Crimean-Congo Hemorrhagic fever
in the Russian Federation

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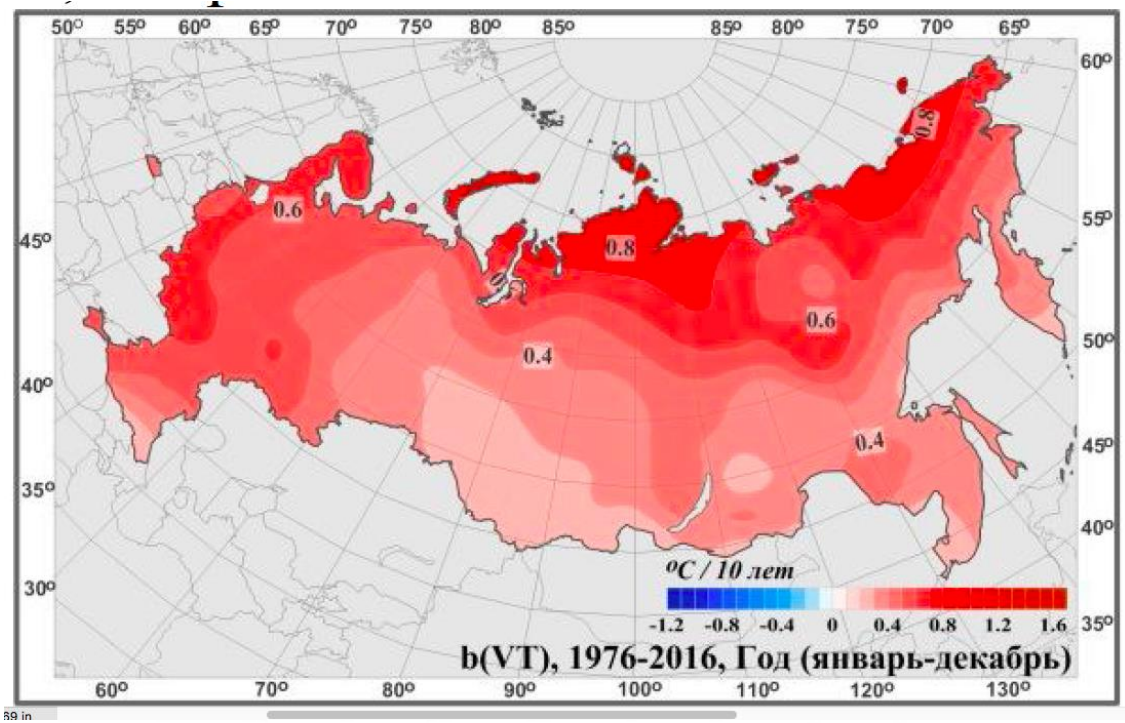
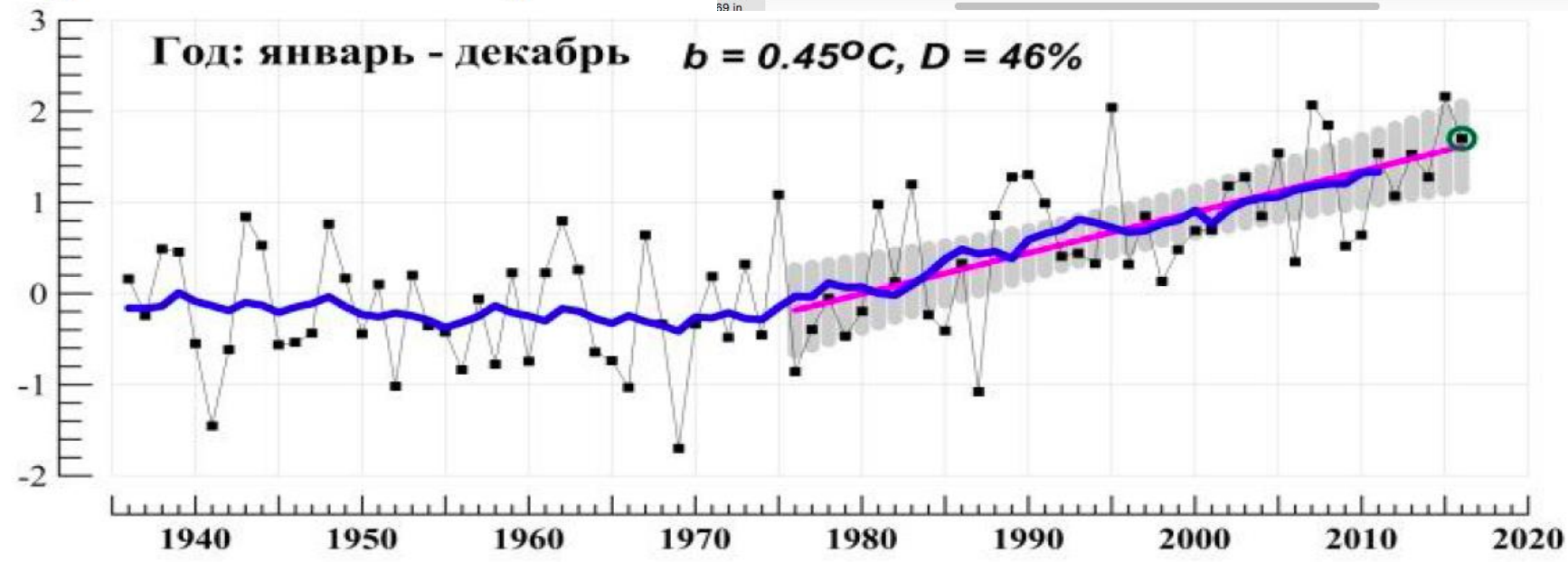
Rostov-on-Don, Russia

Geographic distribution of CCHF in Russia is restricted to the Southern and Northern Caucasus Federal Districts

