

V.V.Maleev¹, Tolno Facely², Konomou K. Victor³, Sow Thierno Idy³, Ya.Yu.Itskov⁴, Yu.V.Demina⁵, A.E.Levkovsky³, E.V.Kolomoets⁴, G.A.Kovalev³, V.Yu.Khoroshilov⁶, Z.M.Omariev⁵

Epidemiological Peculiarities and Clinical Features of Ebola Virus Disease in the Republic of Guinea

¹Central Research Institute of Epidemiology, Moscow, Russian Federation; ²The National Technical Committee for Monitoring and Control of Ebola in the Republic of Guinea, Conakry, Republic of Guinea; ³Scientific Clinical Diagnostic Center of Epidemiology and Microbiology, Kindia, Republic of Guinea; ⁴United Company RUSAL (Russian Aluminum), Moscow, Russian Federation; ⁵Federal Service for Surveillance in the Sphere of Consumers Rights Protection and Human Welfare, Moscow, Russian Federation; ⁶Territorial Subdivision of the Federal Service for Surveillance in the Sphere of Consumers Rights Protection and Human Welfare in Saint-Petersburg, in the Nevsky and Krasnogvardeisky Regions, Saint-Petersburg, Russian Federation

The current outbreak of the Ebola fever in West Africa is unprecedented in terms of its scale. As of today, 27550 suspected cases and 11235 deaths have been reported. The outbreak differs from previous epidemics in terms of epidemiological and clinical progression of the disease. The article covers several epidemiological issues related to Ebola virus disease by the example of the Guinean outbreak, which has been plaguing the country since 2014. Given is the preliminary clinical analysis of the medical observations, performed in the Research and Diagnostic Centre of Epidemiology and Microbiology built by RUSAL. Regarded are epidemiological and clinical features of the Ebola virus disease (EVD) in 83 patients, who were admitted to RUSAL Treatment Center since March 6th till June 30th, 2015. In 28 of the patients, EVD diagnosis was laboratory confirmed. The principle assessment criteria are: morbidity rate, lethality index, gender, age, occupation, time since the onset of the disease until hospitalization, an average duration of the stay at the hospital, complaints, symptoms, complications, and the therapy provided.

Key words: epidemic, Ebola fever, West Africa, Ebola virus, Republic of Guinea, Scientific Medical Diagnostic Centre of Epidemiology and Microbiology, Ebola virus disease.

The first known outbreak of the Ebola virus disease (EVD) occurred in 1976 in the area of the Ebola River in Zaire (Democratic Republic Congo). From 1976 to 2013, 2390 cases of the disease caused by viruses of the genus *Ebolavirus* were registered in Central Africa, of which 1590 people died [1]. Previous outbreaks caused by the Ebola virus Zaire were characterized by high mortality: from 44 % in 2008 in the Democratic Republic of the Congo to 89–90 % in 2003 in Congo and 100 % in 1977 in Congo and in 1996 in the South Africa.

The first case of the disease caused by the Ebola virus was detected in the Forest Guinea region (Republic of Guinea) on December 6, 2013, but the etiological agent – virus ZEBOV was discovered only a few months later [3]. In March 2014, the World Health Organization (WHO) announced an outbreak of the disease caused by the Ebola virus in Guinea. By August, the epidemic spread to several countries in West Africa, including Guinea, Liberia and Sierra

Leone. As of July 1, 2015, WHO cites data on 27,550 cases (probable, suspicious and confirmed) and 11,235 deaths (41 % mortality) in 3 countries – Guinea, Sierra Leone and Liberia. According to reports, the infection spreads by contact. Particular importance in terms of Africa is attached to the traditions of the population to massively participate in funeral events. An important role is assigned to the spread of infection associated with the provision of medical care.

According to the latest data, in the Republic of Guinea as of July 1, 2015, EVD was laboratory-confirmed in 3279 patients, of which 2042 (62.3 %) died; 450 possible cases, according to WHO criteria, were with absolute mortality; among 21 patients classified as suspicious, deaths were not observed. A total of 3750 patients have been registered since the beginning of the epidemic, of whom 2492 (66.5 %) died [11].

The materials of the current epidemic were analyzed only tentatively on the basis of obser-

vations for short time intervals [4, 6, 10, 12].

Countries affected by the epidemic are among the poorest and least prosperous countries in the world. According to WHO, for 2013 in Guinea, with a total population of 11.745 million inhabitants, total health care expenditure per capita was \$ 59, and total health care spending was 4.7 % of gross national income.

