HEALTH RISK ANALYSIS IN EPIDEMIOLOGY

DYNAMICS OF LOCAL EPIDEMIC COVID-19 OUTBREAK THROUGH THE PRISM OF COMPARTMENT MODELING

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Our research goal was to tentatively assess necessary volumes and quality of statistic description necessary for describing coronavirus epidemic outbreak. We took COVID-19 epidemics development in Hubei (China) as an example and showed that an existing system of descriptive epidemiologic concepts based on lethality, mortality and the basic reproduction number can turn out to be insufficient for full-fledged description of an epidemic and prediction of its outcomes. The said province was chosen as an object for analysis at a period when the outbreak was just starting; during that period activities aimed at epidemiologic investigations and coercive limitations of contacts between people didn't yet yield expected results.

Data and methods. We revealed that more qualitative statistic description given for infectious processes in a population could be gained with a relatively simple and well-known compartment-model; deviations of actual epidemiologic observations from its parameters can be interpreted as being purely stochastic ones.

Results. To improve prediction abilities, it is necessary to abandon a conventional epidemiologic approach as it is based on a mixture of effects produced by two completely different biological factors in one or two combined parameters. It is advisable to separately describe a process of epidemic spread and a retrospect relation between risks of death and risk factors spread among an infected part of a population over a period of epidemic.

Unsatisfactory insight into a mechanism of infection development in a population and absence of control over its dynamics can impede efforts aimed at suppressing it. A model of an epidemic process can be applied when individual medical insurance schemes are developed and utilized capacities of infectious hospitals and observators are predicted.

***Key words:** model, SIR, SEIR, parameter, lethality, mortality, reproduction number, hidden variables, confidence interval.*

Introduction and overview. This work is devoted to finding the correct statistical description of infectious outbreaks in the interests of health insurance development [1]; however, this would not have been possible without taking into account certain specific details of any epidemic process, which we will consider in terms of recent events in Wuhan (China).

Despite clear and explicit warnings [2, 3], the massive COVID-19 epidemic caused by the 2019-nCoV coronavirus (type SARS-CoV-2) took local health authorities by surprise. The first reports of sick and dead in Wuhan in December 2019 did not cause much concern, as all reported cases were perceived in the context of seasonal increases in endemic acute respiratory infections. Only by mid-January 2020, it became clear that more than 40 identified cases of severe pneumonia did not respond to traditional treatment, because the patients had recently been carriers of a new form of coronavirus. In January, it was found that the pathogen was a coronavirus with its genome being only about 70 % similar to SARS. This allowed assuming there would be completely new peculiarities in epidemics development and they did not slow down to manifest themselves.

The very first case-control pilot studies [4] made it possible to state that the new virus was significantly transmissible and was predominantly spread via droplet contacts. The onset of the infection proceeds with mild symptoms and a very variable incubation pe-

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riod from 2 to 20 days. The presence of the virus in biological fluids can be determined by the results of the reverse real-time transcriptase-polymerase chain reaction (PCR test) carried out, as a rule, after typical symptoms of the disease have become apparent. Samples are usually taken from the nasopharynx; however, the test does not guarantee error-free operation. The report [5] indicated that when testing the characteristics of the test on a group of SARS-CoV-2 carriers, false-negative results were observed in 28–37 % cases. A smaller proportion of false-negative cases (<7 %) was demonstrated by the analysis of samples of bronchoalveolar fluid. During the asymptomatic period, it was usually impossible to detect carriers of the virus; however, four confirmed cases of COVID-19 transmission in Germany were recorded as a result of contacts during a business negotiation with a Chinese business representative who did not have symptoms of the disease [6]. Reports by Chinese doctors also confirm such contagion is quite possible [7].

