SCIENTIFIC AND METHODICAL APPROACHES TO RISK ANALYSIS IN HYGIENE AND EPIDEMIOLOGY

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RISK-ORIENTED MODEL FOR PREDICTING EPIDEMIOLOGICAL SITUATION WITH CRIMEAN-CONGO HEMORRHAGIC FEVER (ON THE EXAMPLE OF STAVROPOL REGION)

V.M. Dubyanskiy, D.A. Prislegina, A.N. Kulichenko

Stavropol Anti-plague Institute, 13–15 Sovetskaya Str., Stavropol, 355035, Russian Federation

Our research object was a multi-factor prediction of risks related to even a single case of Crimean-Congo hemorrhagic fever (CCHF) on a territory of a particular administrative district in a RF subject (on the example of Stavropol region). Risk-oriented model aimed at yearly prediction of CCHF occurrence was created with heterogeneous sequential statistics clarification procedure. We considered monthly climatic parameters (air temperature, relative air humidity, precipitations quantity, snow mantle size, and air pressure) and epidemiologic data (number of CCHF cases last year and number of settlements where CCHF cases were registered) as predictors for new CCHF cases occurrence. To check our prediction model precision, we took data on risk factors from 2011 to 2015 for each administrative district in Stavropol region. Threshold level of a positive solution probability was set at 99 % (error probability was equal to 1 %).

We tested our prediction model as per retrospective data collected in 2013–2016. It allowed us to predict even a single patient with CCHF occurrence for each administrative district in Stavropol region in 2017. In the course of data analysis we detected high precision in potential prediction results. Totally we revealed six false-positive and two false-negative (actually erratic) results but they can result from objective factors, for example insufficient diagnostics of the disease, as well as imported cases. The obtained data can be applied in practical activities of Rospotrebnadzor offices aimed at planning and organizing CCHF prevention. The next stage in the prediction model development will be creation of a technique for calculating an expected number of CCHF cases for each administrative district where at least one case of the disease is predicted in the forthcoming year.

Key words: *Crimean-Congo hemorrhagic fever, risk-oriented model, morbidity, risk factors, prediction, informative value coefficients.*

Southern territories in Russia are endemic in terms of Crimean hemorrhagic fever (CHF) which is an extremely dangerous natural-nidal infection. The disease cases were registered on the territory of almost each region in the Southern and North Caucasian Federal districts (except Krasnodar region, Adygei Republic, North Ossetia-Alania Republic, and Chechen Republic). Overall, from 1999 to 2016 2,047 patients with CHF were detected, 82 of them died (mortality amounted to 4%). As

Vladimir M. Dubyanskiy – Doctor of Biological Sciences; Head of Epizootologic Monitoring and Prediction Department (e-mail: snipchi@mail.stv.ru; tel.: +7 (865) 226-03-12).

Daria A. Prislegina – Junior Researcher at Epidemiology Laboratory (e-mail: daria775@ rambler.ru; tel.: +7 (865) 226-03-12).

Aleksandr N. Kulichenko – Corresponding Member of the Russian Academy of Sciences, Doctor of Medical Sciences, Professor; Director (e-mail: snipchi@mail.stv.ru; tel.: +7 (865) 226-03-12).

it is the case with many natural-nodal infections, CHF morbidity is cyclic. The first peak was detected in a period from 2005 to 2009. The next morbidity rise started in 2015/ 90 patients with CHF were registered in 2014; 138, in 2015; and 162, in 2016 [1, 2] (Figure 1).

In 2016 the disease cases were registered in 6 southern Russian regions, 37% of them occurred in Stavropol region where epidemiologic situation as regards Crimean hemorrhagic fever has remained unfavorable for the last five years with no morbidity falling trends [3–5]. Favorable landscape-geographic and climatic conditions, as well as a wide range of small mammals and birds which are hosts for Hyalomma-marginatum mites, basic infection carriers, make for evolvement and preservation of the infection natural focuses in the region [6,7]. At the same time, as we analyzed spatial distribution of morbidity with this infection on Stavropol region territory, we noted that there are administrative districts where the disease cases are multiple, but still there are some districts where no disease cases have been registered over the last five years or just single CHF cases occur there periodically [8] (Figure 2).