Global warming and climate change in Russia

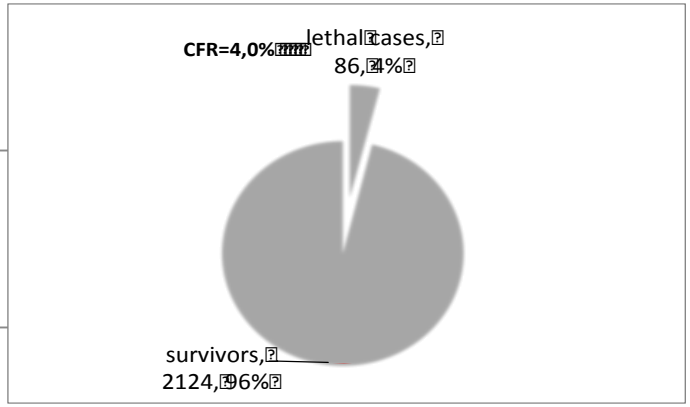




Roshydromet Report about features of climate in Russia in 2016
http://climatechange.igce.ru/index.php?option=com_docman&Itemid=73&gid=27&lang=ru

Number of CCHF cases and deaths in Russia in 1999-2017

2124 – total number



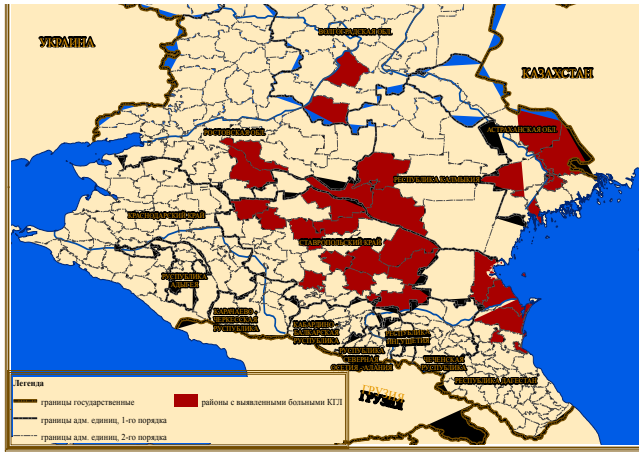
Volynkina A.S., Kotenev E.S., Lisitskaya Ya.V., Maletskaya O.V., Shaposhnikova L.I., Kulichenko A.N. Epidemiological Situation on Crimean Hemorrhagic Fever in the Russian Federation in 2016, and Prognosis for 2017. Problemy Osobo Opasnykh Infektsii [Problems of Particularly Dangerous Infections]. 2017; 1:24–28. (In Russ.). DOI: 10.21055/0370-1069-2017-1-24-28

Volynkina A.S., Kotenev E.S., Maletskaya O.V., Zaikina I.N., Shaposhnikova L.I., Kulichenko A.N. Epidemiological Situation on Crimean-Congo Hemorrhagic Fever in the Russian Federation in 2012 and Prognosis for 2013. *Problems of Particularly Dangerous Infections*. 2013;(1):30-33. (In Russ.) DOI:10.21055/0370-1069-2013-1-30-33

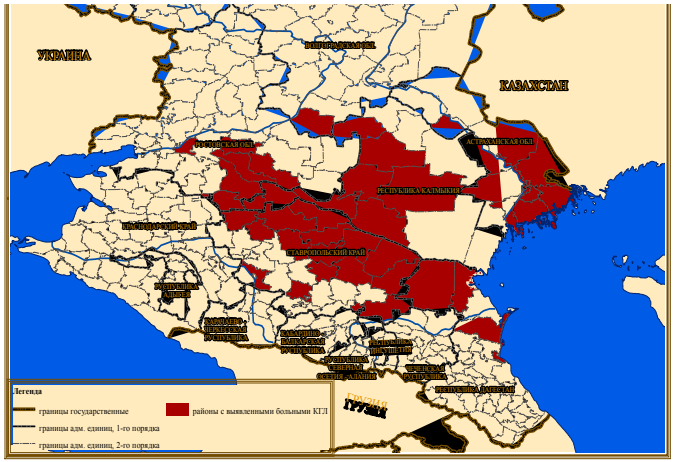
ProMED-mail. Crimean-Congo haemorrhagic fever (Russia, Kazakhstan, preliminary results of 2017) ProMED-mail 2017; 03 Oct: 20171003.5358352. <http://www.promedmail.org>. Accessed 30 Jan July 2018.

Geographical expansion of CCHF in endemic regions based on registration of human cases (1999-2016) - data of Stavropol anti-plague scientific-research institute