It was stated that immunocompromised people or people with chronic diseases san the highest risks of contagion, despite the fact that everyone, regardless of age, had a chance of contracting a new virus. Most people with clinical signs were aged from 28 to 89. Children and young people below 20 were almost absent among people with confirmed infection. According to data as of January 28, the World Health Organization noted that approximately 80 % of the infected people had COVID-19 in a mild form; 14 % – in severe (pneumonia with bilateral diffuse damage to the alveoli, with formation of hyaline membranes, pulmonary edema, and leukopenia); 5 % – in critical one (respiratory tract failure, organ failure, septic shock). Confirmed risk factors included age (older than 65, $RR = 2.15$: 95 % CI: 1.11–4.14; $p = 0.023$); severity of the disease ($RR = 11.12$; 95 % CI: 4.63–26.68; $p < 0.01$); a jump in the level of neutrophils at the beginning of the disease and diffuse darkening on the chest radiograph upon admission ($RR = 3.30$; 95 % CI: 1.42–7.6; $p = 0.005$) [4]. In fact, the same set of risk factors for death was confirmed later in a cohort study [8]. And high fever (≥ 39 °C) was associated with more probable occurrence of acute respiratory syndrome ($RR = 1.77$; 95 % CI: 1.11–2.84) and lower probability of lethal outcome ($RR = 0.41$; 95 % CI: 0.21–0.82). As Zhang Dingyu, the head of Wuhan Jinyintan Hospital, reported to Xinhua News Agency [9], people in Wuhan who had already overcome the disease had antibodies in their blood that inhibited development of the infection, prevented complications and even cured seriously ill patients who were given plasma transfusions from recovered people. Other antiviral medications that were given to patients in grave cases included kaletra (a combination of two medications applied to treat HIV infection, lopinavir and ritonavir) and remdesivir. The first blocks effects produced by enzymes-proteases that are necessary for viruses to infect cells; the second one inhibits functions of a genome corrector that corrects SARS-CoV-2 virus mistakes. Oseltamivir-124 as well as anti-bacterial treatments were also widely used. Patients with acute respiratory syndrome were treated with methyl prednisolone as it reduced risks of lethal outcome ($RR = 0.38$; 95 % CI: 0.20–0.72) [8]. The above-mentioned treatment procedure didn't guarantee complete recovery. However, in spite of all PCR tests errors [10], authenticity of an observed epidemic is undoubted. More than 1,000 medical personnel got infected and several dozens of them died.

In connection with the emergence of a new disease, the natural task arises – assessing the scale of the epidemic or of the possible consequences when it occurs again basing on available descriptive epidemiological data. Understanding a mechanism of infection is important. It may be useful for forecasting, taking into account social and non-pharmaceutical prevention.

The research goal was an attempt to assess the necessary volume and quality of statistical description given to coronavirus epidemic outbreak. The current methodology based on using a system of two or three statistical indicators seems very primitive in this area of knowledge due to the direct borrowing of description tools from non-infectious epidemiology. First of all, it is related to such

concepts as cumulative death rate and case fatality rate. Even experts working at sanitary-epidemiologic establishments tended to confuse these two terms. Both values are used in one of two dichotomous schemes: either «sick – dead» or «infected – dead». It seems none of them can be used to perform a comprehensive analysis of an epidemic process as a whole; however, their limited capabilities are mentioned only in case there is another outbreak, let alone complete absence of specific parameters that could be used by epidemiologists and infectiologists to predict an unfavorable outcome given a combination of certain conditions. Moreover, experience accumulated via observations, both over an epidemic outbreak in Hubei province, and over a pandemic which is now spreading all over the world indicated that death rate and case fatality rate can't be considered constant characteristics assigned to a specific communicable disease; they are a changeable process influenced by multiple factors.

In order to achieve our goal, **the task was set to study** a different technology for assessing the epidemic process development on the basis of compartment modeling which would include the visibility of the traditional epidemiological post factum description along with some predictive capabilities. The SIR (susceptible – infected – removed) [9] and SEIR (susceptible exposed – infected – removed) [10] models were taken as the basis in question; these models have been known for almost a hundred years, but their application in practices by epidemiologists is still under question, or ends with separate sporadic attempts[1]. Basically, this area of research today is more likely to be described as "mathematical epidemiology" [11] and most practicing epidemiologists perceive it as an oxymoron. Meanwhile, the epidemic outbreak of coronavirus in Hubei Province seems unique in terms of the practical verification of epidemiological models due to the unprecedented measures taken by the Chinese authorities and people to limit the infection spread both in the epicenter of infection - the city of Wuhan and throughout China. This circumstance significantly localized the outbreak and made it possible to operate with the concept of "compartment". Direct public monitoring of the epidemic turned out to be directly related to compartment modeling [12, 13].