The Government of the Russian Federation took an active part in assisting the Republic of Guinea in the fight against EVD, and sent there a specialized anti-epidemic team (SAET) with the necessary equipment, laboratory diagnostics specialists, epidemiologists and clinicians. RUSAL made a significant and direct contribution to raising the country's potential to eliminate the epidemic, whose leadership in November 2014 decided to build a specialized biosafety hospital to provide medical assistance to patients with highly contagious infections. During construction, this hospital was transformed into a Scientific Clinical Diagnostic Center for Epidemiology and Microbiology (SCDCEM). Its main functions are the admission of patients with suspected especially dangerous infectious diseases, including the disease caused by the Ebola virus; clinical and etiological diagnosis; organization of treatment of infected patients with anti-epidemic measures provision; research work, staff training, advisory assistance to specialists of local medical institutions.

The purpose of this publication was to summarize the results of the examination and clinical observation of patients during hospitalization in the indicated center.

Methods and materials

The material for the retrospective analysis was provided by epidemiological data presented at meetings of the National Coordination Center for Combating EVD under the Ministry of Health of the Republic of Guinea with international participation, WHO information, in some cases, the results of study of the epidemiological history of hospitalized patients. The clinical component of the analysis was based on the available clinical and laboratory data of patients who were treated at SCDCEM from March 6 to June 30, 2015. The standard case definition of EVD was used, established by WHO and the Ministry of Health

of the Republic of Guinea [5]. The diagnosis of EVD was confirmed by detecting the virus in real-time reverse transcription PCR. In order to detect RNA of the Ebola virus, commercial test system "AmpliSense EBOV Zaire-FL", which was registered in the Russian Federation and received positive conclusion of WHO in comparative study. The study was conducted on the Rotor-Gene Q and Rotor-Gene 6000.

The diagnostics was carried out by the SAET laboratory, which was validated and integrated into the system of laboratories providing assistance in the laboratory diagnostics of EVD in the territory of the Republic of Guinea. According to the WHO Guidelines for Laboratory Diagnostics, the test was performed twice for each patient with an interval of 48 hours [2]. Along with the detection of the Ebola virus in blood, other biological fluids were also studied: urine, saliva, excrement, breast milk, seminal fluid. In order to verify the diagnosis, as well as to diagnose a combined pathology, a search for other pathogens of infectious diseases – viral hepatitis, malaria, HIV infection, etc. was conducted.

The main available criteria for clinical analysis were mortality indicators from EVD, patient characteristics (gender, age, occupation, time of admission from the onset of the disease, geographical distribution of patients, average patient stay in hospital), complaints, symptoms, complications, and treatment.

Results and discussion

According to the National Coordination Center for Combating EVD of the Ministry of Health of the Republic of Guinea, this epidemic, in contrast to previous epidemics in the countries of Central Africa, is characterized by the spread over large territories and coverage of urban population. From December 2013 to the present, 26 of the 33 provinces of the Republic of Guinea were affected by the epidemic. The EVD outbreak began in the province of Guekedu, bordering Liberia and Sierra Leone, and spread not only to Forest Guinea, but also to other prefectures and neighboring countries. Importation of infection also occurred in Senegal and the Republic of Mali. The epidemic has spread not only to small villages in forest areas, but also to

