From the Researcher's Notebook

After studying the dependence of acute respiratory diseases of all etiologies on air temperature and population immunity dynamics, the authors proposed that the air temperature and the immunity level can affect disease resistance. Knowledge of the relationship between these factors must clarify the mechanisms that determine morbidity dynamics.

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The Origin of Acute Respiratory Epidemics

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Upper respiratory tract infections are the most widespread diseases in developed countries. An adult falls ill with acute respiratory diseases (ARDs) 2.5 times a year on average, and children under four, four to five times a year [1]. ARD-induced mortality due to sequelae is 1–2%. Children, elderly people, and HIV patients are susceptible to the highest risk of morbidity and sequelae [2]. Acute respiratory diseases lead to substantial economic loss because of temporary incapacity [3]. In recent years, specialists have largely focused on possible epidemics related to the new flu virus variants (“bird flu,” “swine flu,” etc.). The importance of the ARD and flu problem is widely acknowledged. However, despite considerable efforts to reduce morbidity, population data do not show a positive decrease in ARD frequency. In the search for the possible causes of the current situation, let us consider factors that determine the dynamics of ARD morbidity.

The traditional approach to reduce the frequency of infectious diseases is based on the identification of the causative agent, the development of a vaccine, and the immunization of the population, primarily the risk group. This approach to the suppression of a certain agent is efficient to control smallpox, hepatitises, roseola, and other viral infections. In the case of respiratory diseases, this task is complicated by the variability of viruses. The picture is distorted even more by the fact that ARDs include more than 200 etiologically independent diseases that are united in one group by three characters: the agent transfer mode (airborne, contact), the localization of the main pathological process (breathing passages), and the clinical character. Some respiratory viruses can stay in latency or keep up an asymptomatic chronic infection. When immunity flags or external conditions change, chronic

and latent infections can wake up and cause ARDs. All these infections localize in breathing passages; consequently, resistance and immunity to them are based on the general local structures and resources of nonspecific and immune protection. The described facts give reasons to consider all ARDs as a complex of related diseases.

The main agents of diseases of respiratory passages are assumed to be the rhinovirus, coronavirus, group A and B viruses, parainfluenza virus, and adenoviruses [4, 5]. Different virus types have different seasonal patterns. Thus, the group A virus causes the strongest epidemics in the winter months. The beginning of the school year at educational establishments is annually accompanied by the outbreaks of respiratory infections caused by the type I and II parainfluenza viruses. The type III parainfluenza viruses cause ARDs in summer and late spring [5].

The ARD agents quickly lose infectivity in the environment; therefore, a high population density is necessary for agent transfer. The probability of contagion increases in crowded places, like public transportation and cultural and educational establishments. Another condition for the development of an epidemic is a large quantity of the population. The point is that a patient radiates viruses for only a few days; then the patient's immune system eliminates the virus and forms immune memory for it. During the infectivity period, one patient must infect several people to create the right number of patients after several infectivity cycles to call it an epidemic. If the population is partitioned, for example, includes several cities, the picture becomes distorted not only because of delays in agent transfer but also because of local differences, for example, in weather. Consequently, it is easier to study the development of an epidemic from the example of one city.

Regularities of epidemic development have been studied well [6], but, in terms of general theory, this process needs an agent to which the majority of people are not immune. However, this mechanism does not explain regular rises in ARD morbidity during the

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Fig. 1. The time series of ARD morbidity in Moscow from 1959 through 1989 (thin line).

The long-term trend is shown by the bold line: morbidity grows at a rate of 0.1 cases per 1000 people a year; winter epidemic peaks show clearly.

winter season, which are not always related to the emergence of a new agent. A possible explanation for morbidity rises in winter is reduced to a head cold—related factor of cold weather, which leads to reduced resistance of the immune system, and increased crowdedness, as people tend to spend more time indoors. At the same time, the scientific literature does not give us a qualitative assessment of the role of climate factors in the dynamics of ARD morbidity and the relationship between these factors and the level of specific and nonspecific human resistance.