Data and methods. A statistical forecast of dynamics is possible only basing on generalization of known analogues, observations over the epidemic outbreak itself and an assessment of its quantitative values. First of all, it regards death rate and case fatality rate. The Epidemiological Dictionary by J. Last[2] defines the first value as «… the proportion of representatives of the group who died during a certain period …» (CDR). The second is defined as the ratio of the increase in the number of «… cases of a certain disease ending in a fatal outcome for a certain period … to the number of diagnosed cases of the disease [*for the same period*]» (CFR). It is clear from the definitions that in the first case we deal with n probabilistic cohort value for narrow-specific subgroups of the population (subcohorts); in the second, with the ratio of two speeds, i.e. population value not related to the probabilistic nature of a disease. The values simultaneously characterize not only the properties of viral activity, but also the quality of treatment, which makes it difficult to predict the dynamics when procedures for treating a new disease have not yet been developed. Moreover, both death rate and fatality rate themselves are the processes subject to the influence of a lot of factors. It became quite obvious in case of Chinese coronavirus infections. At that, none of the values claims to be a comprehensive tool for reliable prediction what outcomes an epidemic outbreak can possibly have.

The specificity and limitations of the description with CDR and CFR values has been realized long ago. However, observations demonstrate that the transition to more detailed

[1] Kontarov NA, Grishunina YB, Grishunina SA, Archarova GV. A procedure for analyzing and predicting an epidemic situation caused by socially significant droplet infections. Patent RU-2572227-C2 ot 31.03.2014; Opublikovano 27.12.2015; Byul. № 36 (in Russian).

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schemes with more than two states, for example, based on the well-known nonlinear probabilistic SIR model [11] is also not infallible, as this concept often results in higher expectations of damage to the population. The reason lies in a compartment of «susceptible» to infection not being determined clearly at the stage of initial almost exponential growth in the number of infected. If the latter significantly exceeds single cases, then the dynamics should be well described by the basic nonlinear differential equation of the SIR model:

$$\frac{dI}{dt} = \alpha \cdot S \cdot I - \eta \cdot I \qquad (1)$$

where S, I – are numbers of susceptible and infected; t – is calendar time; α, η – are probabilistic parameters of the process. It is easy to see that at the beginning of an epidemic outbreak, when $S(t) \approx N$, where N – is a potential number of all participants in the epidemic process, the equation (1) does lead to an almost exponential increase for I according to the law $I(t) \sim \exp\left[(\alpha \cdot N - \eta) t\right]$ along with a typical doubling time period $DT \approx \ln(2)/(\alpha \cdot N - \eta)$, that could be observed empirically. The existence of this growth phase is similar to a hypothesis on an increase in a number of infected according to the geometric progression law. However, it is impossible to determine hidden parameters α and N simultaneously and independently and directly from the observations of a single exponent as well as to predict the value N in advance, since the latter is associated not so much with the properties of a viral infection as with social and non-pharmaceutical measures aimed at creating barriers to its spread. For this reason separate monitoring over a rate at which new infected cases occur and new cases in which participants in the epidemic process exit out of it due to death or recovery is usually used in order to assess the initial phase. The ratio of such rates $R0 = \alpha \cdot S/\eta \approx \alpha \cdot N/\eta$ in the framework of this approach is an almost constant value. It is called the base reproductive infection number. According to the reference, [14, 15] it can be considered as an expected number of infections directly caused by one infection carrier in a population where all individuals are susceptible (provided there is no deliberate intervention in the transmission of the disease) during the exponential growth phase. By definition, $R0$ cannot be changed using vaccination campaigns, it is not a biological constant for a pathogen, it is influenced by various environmental factors, and the value of the indicator may depend on the mathematical model used [14, 15].

