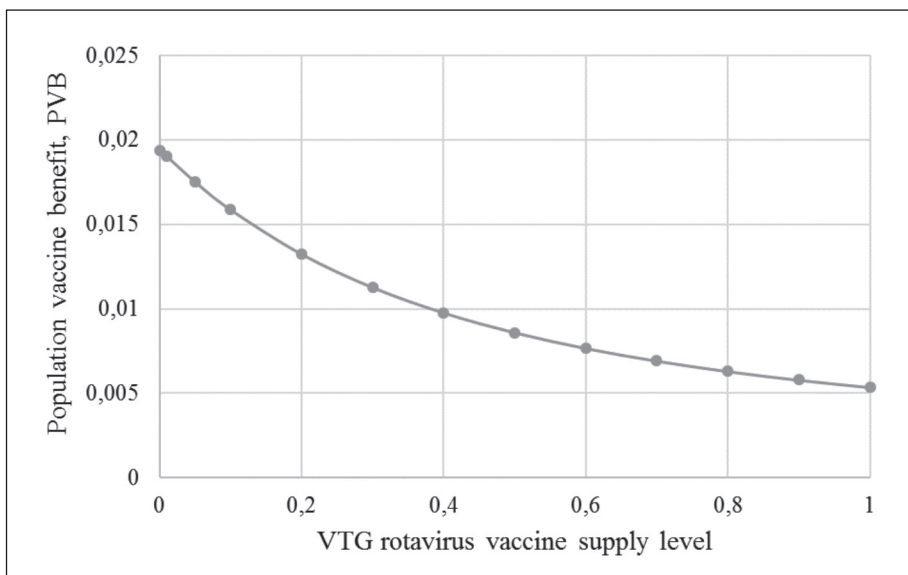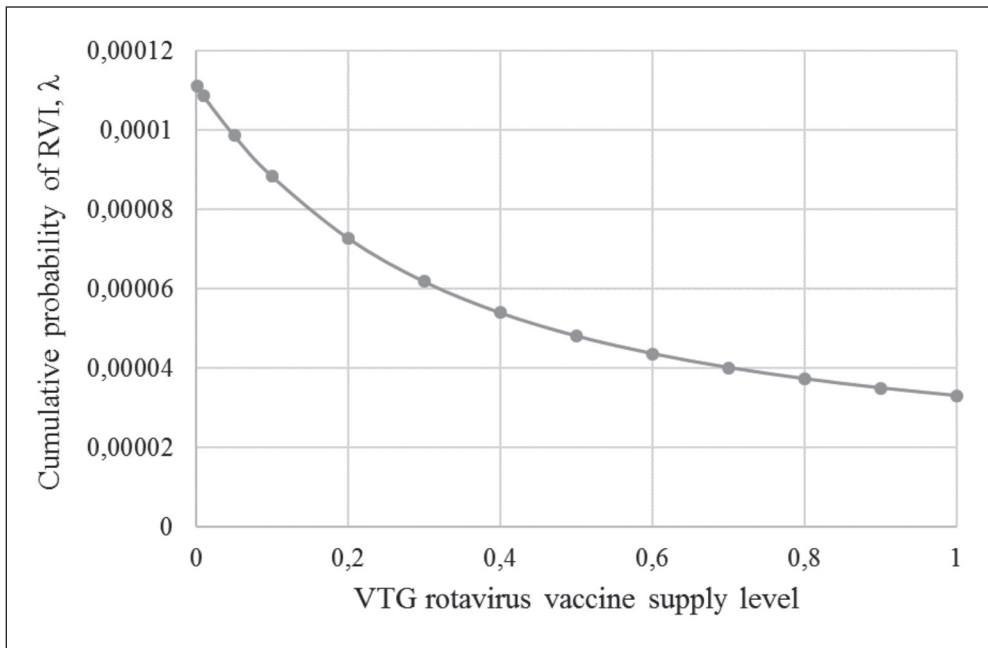

Fig. 5. PVB level
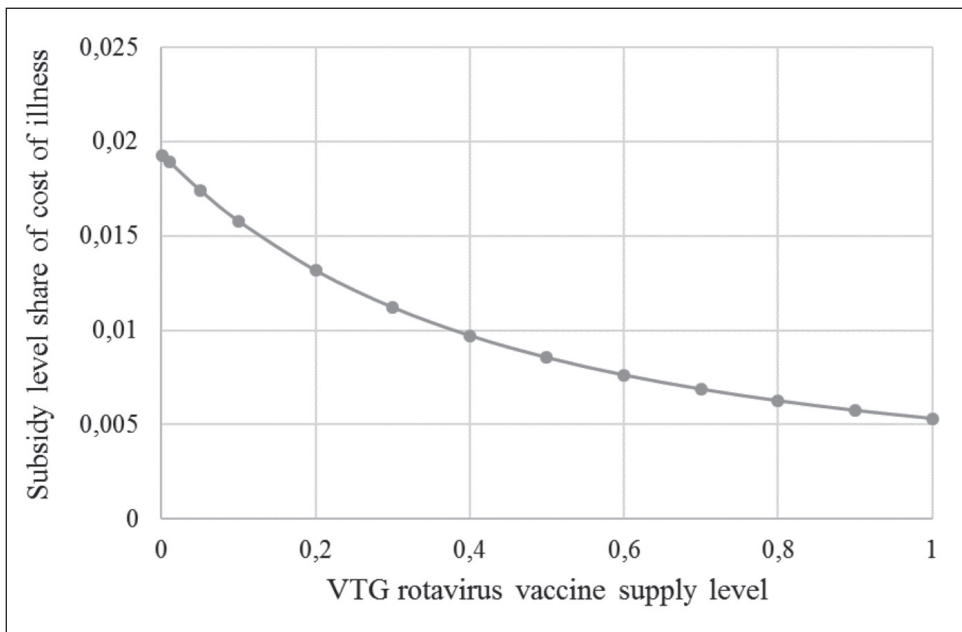
Fig. 6. Cumulative RVI probability

Fig. 7. Potential subsidy level share

/ ill individuals *with introduction of* vaccination *with certain level of vaccine supply at time t*; v_t – number of vaccinated individuals *at time t*.

With introduction of cost of ilness, C_i, and vaccination cost, C_v from pharmacoeconomic perspective total vaccination costs during sertain period of time, $C_v \sum v_t$ must be less than total monetary benefit of prevented RVI cases:

$$C_v \sum v_t < \left(\sum_t i_t - \sum_t i_t^v \right) \cdot C_i$$

(8)

So, pharmaeconomic rule from social perspective allows estimation of ratio threshold for cost-effective vaccination agains RVI:

$$\frac{C_i}{C_v} > \frac{1}{\text{PVB}}$$

(9)

As rotavirus vaccination is voluntary, it is reasonable to analyse it from individual perspective. Rotavirus vaccination would be cost-effective for individual in case of less vaccination costs C_v comparing to expected cost of illness, where is cumulative probability of RVI for one individual during certain period of time.

$$C_v < \tilde{\lambda} \cdot C_i$$
(10)

$$\frac{C_i}{C_v} > \frac{1}{\tilde{\lambda}}$$
(11)

So, from social perspective vaccine costs must be less than:

$$C_v^{social} < PVB \cdot C_i$$
(12)

and from individual perspective:

$$C_v^{individual} < \tilde{\lambda} \cdot C_i$$
(13)

From formula (14) and (15) it can be easy to find subsidy level S as difference between optimal social and individual vaccine cost:

$$S = C_i^{social} - C_v^{individual} = \left[MB - \tilde{\lambda} \right] \cdot C_i$$
(14)

Next, a hypothetical VTG was considered, which is 12.5% (m) among the total susceptible synthetic population, and 67% (n) among all sick synthetic population, which roughly corresponded to children under 5 years old in Ukraine. The results of mathematical modeling of different levels of VTG possible rotavirus vaccine supply showed decrease of PVB and cumulative RVI probability with increase of VTG vaccine coverage (Fig. 5-6).

It allowed finding of potential optimal subsidy level as share of cost of illness with different levels of vaccine coverage. Its decrease was explained by potential epidemiological benefit of vaccination for nonvaccined individuals with vaccine coverage increase (Fig. 7).

CONCLUSIONS

Prediction of possible implications of RVI vaccination and finding optimal level of vaccine supply involves a comprehensive study of the epidemic process peculiarities of this infection with development of an adequate epidemiological model. We have proposed a model of RVI epidemiological process in Ukraine, determining its main parameters with the use of available retrospective data of anual number of RVI cases for the period from 2010 to 2016. The developed model was used as an analytical tool for analyzing influence of different levels of vaccine supply on vaccination cost-benefit. The results of research showed that the use of epidemiological modeling in pharmacoeconomic analysis of rotavirus vaccination made it possible to determine analytically optimal level of vaccination subsidy level.

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Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

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