Given that there are no specific CHF prevention means at the moment, main focus is on general prophylaxis and anti-epidemic activities. The most important is to make sure that medical and prevention organizations are ready for laboratory diagnostics and providing timely and qualified medical aid to patients with CHF. So, to perform scientifically grounded and targeted planning of activities aimed at the disease prevention, it is necessary to make annual quantitative forecasts on morbidity cases risk in each administrative district of Stavropol region [9].

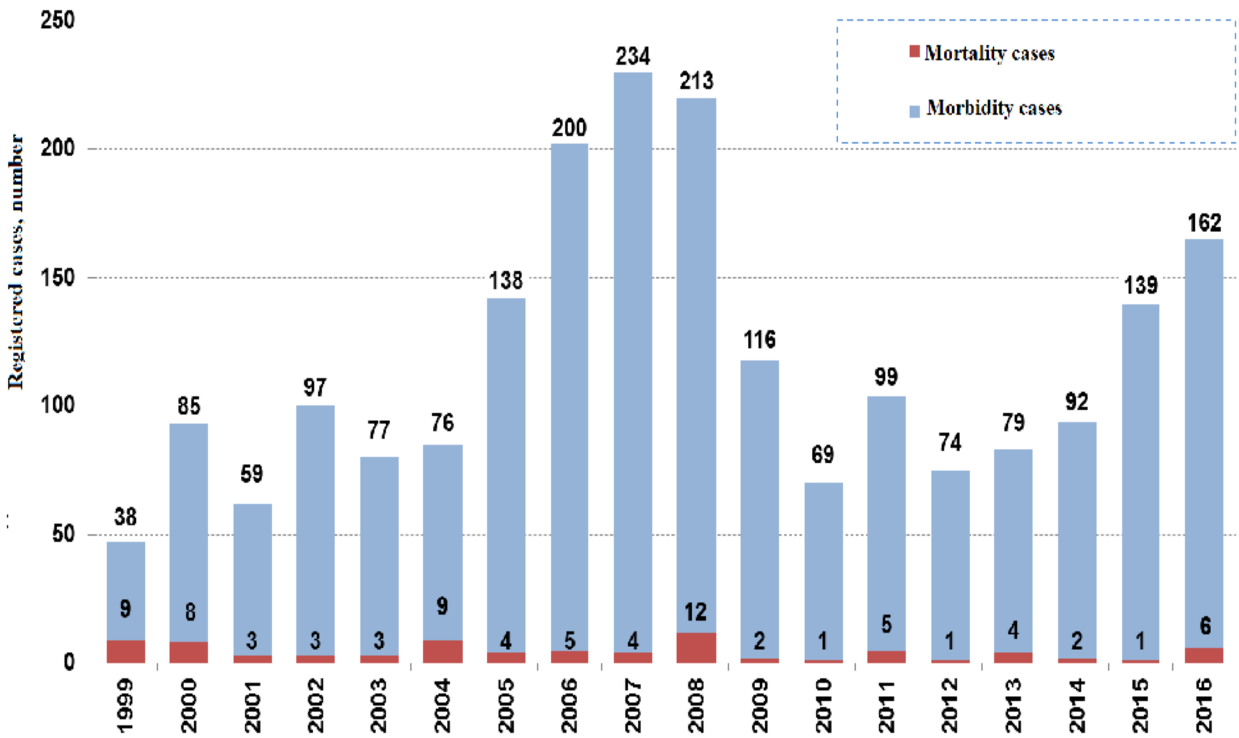

Figure 1. Crimean hemorrhagic fever morbidity dynamics in the Russian Federation over 1999–2016