A couple of estimates $R0$ or DT already allows us to make some predictions, however, practical review of such modeling [16] demonstrates that the predicted results of a coronavirus outbreak in Hubei should have been significantly more destructive than they actually are [12, 13]. Indeed, the SIR model at values $R0 \approx 3 - 5$ leads to the expectation of only $\approx \exp(-R0) < 2\%$ of those not affected by the infection at the epicenter, and blocking an epidemic outbreak would require prevention of infection for $(1 - 1/R0) > 75\%$ of the population. With 12 million people living in Wuhan, the limit of the epidemic growth should have been observed at the level of several million infected people, while in reality by mid-March 2020 their number in the whole China did not exceed 200 thousand people. It is important to note that the available observational statistics [12, 13] make it possible to extend the SIR compartment model not only to the initial phase of the epidemic growth, but also to its middle, when the number of susceptible people is already significantly different from N. However, it turned out that the deviation of real observations from model predictions from a statistical point of view cannot be interpreted as random. This circumstance directly indicates the inadequacy of the three-compartment SIR model along with a system of death rate and fatality rate values.

The research method used in this article was based on a modified version of another well-known model – SEIR [10]. It allowed integrating the concepts of death rate, fatality rate and an analogue of the basic reproductive number, and besides, provided a statistically

significant agreement between observations and predictions. Practically observed deviations [12, 13] in the dynamics of the number of infected and removed from strictly exponential laws also made it possible to obtain reasonable estimates of the total number of participants in the infection process.
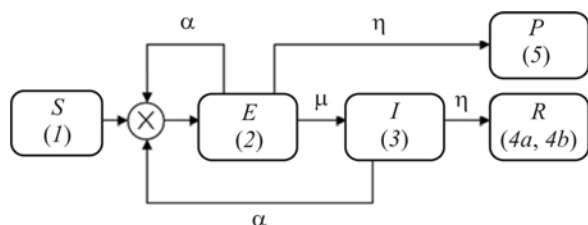

Figure 1. Markov diagram showing states of epidemic process participants. Indications: *1* – susceptible; *2* – exposed; *3* – confirmed infection; *4a* – recovered; *4b* – dead; *5* – resistant

In our opinion, the statistical discrepancy between the known epidemiological models and reality is due to the unaccounted increased transmissibility of COVID-19 and to the uncertain interpretation of the incubation period concept. The fact [6], the source of which is a country with a fairly high level of medical care, indicates that virus carriers are able to infect other people in an asymptomatic period. At the same time, in the same group there is a substantial proportion of persons overcoming the disease asymptomatically and not falling into official statistics. Our modified version of the Markov structural diagram of the model is presented in Figure 1. Its main difference from the original SEIR model was in the fact that the modified model allowed the possibility of infection from both persons with proved infection and from asymptomatic carriers. We neglected mortality from other causes and migration due to the short duration of the epidemic outbreak and severe restrictions for transportation within the province (one focus of infection – one epidemic process). We also neglected the chance of re-infection during the outbreak. It is clear from the diagram that for a complete description of the dynamics, at least 5 values are necessary (3 parameters of the intensity of transitions from state to state and 2 initial conditions for states «E» and «S»). However, it should be noted that the statistics

of the states «S», «E» and «P», unfortunately, are practically unavailable with modern capabilities for monitoring over epidemiological processes. However, we shouldn't view the given modeling as a tool to predict future situation as SEIR model lacks a priori and direct allowing for structure of social relations between persons as well as an overall number of participants in an epidemic process. The value was also estimated as per empirical data as an actual parameter in the model.

In order to obtain a quantitative description, a system of three basic differential equations was solved numerically

$$\frac{dS}{dt} = -\alpha \cdot (S + E) \cdot I , \qquad (2)$$

$$\frac{dE}{dt} = \alpha \cdot (S + E) \cdot I - \mu \cdot E - \eta \cdot E , \quad (3)$$

$$\frac{dI}{dt} = \mu \cdot E - \eta \cdot I , \qquad (4)$$

and was supplemented by three more equations, allowing to find cumulative values for newly infected $C(t)$, resistant $P(t)$ and removed $R(t)$ by calculated continuous process speeds. Using two discrete-valued cumulative processes C_k and R_k observed in practice, the model was adjusted in accordance with the five-parameter functional

$$\Omega(\alpha, \mu, \eta, S_0, E_0) =$$

$$= \sum_{k=1}^{k\max-1} \left[\frac{\left(\ln(C_k) - \ln(C(t_k)) \right)^2}{\sigma_C^2} + \right. \qquad (5)$$