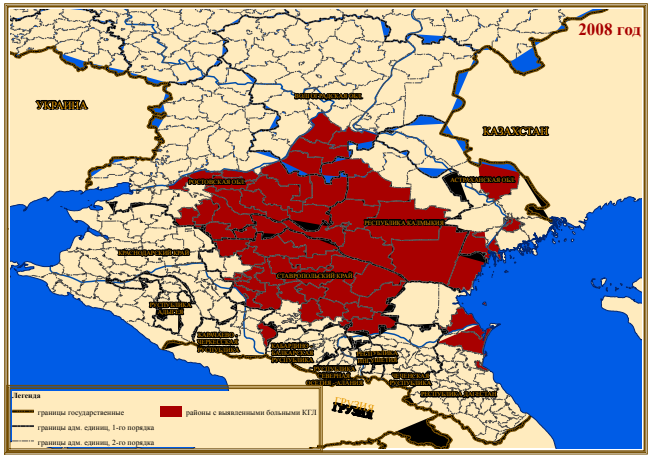
1999



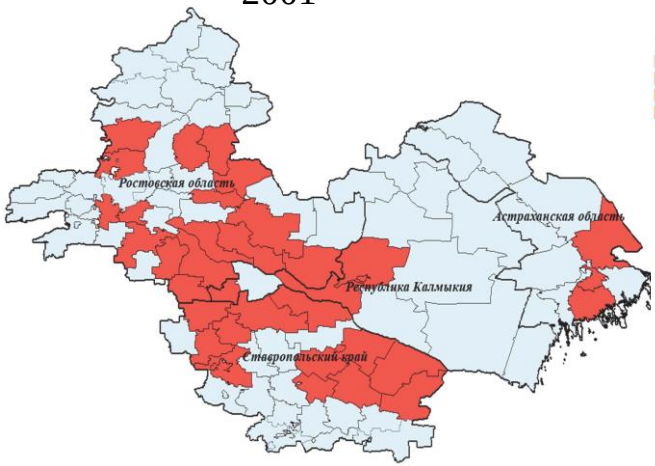
2001



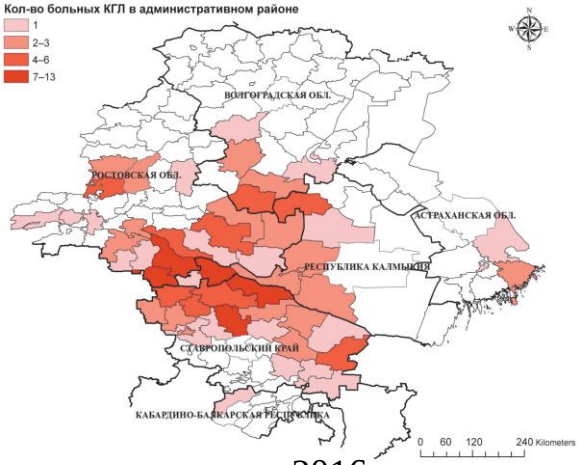
2005



2008



2012



2016

Vladimir Dubyanskiy, Sub-regional meeting on prevention and control of Crimean-Congo Haemorrhagic Fever (CCHF) in the Eastern Mediterranean region Muscat, Oman, 7–9 December 2015;

Volynkina A.S., Kotenev E.S., Lisitskaya Ya.V., Maletskaya O.V., Shaposhnikova L.I., Kulichenko A.N. Epidemiological Situation on Crimean Hemorrhagic Fever in the Russian Federation in 2016, and Prognosis for 2017. Problemy Osobo Opasnykh Infektsii [Problems of Particularly Dangerous Infections]. 2017; 1:24–28. (In Russ.). DOI: 10.21055/0370-1069-2017-1-24-28