To investigate epidemic processes, we selected the Moscow population in the 1960s–1980s. The population of more than eight million people was under the care of the state health system. Migration processes were rigidly regulated and had a limited influence on the population. ARD diagnostic standards practically did not change during the whole period under examination. Morbid events were registered during the issuance of sick leave certificates, which stated the diagnosis. City data were summarized for the assessment of the epidemiological situation. This created a long-term corpus of data on the morbidity with the ARD complex, including the flu, in a population with a known quantity. Note that Moscow territory has several permanent weather stations, which make it possible to compare morbidity data with the continuous flow of weather reports.

The time series under study is characterized by seasonal fluctuations with a long-term trend. The average annual morbidity grew at a rate of 0.1 events per 1000 people a year. Figure 1 shows that minimal morbidity values grew in parallel with the average annual morbidity and maximal values (winter epidemic peaks) rather decreased. To detail these differences, we conducted analysis of the seasonal structure of the long-term trend. To this end, we evaluated the coefficients of the trend curve slope for each week of the year and for each month (Fig. 2). The positive values of the coefficient mean average morbidity growth during the corresponding week or month. We see that the average

Fig. 2. The graph of dependence of the coefficient of the trend curve slope on the week.

The solid line corresponds to the average values of the coefficients for a specific month; the dashed line, for a specific week.

morbidity growth is predetermined by increased morbidity in spring, fall, and early winter. During the epidemic period (January, February), maximal morbidity decreased, and the length of its epidemic rise increased.

Although the focus is on morbidity during the period of epidemic rise (week two through week nine in January and February), the morbidity contribution to total morbidity is 16% on average (from 2 to 33%), the bulk of ARD cases relating to the interepidemic period. Note that, even during an epidemic rise, the flu proper is 15–20% of the total ARD cases [2]. ARD morbidity also greatly changes during interepidemic periods (see Fig. 1). What factors affect these fluctuations? Temperature changes, the “import” of new viral strains, the formation of immunity, or departure on vacations and to dachas? Do these factors act regularly or randomly?

To assess the regularity of the observable ARD fluctuations, let us calculate its autocorrelation function (ACF). This characterizes the dependence between the time series and the same series offset for a certain time period (lag). The ACF for weekly ARD morbidity data looks like an oscillating curve with a period of 52 weeks (Fig. 3). The smoothness of the curve obtained shows regularity in annual morbidity cycles. It is interesting that the ACF has a local maximum equal to 0.52 with a lag of four years (207 weeks); this value is 15% higher than with a lag of one year and 8.9% higher with a lag of two years. This effect may be related to the fact that immunity to certain agents weakens in four years. The effect increases after deducting the linear dependence of morbidity on air temperature; the correlation value decreases; but the expression of growth increases under a lag divisible by four years. This shows the independence of the four-year morbidity cycle from temperature cycles.

In calculations, ACF data were averaged for the whole observation period. Therefore, only the most expressed and stable dependences were identified. At the same time, it is known that in different seasons res-

piratory infections are caused by agents with different epidemiological characteristics (the spread rate, the duration of latent and contagious periods, etc.). In addition, in winter the agent propagation process involves the majority of the population, and in summer morbidity is 20–30 times lower. Consequently, we may expect that correlation between the morbidity levels of neighboring weeks will differ. Figure 4 shows curves that describe the sequences of correlation coefficients for the fifth and 22nd weeks. We see that the morbidity level of the 22nd week (end of May) correlates with the morbidity levels of the following 15th–20th weeks. The morbidity of the fifth week (end of January) has a significant correlation only with the morbidity of the following five weeks.