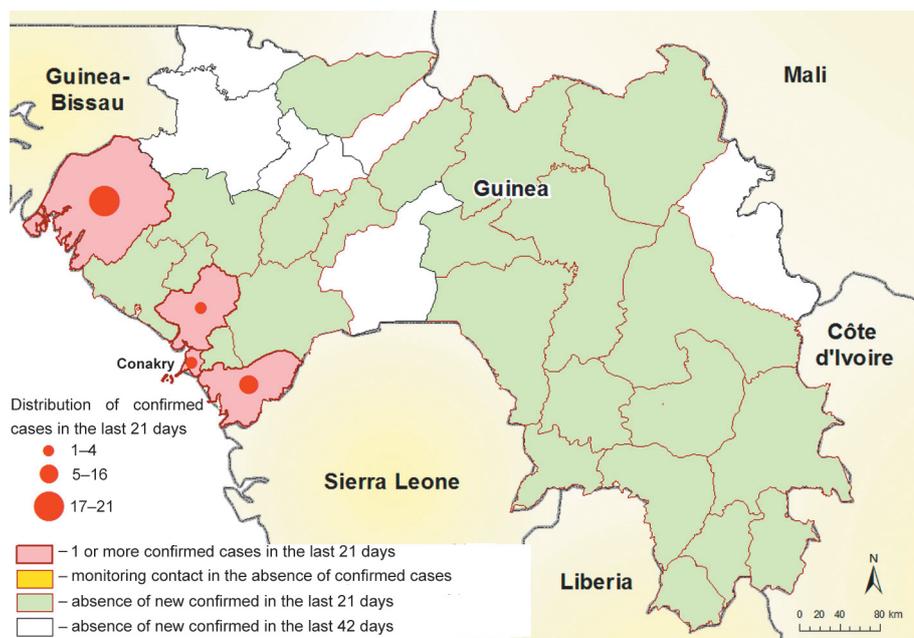


Fig. 1. Distribution of confirmed cases of EVD in the prefectures of the Republic of Guinea (as of 03.07.2015)

large settlements, as well as cities with a population of one million, aided by the intensive migration of inhabitants.

The current spread of EVD infection in the territory of the Republic of Guinea is presented in Fig. 1 [11], which shows that the most affected are the prefectures of Boke, Dübrek, Forekaria and Coya, where there were from 5 to 20 cases of EVD in the last 21 days. The highest incidence was recorded in Boke prefecture: from 12 to 20 cases in the last 21 days, which represents a threat of an epidemic spreading to the bordering Guinea-Bissau.

The feature of the current epidemic is also an unusually long and undulating course (Fig. 2) [11]. Some authors suggest that climatic conditions may influence the spread of EVD [10]. As seen in fig. 2, the epidemic has 4 pronounced waves, the largest and longest lasted about 5.5

months (from week 33 of 2014 to week 3 of 2015), when the largest number of confirmed cases were recorded per week. In this case, the rainy season in Guinea lasts from May to October (from 20 to 40 week), the dry season, respectively, from November to May. During the rainy season, the effectiveness of anti-epidemic measures is markedly reduced due to off-road and corresponding difficulties in identifying contact persons and carrying out prophylaxis. It is possible that this wave of morbidity is due to more active identification and registration of patients. Increased migration could also be a contributing factor due to panic and the ineffectiveness of health education.

Mortality recorded at this time was slightly lower than at the beginning of the epidemic. The greatest mortality was observed at the early stage of the epidemic (from 11 to 32 weeks of

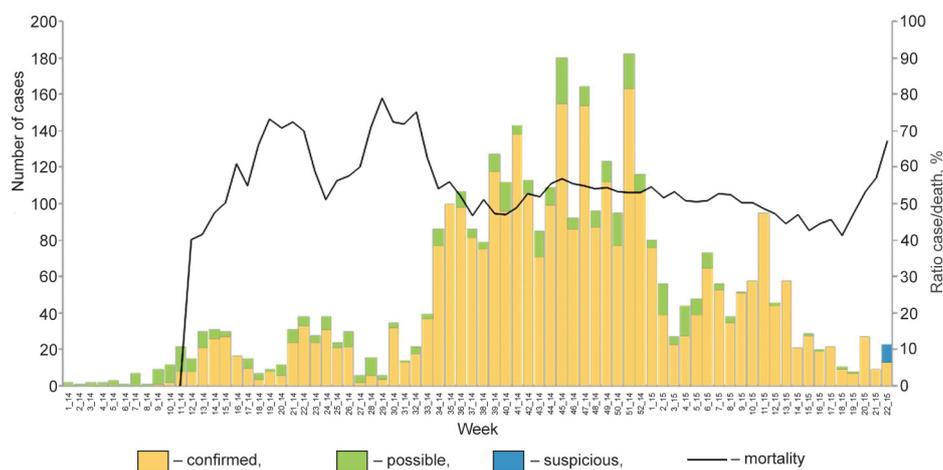


Fig. 2. Distribution of confirmed cases of BVVE (n = 3223), possible (n = 419) and suspicious (n = 10) weekly, mortality among hospitalized confirmed cases in the Republic of Guinea

2014), when anti-epidemic measures were carried out to a minimum extent and there were a large number of contact persons participating in funeral rituals involving unprotected contact with the body of the deceased (washing, shaving body and face hair, rubbing aromatic oils).

The leading role of contact spread of infection is indicated by the data of the epidemiological history of those hospitalized in SCDCEM. Of the 28 patients whose diagnosis of EVD was confirmed laboratory, in 100 % of cases there was a contact route of infection as a result of close communication with sick relatives, further confirmed laboratory. Only one patient indicated participation in the funeral. Especially close contact with sick mothers was observed in three infants, who subsequently developed a generalized infection, which was fatal.