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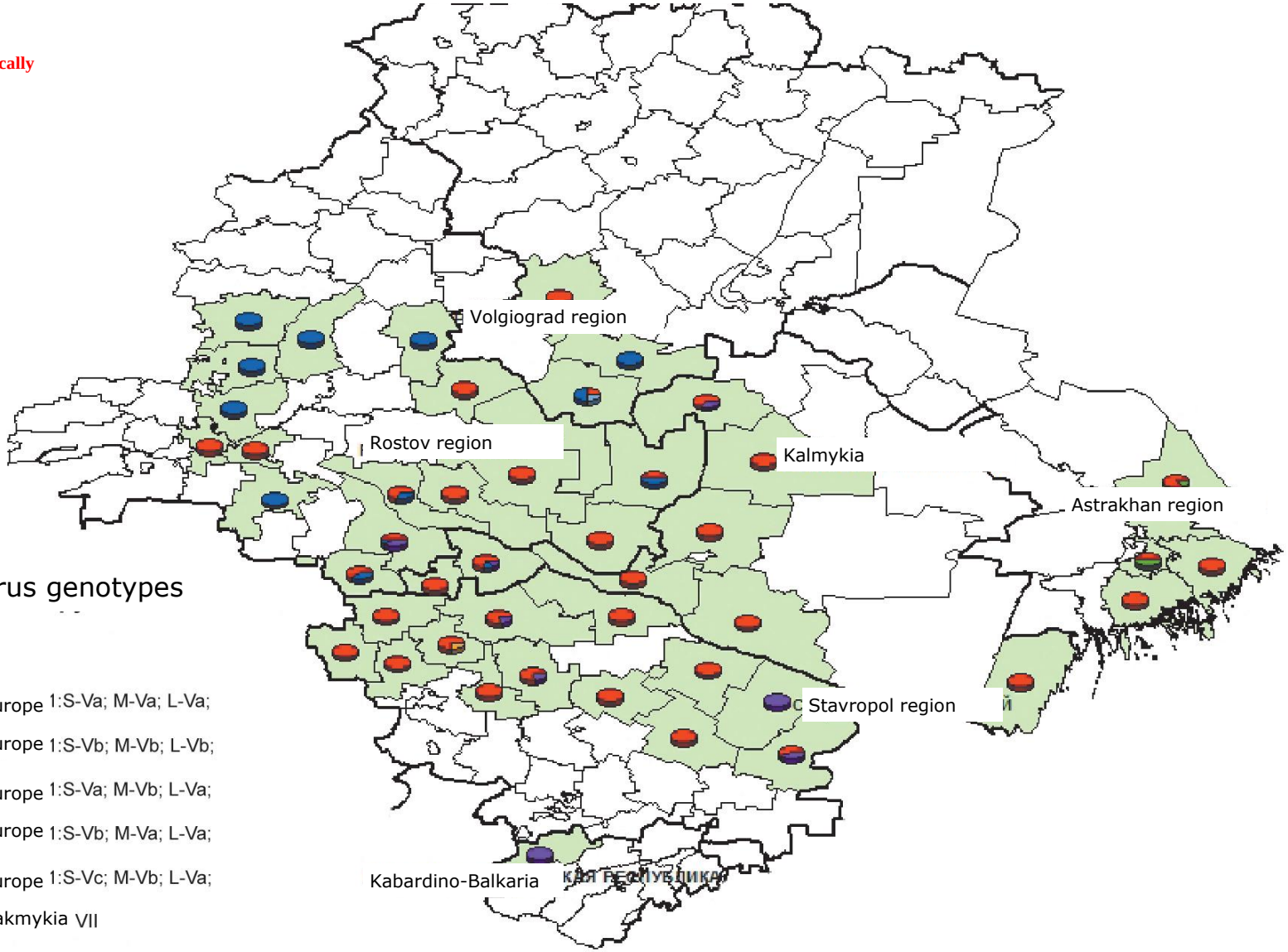
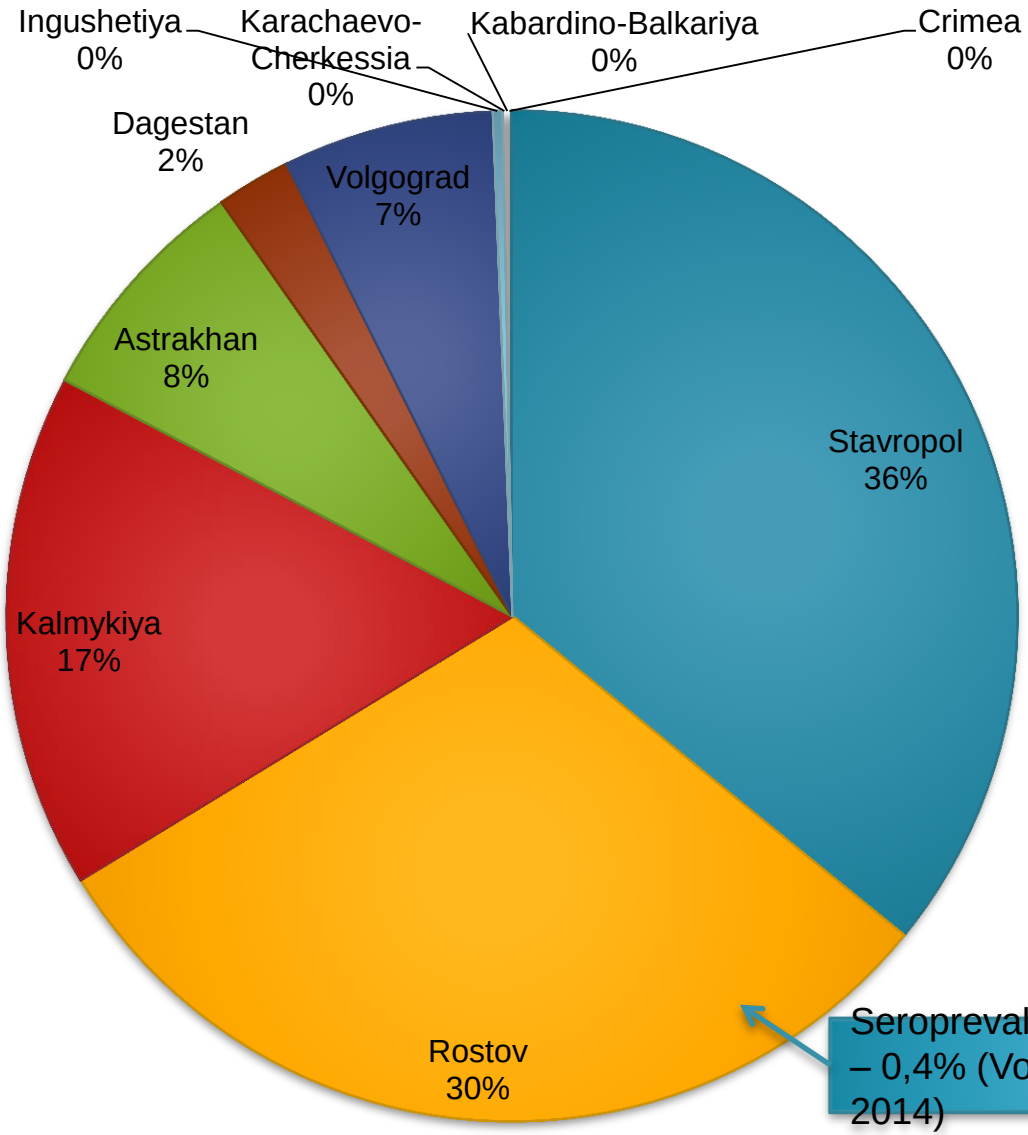
Genetic variants of the Crimean-Congo hemorrhagic fever virus circulating in the South of Russia in 2016 - data of Stavropol anti-plague scientific-research institute

Vectors:
Hyalomma marginatum – basically
Others:
Boophilus annulatus;
Dermacentor marginatus
Dermacentor reticulatus
Haemaphysalis punctata
Hyalomma scupense
Ixodes ricinus
Rhiphicephalus sp.
Rhipicephalus rossicus
Rhipicephalus sanguineus
Rhipicephalus turanicus



Volynkina A.S., Kotenev E.S., Lisitskaya Ya.V., Maletskaya O.V., Shaposhnikova L.I., Kulichenko A.N. Epidemiological Situation on Crimean Hemorrhagic Fever in the Russian Federation in 2016, and Prognosis for 2017. Problemy Osobo Opasnykh Infektsii [Problems of Particularly Dangerous Infections]. 2017; 1:24–28. (In Russ.). DOI: 10.21055/0370-1069-2017-1-24-28

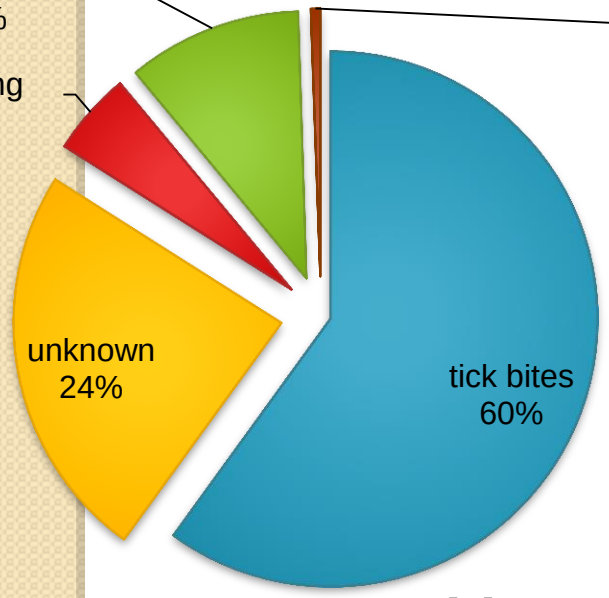
Proportion of affected regions in the geographical structure of CCHF incidence in Russian (1999-2016)