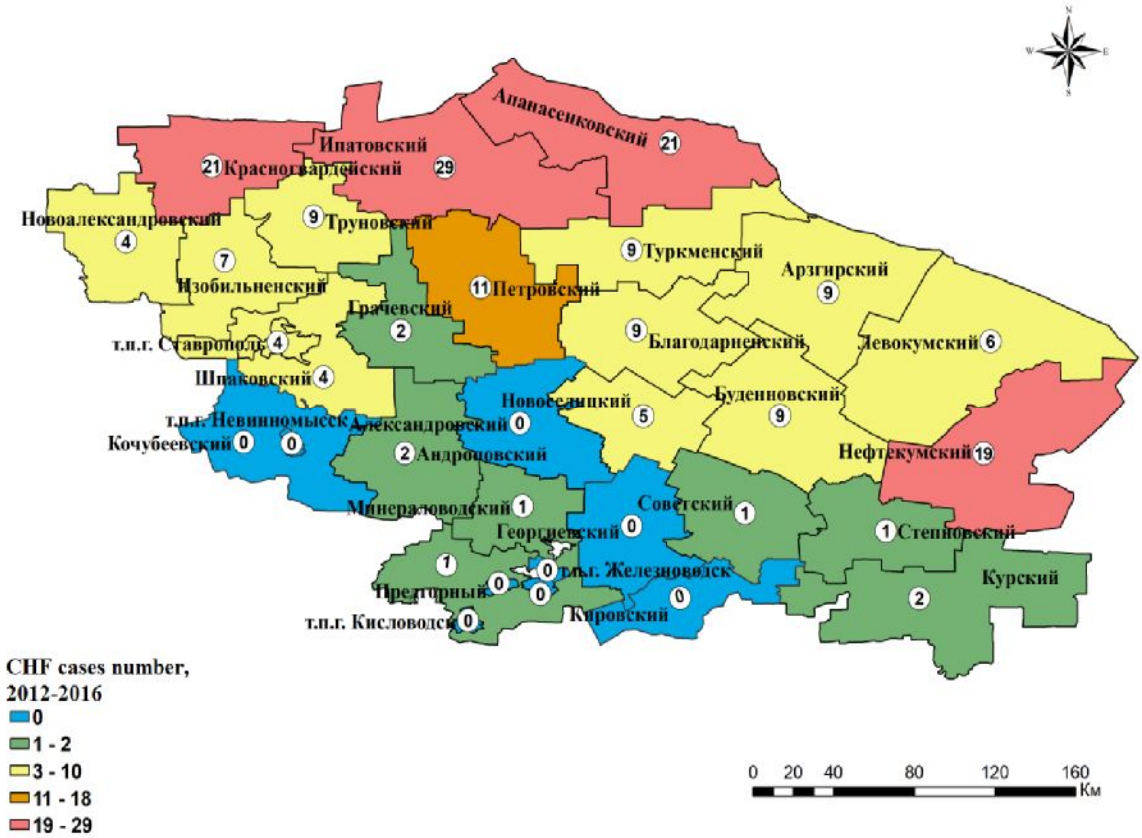

Figure 2. Distribution of the registered CHF morbidity cases in various administrative districts of Stavropol region (2012–2016)

The existing CHF morbidity prediction techniques are based only on epidemiologic or climatic data and don't allow for the whole set of factors influencing the infection epidemic process. Thus, a mathematic model applied for short-term prediction of CHF cases number which is based on "maximum stability" determination and regression analysis allows to determine an expected number of patients (annual parameter) in the current year as per morbidity parameters in a "key" month [10]. There is also another technique based on a SIR type agent model for a disease prevalence. This prediction technique involves dividing all individuals in an examined population into three groups: healthy susceptible ones (S); infected who are infectious agents sources (I); and recovered or individuals with specific immunity (R). This model functioning is based exceptionally on analyzing stages in infectious disease development and reflects only probabilistic nature of an epidemic process [11]. Other mathematical procedures make it possible to draw up forecasts for the general CHF mortality dynamics depending on climatic factors for the whole territory of an examined region [12–15]. So, at present we don't have a risk-oriented model based on multifactor analysis of predictors and applied for quantitative predicting whether CHF cases will occur next year on a territory of each administrative district in a region.