$$\left. + \frac{\left(\ln(R_k) - \ln(R(t_k)) \right)^2}{\sigma_R^2} \right]$$

where σ_C and σ_R – are observational log-normal variation parameters C_k and R_k, defined empirically by their stochastic bias from the time trend in semi-logarithmic coordinates. Minimization of functional (5) allows finding the transition intensity parameters α, μ, η alongside with the initial conditions S_0, E_0. The parameter η was responsible for the in-

tensity of individuals being removed from the compartments «E» and «I». It is accepted the same in both cases, since there was no reason to assume otherwise. The same applies to the parameter α, which is a contribution to the intensity of each new infection from individual representatives of either compartment «E» or compartment «I». The initial conditions for the instantaneous values of the variables I, R, P, C were borrowed from empirical observations as of January 15, 2020.

The use of the functional (5) can be approximately interpreted as a Bayesian method for estimating model parameters under the assumption of a lognormal distribution of cumulative values C_k and R_k subject to the choice of a uniform prior in the most practically significant part in the space of logarithmic parameter values. Logarithm operations were used because it was necessary to work with fundamentally non-negative quantities, as well as for approximation purposes. Such an interpretation allows not only to find the best values of the model parameters, but also to estimate confidence intervals, despite the obvious incompleteness of the description of observations. It also allows you to evaluate the quality of the approximation achieved by recording the inevitable minimum deviation of the functional Ω from the ideal zero value due to independent random fluctuations of a real discrete-valued process (analog of the chi-square test) during daily observation.

Results and discussion. It turned out that within the framework of the proposed scheme, it is possible to give a satisfactory description (Fig. 2) of the available data [12, 13] based on the cumulative dynamics of those infected and those who left without even appealing to additional information on the impact exerted by the identified risk factors and age structure of the population in Hubei Province.

The analysis was based on data for 45 days of the outbreak from January 15 to February 28. The results obtained via comparing the model and actual data are presented in Fig. 2, and a full forecast of the epidemic outbreak for Hubei is shown in Fig. 3, which demonstrates the dynamics of the current
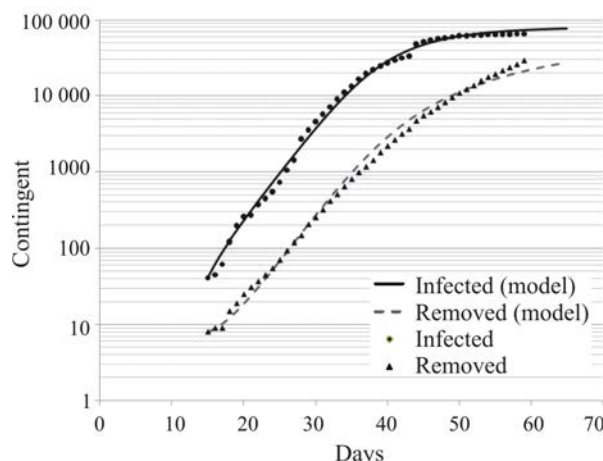

Figure 2. Comparison of cumulative dynamics of infected and removed due to death or recovery with SEIR model calculations. The beginning of 2020 is taken as zero abscissa
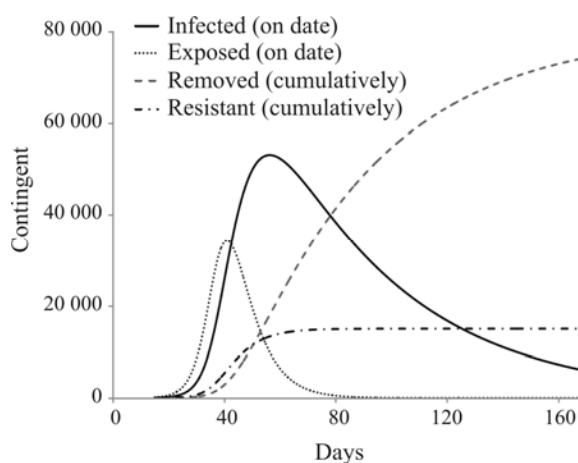