Relatively high prevalence of affected health workers is noteworthy. During the current epidemic in the Republic of Guinea, Liberia and Sierra Leone, a total of 874 confirmed cases of EVD were recorded among medical personnel, of which 509 people died (the death rate was 58 %) [8]. The leading cause of the spread of infection associated with the provision of medical care is undoubtedly the failure to comply with safety measures due to insufficient training of personnel and the lack of protective equipment and disinfection. A certain role can also be played by close communication of health workers with the local population and the location of medical institutions without adequate isolation from dwellings.

To prevent infection of medical personnel, unlike other hospital bases in countries covered by the epidemic, it was possible thanks to the creation of a specialized hospital center with the highest level of safety and the implementation of permanent hospital anti-epidemic monitoring. All SCDCEM patients received proper medical care and treatment with the help of staff who received special training. This training included skills in the use of personal protective equipment, assistance to highly contagious patients, including invasive procedures, and handling of waste products containing Ebola virus. Personnel actions were preliminarily worked out at trainings. There were no cases of infection of medical personnel in SCDCEM, although one of the hospitalized was a nurse who contracted

EVD at the site of infection.

The protracted nature of the epidemic, according to international organizations, was promoted by the poverty of the population, illiteracy, the impossibility of carrying out full-scale sanitation and hygiene measures, the low availability of medical care, and the lack of trust in health workers. Probably for this reason, the focus of Ebola fever was detected only three months after the first (suspected) case of EVD [1].

For clinical analysis, information was used on 83 patients admitted to the Center for the period of its operation with suspicion of EVD. All suspicious were examined twice in the laboratory (on admission and after 48 hours) and with negative results of the study were discharged or transferred to municipal hospitals (in 36 cases in connection with tropical malaria). The diagnosis of EVD was confirmed by the laboratory tests only in 28 people (33.7 %), information about these cases was of interest to study. Among this category of patients, there were 18 women and 10 men, which was not entirely consistent with the structure of the cases in the Republic of Guinea, where no significant gender differences in incidence were found.

In half of the cases, the patients were children and adolescents, while three were under the age of 5 years. Among adults, most were middle-aged and only two were elderly. Only two were engaged in agriculture and could be related to the natural factors of infection. As stated above, among the cases was a medical professional. All patients were active, often moving around the Republic of Guinea and neighboring countries, where they were infected as a result of contacts.

In the first three days of the disease, when it is possible to control the pathological process in a timely manner, only 11 patients were hospitalized (39.3 %), another 8 were admitted on the 4–6th day, the rest were hospitalized on the second and third week of the disease. In terms of location, the patients were hospitalized initially from the focus of EVD, located in the nearby region (Kindia), and later, after the liquidation of this focus, were delivered from the zone of the continuing epidemic in the prefecture of Boke.

All EVD patients were tested for the presence of virus in the blood, 14 people were tested

for the presence of virus in the urine. A positive result was in 6 patients (42.8 %); saliva was examined in 17 patients, 7 of them excreted the virus (41.2 %); two women had the virus in breast milk, and in one of them, Ebola RNA was detected for 58 days. The long-term isolation of the RNA of the virus from the breast milk, as well as the well-known data from the literature on the long-term presence of the virus in seminal fluid, first discovered by the Russian specialists, no doubt need to be investigated from the standpoint of epidemiological significance.

Of the 28 patients with a confirmed diagnosis of EVD, 9 people died: three men and six women, five of them were children under the age of 15 years, four – from 18 to 40 years. Mortality rate was 32.1 %. Lethal outcomes in children were observed even in spite of early hospitalization; in one child, symptoms developed in the hospital while in isolation with a sick mother. Hepatitis B (female, 30 years old) and malaria (child, 16 months) are registered in two deceased patients.

The duration of the incubation period was established in four patients – from 2 to 11 days.

The symptomatology of the disease presented in the table was similar to the data of other observations published in the literature. Intoxication manifestations dominated in the form of fever, weakness, anorexia, pain in muscles, joints, and headache. Relatively fre-

quent registration of diarrhea, nausea, vomiting, and abdominal pain is noteworthy in comparison with previous epidemics. Liquid losses that occur in this case often lead to significant dehydration and electrolyte imbalance, without correction of which the risk of death increases (6, 12).