Our research goal was to create a risk-oriented model which would allow to predict whether at least one CHF case was likely to occur in each administrative district (on Stavropol region example) in the forthcoming year.

We tested the suggested technique (on the bases of retrospect data collected in 2012–2016) and made predictions for 2017; this paper contains the test results and the prediction.

Data and methods. We took final annual data on CHF morbidity collected by the Federal Service for Surveillance over Consumer Rights Protection and Human Well-being (Stavropol regional office), results of laboratory research performed on field materials by Rospotrebnadzor's Stavropol Scientific Research Anti-Plague Institute and Stavropol Regional Center for Hygiene and Epidemiology, demographic statistical parameters by Federal Statistics Service (ROSSTAT). Hydrometeorological data were obtained from Russian Scientific Research Institute for Hydrometeorological Information – World Data Center (http://www.meteo.ru), and from meteorological stations achieves which are stored on "Weather Schedule" LLC web-site (https://rp5.ru) and weather logs by Gismeteo (https://www.gismeteo.ru/diary).

To create our risk-oriented model, we applied a heterogeneous sequential clarification procedure (HSCP). This technique is widely used in various medical research to calculate pathological processes outcomes risks and is based on selecting most informative clinical and laboratory signs; it is also applied in epidemiologic and epizootologic predictions, in particular, in case of natural plague focuses [16–23]. Basic HSCP advantages are possibility to allow for multi-directional influences exerted by predictors values and presentation of results in an alternative form, that is, one of two possible prediction variants will be obtained for a year which follows after an initial one: "conditionally positive" (the disease cases occurrence), or "conditionally negative" (no disease cases). Intermediate results cases most frequently mean there is not enough information. Besides, the above mentioned technique is quite simple to apply, doesn't require use of complicated multi-dimensional statistic techniques and is relevant in case of any signs distribution.

We considered all the basic factor groups influencing CHF epidemic process as our risk predictors: biotic (basic CHF carriers contamination as per results of laboratory research performed on mites and aimed at CCHF viruses markers detection), abiotic (monthly climatic factors parameters: air temperature, relative air humidity, precipitations, snow mantle size, and air pressure), social (annual population density in various administrative districts per 1 square kilometer), and epidemiologic data (number of people who applied to medical-prevention organizations because of mites bites, number of patients with CHF, and number of settlements where CHF cases were registered in each administrative district in Stavropol region in 2011–2015). Anti-mites treatment of pasture lands, natural biotopes, and epidemiologically significant objects, as well as acaricide treatment of agricultural animals which took place during the examined period on territories of all the administrative districts in Stavropol region were quite sufficient, but they didn't exert any influence on CHF morbidity. In relation to that, we didn't allow for this factor in our research.

To select the most significant predictors, we calculated informative value coefficient for each of them; this coefficient showed significance of contribution made by this factor into approaching one of prediction variants. Predictors with low informative value coefficient (<0.5) were excluded from the further research as their application was pointless since they didn't increase the overall informative value but instead made analysis procedures longer and could lead to more errors [16]. The remaining predictors were then ranked in their informative value coefficient descending order; thus we obtained an optimized risk factors list necessary for the further model construction.