Figure 3. The result of modeling the population dynamics of various compartments. The beginning of 2020 is taken as zero abscissa

numbers of exposed and infected as of the date of observation. According to the forecast, provided that the unprecedented measures aimed at isolating the population living in the province are maintained, the current number of infected peaks at 53 thousand people on February 26, 2020, but this value should decrease quite slowly throughout the first half of the year. The total number of people infected in Hubei Province for a year will not exceed 100 thousand people. It is interesting to note that this estimation doesn't contradict an expert opinion expressed by M.O. Favorov, Doctor of Medical sciences and a famous Russian and American field epidemiologist. Using his own experience, he predicted that Chinese epidemiologists would take extreme measures as well as expected outcomes in his interview to «Echo of

Moscow» radio station on February 03, 2020. He said that «…my colleagues and I… professors from Soviet times held a conference over Skype and concluded that [there will be] 100 thousand immunized, very roughly… some having a mild form of the disease, some a severe one…» [18].

As a result of the calculations, an estimate of the total number of participants in the infection process that has not yet ended in Hubei was obtained: N = 95 thousand people (95 % CI: 64.4–140.3), as well as process intensity parameters – α = 3.2 per day per million carriers of the virus (95 % CI: 2.21–4.65); η = 0.021 per day (95 % CI: 0.019–0.022); μ = 0.113 per day (95 % CI: 0.041–0.316). It should be noted that the reciprocal value for μ can be interpreted as the characteristic transition time between the «E–I» states, which will be part of the incubation period, i.e. 8.9 days (95 % CI: 3.2–24). The central values in our case are close to the median estimates.

The achieved extreme value of the evaluation functional (5) was 88.03 units, which did not go beyond the 95 % confidence area with 83 degrees of freedom of the functional (5) and χ^2_{crit} = 105.3. For comparison, this is significantly better than the result of applying a competing three-parameter SIR model with a minimum value of the evaluation functional $\Omega_{\min} \approx 161.81$, which allows us to assert the existence of a statistically significant difference in the quality of the description by the likelihood ratio test (P < 0.001). Obviously, the parameters η and μ characterize both the disease itself and the physiological properties of the infected population; on the contrary, the parameter α carries not only information about the transmissibility of the SARS-Cov-2 virus, but also reflects the inherent intensity of social relations in the Chinese province. This knowledge may be useful for future predictions when, due to the transition of the epidemic to its pandemic stage, it would be possible that the diseases returned to China again. It is also important to note that the latent number of people exposed at the beginning of the period of systematic observation (January 15) was estimated to be 165 people (95 % CI: 87–312), that is more than the officially confirmed total number of infected people at this

date. According to sources in the Chinese press opening stepwise, this estimate starts to be proved, although it is not (will not be) included in official statistics. There is no doubt that in other foci of infection – in the cities of Bergamo (Italy), Daegu (South Korea), Qom (Iran) – a sharp outbreak of the infection process was due to the same circumstance.

It also seems important to point out a number of unexpected features in the compartment models, the existence of which was difficult to assume based on the type of structural diagram in Figure 1. Many epidemiologists closely monitoring the behavior of the fatality rate in different periods of epidemic outbreaks and in different countries had noted that the fatality rate for the one and same virus varies markedly in different regions, and over time behaves extremely non-monotonously. Fatality rate as the ratio between two cumulatively determined process rates over a period has a statistically significant decline at the beginning of the epidemic and a statistically significant increase towards its end. The usual explanations given in this case associate the initial decline with the adaptation of the virus to virus carriers directly during the epidemic, and the subsequent increase with a delay in the processes of death and recovery in relation to the infection processes, which should lead to an agreement between fatality and death rates after the end of the epidemic if their cumulative values are equally expressed in percentage form [18]. As it turned out in our case, the adaptation/maladaptation hypothesis is redundant here, because the system of equations (2–4) essentially describes the transition process of switching a population from one almost stationary state to another. The nonmonotonic dynamics of a certain combination of system state variables in this case may be its intrinsic feature. The degree of non-monotony intensity depends on the ratio between the initial variables, and the presence of single superspreaders at the start of the epidemic can play a certain role in this. Judging by model calculations and their agreement with empirical data, this concerns not only the fatality rate, but also the effective reproductive number (Figs. 4 and 5). The trend of the removing rate is the closest analogue to the trend of cumulative fatality