As can be seen from the table, the frequency of occurrence of the main symptoms is almost the same in deceased and surviving patients, with the exception of slightly more frequent diarrhea and significantly higher bleeding in the deceased: two of them presented bleeding from the gastrointestinal tract, in one case – vaginal bleeding.

All patients underwent pathogenetic and symptomatic therapy according to WHO recommendations [9]. A prophylactic administration of broad-spectrum antibiotics was used in connection with the possibility of activating bacterial infections against the background of secondary immunodeficiency characteristic of EVD. Most patients required antimalarial drugs. Antiviral, experimental treatment, vaccination, transfusion of donor plasma of EVD survivors, was not carried out in the hospital. The average time of hospitalization of patients with EVD was 5.5 days, although in some cases it lasted up to 15 days.

The current EVD epidemic in West Africa has a number of features: a low level of economic development of countries affected by the epidemic process, the inclusion of large settlements and capital cities in the epidemic, a high level of population migration, underdevelopment of the health system, active involvement of the most working population from (25 to 50 years), as well as children. The most vulnerable group was from 25 to 60 years (56 and 62 cases per 100 thousand inhabitants, respectively) [11]. The protracted and wavy nature of the epidemic is largely due to the untimely and not systematic holding of anti-epidemic measures. Relatively high morbidity and mortality among health care workers and cases of illness associated with the provision of medical care, can be prevented with the creation of specialized hospitals, staff training and the availability of sufficient means of protection, effective hospital monitoring, as evidenced by the experience of SCDCM.

Some researchers have noted that the young

Comparison of symptoms in patients who survived and died of EVD

Symptoms EVD	Registration frequency in deceased patients (N /%)	The frequency of registration in all laboratory-confirmed patients (N /%)
Fever	8/88,9	24/85,7
Nausea/vomiting	4/44,5	13/46,4
Diarrhea	4/44,5	9/32,1
Weakness	8/88,9	21/75
Anorexia	5/55,6	14/50
Abdominal pain	4/44,5	10/35,7
Cough	1/11,1	3/10,7
Drowsiness	1/11,1	-----
Dizziness	1/11,1	-----
Bleeding	3/33,3	5/17,8
Constipation	2/22,2	-----
Hematuria	1/11,1	-----
Chest pain	2/22,2	5/17,8
Muscle aches	-----	7/25
Pain in joints	-----	4/14,3
Headache	-----	6/21,4

age of patients with EVD is favorable for survival [12]. However, according to others studies [10] and data of SCDCEM, deaths in children are more common, despite the presence of comorbidities in older patients.

The clinical picture of the disease is characterized by a severe course and, unlike previous epidemics, it is characterized by a more frequent lesion of the gastrointestinal tract, the later appearance and slightly lower frequency of hemorrhagic symptoms [6, 12]. Possible adverse outcome of the disease could be predicted by high frequency of bleeding and diarrhea with the development of dehydration. In this regard, in the treatment of patients, in the absence of etiologic agents currently, the main importance should be given to intensive pathogenetic therapy.

In terms of the identity of many symptoms in a severe course of a number of infections that are common in Africa, timely etiologic diagnosis is crucial, allowing to limit contact and prevent excessive hospitalization. In this study, only one of the three patients confirmed the diagnosis of EVD, although similar symptoms were observed in all cases.

It should be noted the importance of adherence to the anti-epidemic regime in the infectious diseases hospital, receiving patients with suspected dangerous infections. The functioning of the Russian-Guinean hospital in Kindia under strict epidemiological control showed 100 % prevention of infection of medical personnel while observing the rules for using personal protective equipment, waste management, rotation of the flow of patients and convalescents, and disinfection.

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References

1. Platonov A.E., Platonova O.V., Maleev V.V. [Ebola, 2014. Epidemiological and Social Aspects]. *Epidemiol. Infek. Bol. Aktual. vopr.* 2014; 5:34–49.
2. Laboratory guidance for the diagnosis of Ebola virus disease. 19 Sep 2014 [cited 01 Jul 2015]. Available from: http://www.euro.who.int/_data/assets/pdf_file/0016/262033/Laboratory-guidance-for-the-diagnosis-of-Ebola-virus-disease-Rus-updated.pdf.
3. Shchelkanov M.Yu., Magassuba N.F., Boiro M.Y., Maleev V.V. [Causes of Ebola fever development in West Africa]. *Lechashchiy Vrach.* 2014; 11:30–36.