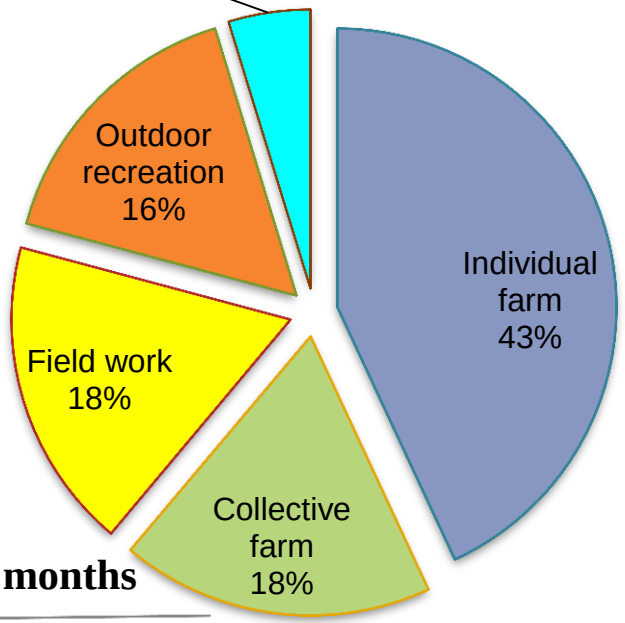
Seroprevalence of anti-CCHF IgG – 0,4% (Vodyanitskaya S Y et al, 2014)

Volynkina A.S., Kotenev E.S., Lisitskaya Ya.V., Maletskaya O.V., Shaposhnikova L.I., Kulichenko A.N. Epidemiological Situation on Crimean Hemorrhagic Fever in the Russian Federation in 2016, and Prognosis for 2017. Problemy Osobo Opasnykh Infektsii [Problems of Particularly Dangerous Infections]. 2017; 1:24–28. (In Russ.). DOI: 10.21055/0370-1069-2017-1-24-28

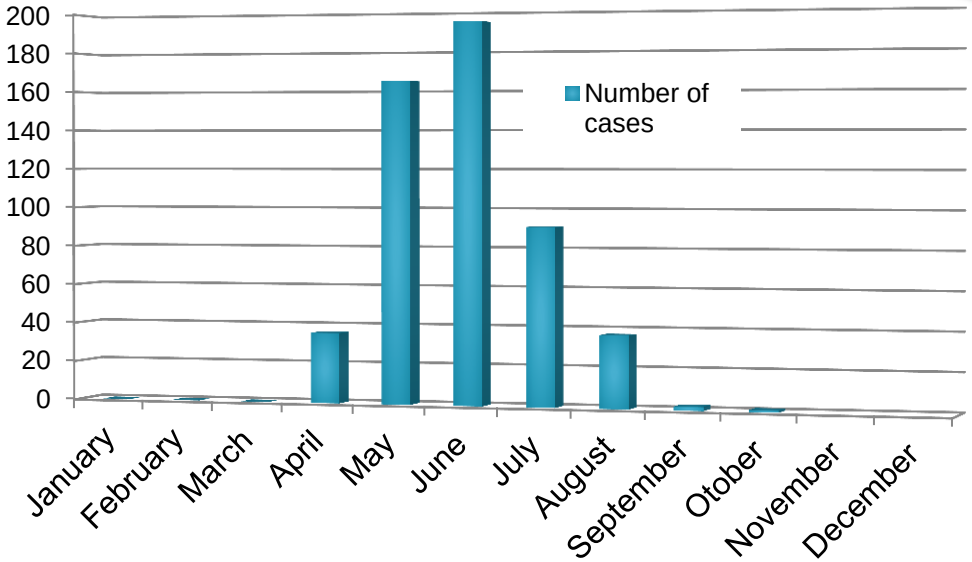
Way of CCHF transmission



Circumstances associated with the contamination



Annual dynamics of CCHF cases by months



Volynkina A.S., Kotenev E.S., Lisitskaya Ya.V., Maletskaya O.V., Shaposhnikova L.I., Kulichenko A.N. Epidemiological Situation on Crimean Hemorrhagic Fever in the Russian Federation in 2016, and Prognosis for 2017. Problemy Osobo Opasnykh Infektsii [Problems of Particularly Dangerous Infections]. 2017; 1:24–28. (In Russ.). DOI: 10.21055/0370-1069-2017-1-24-28;

ProMED-mail. Crimean-Congo haemorrhagic fever (Russia, Kazakhstan, preliminary results of 2017) ProMED-mail 2017; 03 Oct: 20180127.5589232. <http://www.promedmail.org>. Accessed 30 Jan July 2018.

Aerosol way of CCHF transmission

International Journal of Infectious Diseases
journal homepage: www.elsevier.com/locate/ijid

Perspective

Probable Crimean-Congo hemorrhagic fever virus transmission occurred after aerosol-generating medical procedures in Russia: nosocomial cluster

Natalia Yurievna Pshenichnaya *, Svetlana Alexeevna Nenadsk

Rostov State Medical University, Rostov-on-Don, Russia

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Keywords:
Crimean-Congo hemorrhagic fever
nosocomial cluster
airborne transmission

SUMMARY

We report here a fatal case of laboratory c
caused nosocomial infection in eight health
patient. All the HCWs survived.