Threshold level of positive solution probability for each administrative district was set at 99% (probability of error was equal to 1%). Accordingly, total diagnostic coefficient for each administrative district was equal to 20 («+» meant «positive results» or registration of even 1 CHF case; «-» meant «negative result» or CHF cases absence). A learning sample comprised data on registered patients number and risk predictors for all 32 administrative districts In Stavropol region over the previous year. A training sample comprised data on occurrence of at least 1 patient with CHF in the following year. We performed retrospect checking of at least 1 disease case risk in an administrative district of Stavropol region for the following pairs of years: 2013–2014, 2014–2015, 2015–2016 г. In January 2017 we presented our 2017 epidemiologic zones calculation based on 2016 data.

To automate risk-oriented model creation procedure, we developed a program in Microsoft Excel 2010.

Results and discussion. Table shows results of risk-oriented model testing (on retrospect data) and an operating prediction for 2017.

When we analyzed our model testing results, we detected that potential prediction results were highly precise. Total coincidence with actual parameters in all administrative districts was obtained for

Results of predicting CHF cases occurrence or absence for each of 32 administrative districts in Stavropol region over 2013–2017

Prediction results	Years									
	2013		2014		2015		2016		2017	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%
Correct	31	96,9	30	93,8	30	93,8	32	100	29	90,6
False positive*	1	3,1	2	6,2	0	0	0	0	3	9,4
False negative **	0	0	0	0	2	6,2	0	0	0	0

Note : * – false positive result means that at least one morbidity case was predicted but eventually didn't occur in reality.;

** – false negative result means we didn't predict any morbidity cases but actually a morbidity case was registered.

2016. When explaining three detected false positive results, we should allow for the following objective factor: the disease wasn't possibly diagnosed due to prevalence of CHF forms without any hemorrhagic syndrome in the recent years. Two false negative results which can be considered truly erratic were obtained only in 2015 and can be explained by imported disease cases when patients got infected during their staying in other administrative districts or even in another region. 2017 operating prediction results coincided with actual data in 29 out of 32 administrative districts, and we didn't obtain any false negative ("truly erratic") results. Air humidity and precipitations (in spring and summer), as well as snow mantle size in February-March, were the most informative and significant risk factors for prediction out of all the examined climatic parameters in the stated period. It can be explained by their direct influence on number and activity of Hyalommamarginatum mites and other mites which are the main

CCHF infectious agents; this influence was proved in some works [6,7,14]. Such factors as wind speed, population density in administrative districts, and results of laboratory tests performed on mites in order to detect CCHF virus markers, turned out to be not informative. The last factor's low informative value coefficient can be explained by materials sampling being not representative enough. Accordingly, territories in Stavropol region were divided as per predicted risks of at least one individual being infected with CCHF agent on the basis of climatic factors values (air temperature, relative air humidity, precipitations, snow mantle size, and air pressure) and epidemiologic data (number of patients with CHF in the previous year and a number of settlements where the disease cases were registered) obtained for each administrative district.

To sum up, after testing our risk-oriented model for predicting CHF cases occurrence we can state that it is quite relevant and can be applied in practice. The obtained results as self-sufficient data can be applied by Rospotrebnadzor offices for targeted planning of prevention activities in administrative districts with high risks of CHF cases occurrence (medications supplies for CHF treatment can be accumulated in advance, laboratory bases can be prepared for clinical materials examinations, and workshops on CHF epidemiological and clinical issues can be held for primary medical personnel thus raising their epidemiological awareness).

We should note that it was the first time when we applied HSCP to calculate predictors informative value in relatively great number of spatial points (32 administrative districts). Previously this technique was applied in epizootology and epidemiology of natural-nidal infections to calculate predictors informative value in time and relative to only one spatial point. The authors don't have any information about other existing techniques for spatial multifactor prediction of at least one CHF case occurrence in each administrative district. It is a very significant advantage of the developed model over other ones which were developed earlier.

We tested a possibility to predict a risk of at least one disease case occurrence in the year which followed the current one in administrative districts of Stavropol region. The next stage in our prediction model development will be an attempt to calculated an expected number of CHF disease cases for each administrative district where we predict at least one patient with CHF in the forthcoming year.

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