4. Bwaka M.A., Bonnet M.J., Calain P., Colebunders R., De Roo A., Guimard Y., Katwiki K.R., Kibadi K., Kipasa M.A., Kuvula K.J., Mapanda B.B., Massamba M., Mupapa K.D., Muyembe-Tamfum J.J., Ndaberey E., Peters C.J., Rollin P.E., Van den Enden E. Ebola hemorrhagic fever in Kikwit, Democratic Republic of the Congo: clinical observations in 103 patients. *J. Infect. Dis.* 1999; 179(1):S1–7.

5. Case definition recommendations for Ebola or Marburg virus diseases. 9 August 2014 [cited 01 Jul 2015]. Available from: <http://www.who.int/csr/resources/publications/ebola/ebola-case-definition-contact-en.pdf>.

6. Chertow D.S., Kleine C., Edwards J.K., Scaini R., Giuliani R., Sprecher A. Ebola virus disease in West Africa – clinical manifestations and management. *N. Engl. J. Med.* 2014; 371(22):2054–7.

7. Ebola situation report – 1 July 2015. [cited 01 Jul 2015]. Geneva: WHO; 2015. Available from: <http://apps.who.int/ebola/current-situation/ebola-situation-report-1-july-2015>.

8. Ebola virus disease. Fast sheet № 103. Updated April 2015 [cited 06 Aug 2015]. Available from: www.who.int/mediacenter/factsheets/fs103/en.

9. Manual for the care and management of patients in Ebola Care Units. Community Care Centres. Interim emergency guidance. January 2015 [cited 01 Jul 2015]. Available from: http://apps.who.int/iris/bitstream/10665/149781/1/WHO_EVD_Manual_ECU_15.1_eng.pdf.

10. Qureshi A.I., Chughtai M., Bah E.I., Barry M., Béavogui K., Loua T.O., Malik A.A. High survival rates and associated factors among Ebola virus disease patients hospitalized at Donka National Hospital, Conakry, Guinea. *J. Vasc. Interv. Neurol.* 2015; 8(1.5):S4–S11.

11. Rapport de la Situation Epidémiologique Maladie a Virus Ebola en Guinée 03 Jul 2015. N 444. [cited 03 Jul 2015]. Available from: <http://guinea-ebov.github.io/sitreps.html>.

12. Schieffelin J.S., Shaffer J.G., Goba A., Gbakie M., Gire S.K., Colubri A., Sealfon R.S., Kanneh L., Moigboi A., Momoh M., Fullah M., Moses L.M., Brown B.L., Andersen K.G., Winnicki S., Schaffner S.F., Park D.J., Yozwiak N.L., Jiang P.P., Kargbo D., Jalloh S., Fonnio M., Sinnah V., French I., Kovoma A., Kamara F.K., Tucker V., Konuwa E., Sellu J., Mustapha I., Foday M., Yillah M., Kanneh F., Saffa S., Massally J.L., Boisen M.L., Branco L.M., Vandi M.A., Grant D.S., Happi C., Geva S.M., Fletcher T.E., Fowler R.A., Bausch D.G., Sabeti P.C., Khan S.H., Garry R.F.; KGH Lassa Fever Program; Viral Hemorrhagic Fever Consortium; WHO Clinical Response Team. Clinical illness and outcomes in patients with Ebola in Sierra Leone. *N. Engl. J. Med.* 2014; 371(22):2092–100. DOI: 10.1056/NEJMoa1411680.

Authors:

Maleev V.V. Central Research Institute of Epidemiology. 3-a, Novogireevskaya St., Moscow, 111123, Russian Federation. E-mail: maleev@pcr.ru

Tolno Facely. The National Technical Committee for Monitoring and Control of Ebola in the Republic of Guinea. Conakry, Republic of Guinea.

Konomou K. Victor, Sow Thierno Idy, Levkovsky A.E., Kovalev G.A. Scientific Clinical Diagnostic Center of Epidemiology and Microbiology, Kindia, Republic of Guinea;

Itskov Ya.Yu., Kolomoets E.V. United Company RUSAL (Russian Aluminum). Moscow, Russian Federation.

Demina, Yu.V. Omariev Z.M. Federal Service for Surveillance in the Sphere of Consumers Rights Protection and Human Welfare. 18, Bld. 5 and 7, Vadkovsky Pereulok, Moscow, 127994, Russian Federation.

Khoroshilov V.Yu. Territorial Subdivision of the Federal Service for Surveillance in the Sphere of Consumers Rights Protection and Human Welfare in Saint-Petersburg, in the Nevsky and Krasnogvardeisky Regions, Saint-Petersburg, Russian Federation

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