The report demonstrates that airborne
patient is in a ventilator. During performanc
patient airborne precautions should alway
protective N95 mask or equivalent standarc
ventilated setting.

1. Introduction

Human cases of Crimean-Congo hemorrhagic fever (CCHF) most frequently occur among agricultural workers or inhabitants of rural areas after bites of infected Hyalomma ticks or direct contact with ticks, for instance, by removing ticks by unprotected hands, and more rarely among slaughterhouse workers exposed to the blood and tissues of infected livestock and medical personnel through contact with the body fluids of infected patients.[1–4]

The South-Western regions of Russia (Astrakhan, Rostov and Volgograd, Krasnodar and Stavropol regions, Kalmykia, Dagestan and Ingushetia Republics) are endemic for CCHF.[5,6] 1,654 CCHF cases with 73 fatalities (CFR 4,4%) were recorded from 1999 to 2013.[7] More than 400 cases of CCHF were diagnosed in the Rostov region alone from 2000 to 2013.

Nosocomial cases of CCHF among health workers (HCWs) in Russia are rare, and are connected with direct contact between infected blood and unprotected skin or eye mucosa. In the Rostov region nosocomial cases were reported in 1961 (1 person), 1966 (2 persons) and in 1999 (5 persons)[8]; isolated cases have also been identified in 2003, 2006 and 2007. Between 1999 and 2005

6 nosocomi
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In May 2
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A nosoco
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1.1. Index ca

A 23-yea
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illnesses (ILI
for CCHF, an
2 weeks be
picnic 2 –

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E-mail addresses: pshenichnaya.natalia@gmail.com, natalia-pshenichnaya@yandex.ru (N.Y. Pshenichnaya).

http://dx.doi.org/10.1016/j.ijid.2014.12.047

CCHF transmission via sexual contacts

International Journal of Infectious Diseases
journal homepage: www.elsevier.com/locate/ijid

Case Report

Possible sexual transmission of Crimean-Congo hemorrhagic fever

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Keywords:
Crimean-Congo hemorrhagic fever
Family cluster
Sexual contact
Transmission of infection

SUMMARY

Three cases of family transmission of laboratory-confirmed Crimean-Congo hemorrhagic f
among spouses are reported. These spouses had sexual contact at the end of the incubatic
during the early stage of the mild form of CCHF, without any hemorrhagic symptoms in the f
spouse. This report demonstrates that sexual contact may represent a real risk of CCHF tr
even if the patient only experiences mild symptoms.

1. Introduction

Crimean-Congo hemorrhagic fever (CCHF) most frequently occurs among inhabitants of rural areas and agricultural workers. The disease occurs following the bite of an infected Hyalomma tick, or by direct contact of unprotected hands with ticks, and more rarely through exposure to the blood and tissues of infected livestock, particularly among slaughterhouse workers.[1]

Medical personnel and family members usually contract CCHF through contact between body fluids of infected patients and unprotected skin or eye mucosa.[2] The performance of aerosol-generating medical procedures in CCHF patients can also lead to the nosocomial distribution of the infection among healthcare workers (HCWs).[3]

The southern regions of Russia (Astrakhan, Rostov, Volgograd, Krasnodar, and Stavropol regions, and Kalmykia, Dagestan, and Ingushetia Republics) are endemic for CCHF. One thousand seven hundred and forty-five CCHF cases with 75 fatalities (case-fatality rate 4.3%) were recorded between 1999 and 2014; 487 cases of CCHF were diagnosed in the Rostov region alone between 2001 and 2015.[4] The most affected territory in this region has been the district of Salsk, where 122 CCHF cases (25% of all ca
Rostov region) were recorded during the last 10 years. T
researchers recently described probable CCHF virus tra
after aerosol-generating medical procedures, which
nosocomial cluster involving eight HCWs in the district

Three cases of family transmission of laboratory-
CCHF among spouses are reported herein. These sp
sexual contact with the index cases at the end of the i
period or during the early stage of a mild form of CCHF, w
hemorrhagic symptoms in the first infected spouse.

2. Case reports

The three cases were diagnosed in the district of Salsk region within the last 10 years (2005–2015). The auth
that CCHF virus could have been transmitted sexually in
122 cases occurring during the last 10 years.

Ribavirin was administered to all of the patient
recovered successfully. PCR confirmation of CCHF bec
able in the region in 2008; prior to this, only ELISA wa

2.1. Case 1

A 27-year-old man, a slaughterhouse worker, was a
hospital on day 7 of disease (May 22, 2005). On days
illness, he had a fever of up to 38.0–39.0 °C, but durin

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Clinical findings

Severe course of CCHF in pregnancy

International Journal of Infectious Diseases
journal homepage: www.elsevier.com/locate/ijid

Crimean-Congo hemorrhagic fever in pregnancy: A systematic review and case series from Russia, Kazakhstan and Turkey

Natalia Yurievna Pshenichnaya[a], Hakan Leblebicioglu[b], Ilkay Bozkurt[b], Irina Viktorovna Sannikova[c], Gulzhan Narkenovna Abuova[d], Andrey Sergeevich Zhuravlev[e], Sener Barut[f], Mutabar Bekovna Shermetova[g], Tom E. Fletcher[h,i,*]

[a] *Rostov State Medical University, Department of Infectious Diseases, Rostov-on-Don, Russia*
[b] *Ondokuz Mayis University, Department of Infectious Diseases and Clinical Microbiology, Samsun, Turkey*
[c] *Stavropol State Medical University, Department of Infectious Diseases and Tuberculosis, Stavropol, Russia*
[d] *South-Kazakhstan State Pharmaceutical Academy, Department of Infectious Diseases and Dermatovenerology, Shymkent, Kazakhstan*
[e] *First State Medical University n.I. M. Sechenov, Research Department, Moscow, Russia*
[f] *Gazi Osmanpasa University, Tokat, Turkey*
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pregnancy
healthcare associated infection
viral hemorrhagic fever

ABSTRACT

Background: Crimean-Congo hemorrhagic fever (CCHF) is acute viral infection and a major emerging infectious diseases threat, affecting a large geographical area. There is no proven antiviral therapy and it has a case fatality rate of 4–30%. The natural history of disease and outcomes of CCHF in pregnant women is poorly understood.