rate, but unlike the latter, it has not only the number of deaths in the numerator, but also the number of recovered. By analogy with the «case fatality rate/ratio», it could be called the «case removing ratio» (CRR). Obviously, it does not reflect the quality of treatment provided for patients or the conditional risk of their death, but the dynamics of competition between the flows of events in the infection process. If a death rate is known, which depends to a large extent on the distribution of risk factors among infected people, on the strength of the «factor – effect» relationships and on the quality of treatment, then one can switch from CRR to fatality rate by simple multiplication. A report [17] could be an example of such prototype if its authors did not rely on the poorly chosen CFR and the inappropriate concept of person-days at risk, used by analogy with person-years in non-infectious epidemiology. Assessment of methylprednisolone usage can also serve as an example of an analysis of the impact of treatment quality on traditional indicators of the infectious process [8]. In this case, it is important to take into account the statistically significant difference in the intensity of death rate processes, with a slight difference in the probabilities of survival, indicating low treatment efficiency.

For example, it is known that death rate from coronavirus in Hubei Province at the beginning of the epidemic varied around 30–50 %, then from Fig. 4 it follows that the nominal fatality rate at the end of January 2020 reached 2–3 %, which is in good agreement with the recorded statistics.

Conclusion. Thus, it was stated that in context of a rapidly developing infectious and epidemic process its traditional statistical description using death rates and fatality rates is not quite consistent with the purposes of descriptive epidemiology as it does not allow assessing or predicting the expected consequences and to take response measures that are adequate to the situation. Attracting an additional concept of the epidemic's basic reproductive number also does not save the situation. Moreover, the observed values of $R0$ can diverge significantly from those that are theoretically assumed. The main dynamics of the epidemic process within one infectious focus
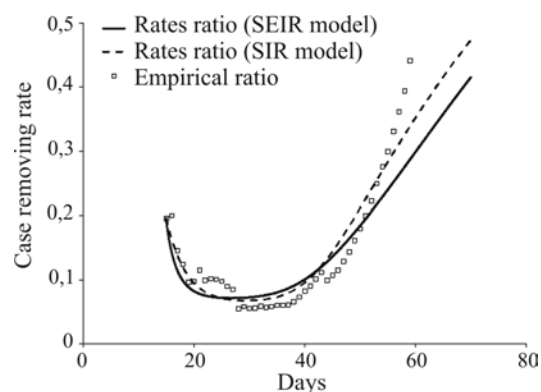

Figure 4. Comparison of the model and empirical dynamics of the cumulative removal rate, introduced by analogy with the fatality rate, taking into account both reasons for leaving the epidemic process. The beginning of 2020 is taken as zero abscissa
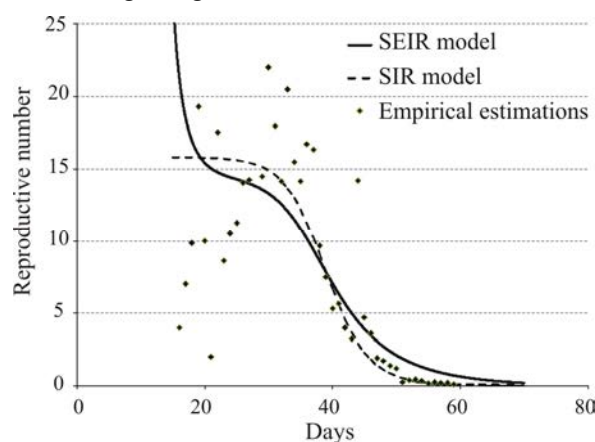

Figure 5. Evaluation of effective reproductive numbers in an epidemic process using three approaches. The beginning of 2020 is taken as zero abscissa.

can and should be described at least in the framework of the simplest compartment models, not narrowed down to 1–2 values. In addition to the dynamics, the traditional retrospective cohort study «factors – risk» taking into account the severity of the course of the infectious disease and the quality of treatment should be an additional the object of the epidemiological study. The description of the transition from the epidemic stage to the pandemic stage will require even more significant complication of the descriptive language due to considering the age, social and geographical stratification of the population of countries, which will inevitably lead to the convergence of traditional and mathematical epidemiology in the future.

Conflict of interest. The authors declare there is no any conflict of interests.

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