If we plot the dependence of the length of the correlation period for morbidity levels on the week number, the graph will show a characteristic pattern: from week 20 through week 36 (mid-May through early September), a monotonous decrease in the length of the correlation period occurs from 22 to four weeks (according to the data with a 95% confidence level) (Fig. 5). The rest of the graph is characterized by irregular fluctuations of the correlation period length from four to eight weeks. Note also a less pronounced feature at the end of September (week 38 through week 41) with a correlation period of about 20 weeks. Although the confidence level here is slightly lower, this dependence is interesting because it implies a possible relation between morbidity levels at the end of September and during the winter epidemic rise between the end of January and the beginning of February the next year. If this relation reflects a functional dependence, it is critical in terms of predicting and controlling the morbidity level during winter epidemiological rises [2].

A lengthy correlation period of morbidity levels allows us to assume that, despite the diversity of agents, ARD morbidity is controlled by general factors. One of them is air temperature. The dependence of ARD morbidity on air temperature is shown in Fig. 6. At temperatures above 0°C, morbidity grows linearly as temperature falls; at temperatures below zero, high morbidity values occur and break this linear dependence. These values relate to winter epidemics. To exclude them from analysis, we can use the notion of an epidemic threshold (a norm that medical administrations determine annually on the basis of the epidemic situation analysis). Assume that there is a flu and ARD epidemic if morbidity exceeds 15 per 1000 people during at least one week. Let us call this value the epidemic threshold. Analysis has shown that ARD morbidity during the interepidemic period grows linearly as air temperature drops.

Let us consider the epidemic data in detail. From 1959 through 1988, ARD morbidity exceeded the epidemic threshold for 129 weeks, which was 8.6% of the total observation period and included 22 epidemics, 82% of which occurred from mid-December through

Fig. 3. The autocorrelation function.

The thin line represents the ACF for weekly ARD morbidity data; the thin horizontal lines, the boundaries of the 95% confidence intervals; the bold line, the ACF of the series obtained from the initial series after deducting the linear dependence of morbidity on air temperature.

Fig. 4. The sequence curves of correlation coefficients.

On the left, for morbidity in the fifth week with morbidity in the following weeks; the gray area corresponds to the 90% confidence intervals; and on the right, the same for morbidity in the 22nd week.

Fig. 5. The length of morbidity level correlation period vs. week number.

Time intervals are presented during which the coefficient of correlation between morbidity in the first week and morbidity in the following weeks is larger than zero (circles) and larger than zero with a 95% probability (crosses).

Fig. 6. The morbidity level and average daytime air temperature for the corresponding week for the 1959–1989 period (black dots).

For morbidity below the epidemic threshold (gray line), the temperature correlation coefficient is -0.78 .

mid-February. The average epidemic duration was 5.6 weeks, and the longest exceedance of the epidemic threshold occurred in winter 1969/1970 and lasted for 12 weeks. What does an average epidemic look like? Does air temperature affect its amplitude and duration?

The averaged morbidity dynamics during an epidemic is shown in Fig. 7a. To plot this graph, we synchronized data about various epidemics by the time when the epidemic threshold was exceeded. Figure 7b also shows the dependence between the morbidity correlation coefficients and air temperature for each epidemic week. We see that the morbidity level directly before the epidemic, as well as during the first three weeks, does not depend on air temperature. Starting with the fourth week, morbidity has a significant negative correlation with air temperature. Consequently, as temperature drops, epidemic duration increases.

The results of processing a unique corpus of data on ARD morbidity in Moscow in 1959–1988 show that, despite diverse agents, respiratory infections may be viewed as a complex of interrelated diseases, whose epidemiology depends on social and weather conditions. Data analysis allows us to assume that winter flu epidemics are not isolated events caused by new viral strains. The amplitude of winter epidemic rises

Fig. 7. Average morbidity dynamics.

(a) ARD morbidity dynamics during an epidemic; the black dots are average morbidity; and the gray line is the epidemic threshold; (b) dependence between morbidity correlation coefficients and air temperatures for the corresponding epidemic week.

depends not only on virus characteristics but also on ARD morbidity levels in the previous year. Consequently, flu epidemic controls should not be limited to immunization against certain strains of the flu virus but should be aimed to reduce the total infective load related to respiratory infections.

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