Objectives: To systematically review the characteristics of CCHF in pregnancy, and report a case series of 8 CCHF cases in pregnant women from Russia, Kazakhstan and Turkey.

Methods: A systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement protocol. PubMed, SCOPUS, Science Citation Index (SCI) were searched for reports published between January 1960 and June 2016. Two independent reviewers selected and reviewed studies and extracted data.

Results: Thirty-four cases of CCHF in pregnancy were identified, and combined with the case series data, 42 cases were analyzed. The majority of cases originated in Turkey (14), Iran (10) and Russia (6). There was a maternal mortality of 14/41(34%) and fetal/neonatal mortality of in 24/48 cases (58.5%). Hemorrhage was associated with maternal ($p = 0.009$) and fetal/neonatal death ($p < 0.0001$). There was nosocomial transmission to 38 cases from 6/37 index pregnant cases.

Conclusion: Cases of CCHF in pregnancy are rare, but associated with high rates of maternal and fetal mortality, and nosocomial transmission.

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is an acute tick-borne viral infection and a major emerging infectious diseases threat. It affects a wide geographical area, centered in Eurasia including Turkey, Russia and Kazakhstan but is under-reported and diagnosis is often delayed. Fever, thrombocytopenia and hemorrhage are the characteristic clinical features, with supportive care forming the mainstay of treatment protocols, although ribavirin is utilized by some centers. Provision of blood product support and access to critical care interventions can improve outcomes, with reported case fatality rates (CFR) being 4–20%.[1]

The majority of cases of CCHF report a history of tick bite, but healthcare related transmission of CCHF is well reported, and occurs in both high and low-resource settings. Failure to recognize CCHF and as a result implement appropriate infection, prevention and control procedures results in significant nosocomial risk, especially in the context of critical care

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Probable CCCHF virus transmission occurred after aerosol-generating medical procedures in Russia: nosocomial cluster

Cluster of 9 CCHF cases in the Salsk district of the Rostov region

Secondary case
Nurse (ID) assisted in central venous catheterization, performed intravenous injections through a catheter, and monitored inhalation use hourly ;
PCR "+", alive

Secondary case
Obstetrician who examined the patient from the first day of admission to the hospital until the death;
PCR "+", alive

Index case
A 23-year-old pregnant woman (22 weeks) was admitted to the hospital on 6 May 2011 (2th day of illness) with ILI, died on 11 May 2011 (7th day of illness).
She developed severe double sided pneumonia (7May), hematemesis, hemoptysis, metrostaxis, and haemorrhage from the subclaviar catheter (8-9 May). The patient received support therapy and mucolytics and broncholytics through compression inhaler NEBULFLAEM on May 9-10. Due to a low oxygen saturation the patient was intubated on May 10 and mechanically ventilated until her death.
PCR "+" on the 5th day of disease (9 May), ribavirin was not prescribed due to late stage of disease confirmation, pregnancy, anemia.

Secondary case
Nurse from ICU department, who installed the equipment for ventilation with 20 min and had no any direct contact with patient or her fluids;
PCR "+", alive

Secondary case
Anesthesiologist from the ICU who took care of the ventilator treatment;
PCR "+", alive

Secondary case
who performed change of linen, cleaning room, and disinfection of the bedpan;
PCR "+", alive

Secondary case
Anesthetist who was in the ICU ward not more than 10 min, while the patient was in the ventilator, no any contacts with patient or her fluids;
PCR "+", alive

Secondary case
Clinician from ID department who attended the patient, doing rounds when she was in the ventilator; PCR "+", alive

Secondary case
Nurse (ID), who performed i/v injections through a catheter, and monitored inhalation use hourly ;
PCR "+", alive

WHO Publication/Guidelines

Natural Ventilation for Infection Control in Health-Care Settings

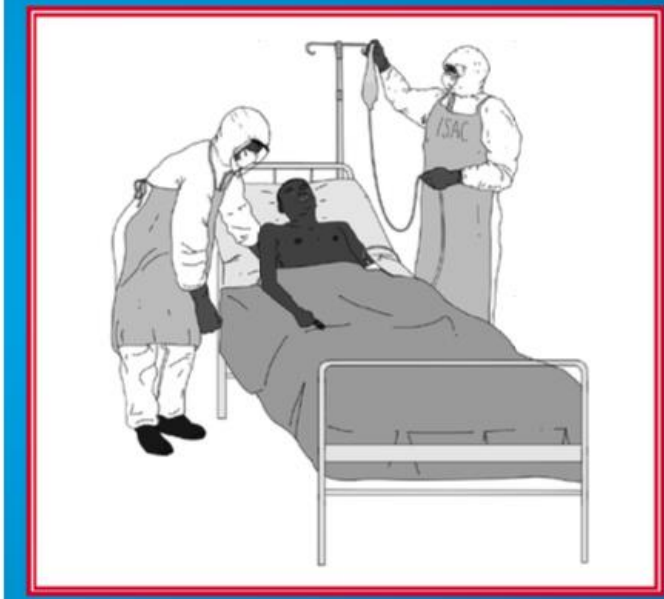
Edited by:
James Atkinson, Yves Chartier, Carmen Lúcia Pessoa-Silva, Paul Jensen, Yuguo Li and Wing-Hong Seto

2009

Clinical management of patients with viral haemorrhagic fever

A pocket guide for front-line health workers

FEBRUARY 2016



Interim emergency guidance for country adaptation

World Health Organization

Transmission via sexual contacts - close contact way?

(observation of 3 couples with CCHF in the Salsk district of the Rostov region of Russia, 2004-2015)

	Primary case	Difference between date of onset of symptoms	Secondary case
 1th couple	**Wife, 45 years old**, admitted to the hospital on the **2th day of disease (22.04.2010)**, on the 5th day after **tick bite** (19.04). No any hemorrhages at the day of admission, fever 38-39 C, Hb -119 g/l, WBC - 3,4*10⁹, PLTs - 123*10³**,** on the 3th day of disease hemorrhages at the places of i/v injections. ELISA (29.04) anti CCHF IgM 1:800, IgG - negative.	4 days	**Husband,** the 1th day of disease **(25.04.2010)**, there was no any rick factors in anamnesis, **sexual contact with wife between 20-21.04.** No hemorrhages at the day of admission, fever 39-40 C, Hb-107 g/l, WBC- 3,2*10⁹, PLTs - 95*10³**,** on the 3th day of disease gastrointestinal bleeding and massive hemorrhages in the places of i/v injections. ELISA (5.05 anti CCHF IgM 1:1600, IgG –
 2th couple	**Husband, 27 years old**, the slaugther, admitted to the hospital on the 7th day of disease (23.05.2005). No any hemorrhages were detected during whole course of disease, on the first 1-2 days of illness fever was 38,0-39,0 C, next 5 days before hospitalization -32,2-37,3 C, Hb 144 g/L, WBC - 3,2*10⁹, PLTs -146*10³. ELISA (30.05) anti CCHF IgM 1:800, IgG- negative.	8 days	**Wife, 29 years old** admitted to the hospital on the 2th day of disease (25.05.2005), unemployed, there was no any tick bites in anamnesis**, sexual contacts with husband between 19-22.05.** Fever 39,0 C at the day of admission, Hb-118 g/l, leucocytes - 3,4*10⁹, PLTs - 123*10³**,** on the 3-4th day of disease small hemorrhages were observed at the places of i/v injections. CCHF confirmed by ELISA (06.06) anti CCHF IgM 1:800, IgG –
 3th couple	**Husband, 55 years old, store manager,**, admitted to the hospital on the **3th day of disease (18.06.2014**), on the 5th day after tick bite(13.06). On the 1th day of disease fever was 37,2 C, on the 2 and 3th days - 38-39 C, Hb 150 g/l, WBC - 4,3*10⁹, PLTs - 128*10³**.** No any hemorrhages during whole course of disease were detected. PCR (20.06) positive, ELISA (24.06) anti	5 days	**Wife, 52 years old, seller,** admitted to the hospital on the 2th day of disease (21.06.2014)**,** she had **sexual contacts with husband between 16-17.06.** Fever was 39,0 C at the day of admission, Hb-118 g/l, WBC-2,1*10⁹, PLTs-140*10³**.** No any hemorrhages during whole course of disease were detected. PCR (22.06) positive, ELISA (30.06) anti CCHF IgM 1:6400, IgG – negative.

Core factors, which are important for probable transmission via sexual contacts:

1. All sexual partners of CCHF patient should be under medical observation with 2-times thermometry within 14 days

1. Ribavirin preventive dose (500 mg qid 7-10 days) should be administer for partners who had sexual contacts with CCHF patients during disease or 1-2 days before it.

CCHF and pregnancy: systematic review and case series (42 cases totally)

International Journal of Infectious Diseases 58 (2017) 58–64

Contents lists available at ScienceDirect

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Crimean-Congo hemorrhagic fever in pregnancy: A systematic review and case series from Russia, Kazakhstan and Turkey

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	Administration of ribavirin , n=13	No ribavirin, n=23	p
Lethal cases in pregnant women	5 (38,5±13,5%)	10 (43,4±10,3%)	>0,05
Fetus death	5 (38,5±13,5%)	15 (65,2±9,9%)	>0,05

Common mortality rate in pregnancy – 35,7%; before 20th week of pregnancy - 9%; after 20th weeks of pregnancy -48,4%

Russia – 6 cases

	Administration of ribavirin, n=2	No ribavirin,n=4
Lethal cases in pregnancy	0	3
Fetus death	0	4

Patients with suspected or probable case of CCHF usually hospitalized in ID department close to their place of living, as rule, in district hospital – difficulties for potential clinical trials

Rostov region – 37 cases in 2017

Situation is partially possible to change with support of MoH - tertiary ID isolation unit for HTPs for 12 beds (including 4 ICU beds) was built in the end of 2017 in Rostov – unique unit in the south of Russia

Regional hospital in Rostov-on-Don – only 2 cases;

What we have for surveillance, diagnostics and treatment? (1)

Surveillance:

Stavropol scientific research anti-plaque institute – all-Russian reference CCHF center and regional centers of Rospotrebnadzor (Federal Service for Supervision of Consumer Rights Protection and Human Well-Being) which provides:

- surveillance under the vectors of diseases on endemic areas, studying of CCHF natural foci,

- forecast regarding CCHF distribution,

- retrospective and prospective epidemiological analysis of CCHF in human (morbidity, mortality, places and ways of transmissions, occupational risks, etc.),

- ELISA and PCR diagnostics in humans and vectors of CCHF,

- analysis of genome (sequence) in collaboration with Central Scientific Research Institute of epidemiology (Moscow)

What we have for surveillance, diagnostics and treatment? (2)

Case definition

Suspected case

- Acute onset of illnesses with high fever (>38.0° C)
- Spring-Summer season
- History of tick bite or contact with tick on the endemic area
- History of contact with CCHF patient during health care for patient
- Occupation (agriculture of field work, cowherd, cattleman, etc.)

Probable case

- Acute onset of illnesses with high fever (>38.0° C)
- Spring-Summer season
- At least two of the following haemorrhagic manifestations: petechiae, purpuric rash, rhinorrhagia, haemorrhage, bloody vomiting, epistaxis, hemoptysis
- the absence of any known precipitating factor for haemorrhagic manifestation
- absence of any known reasons of haemorrhagic manifestation
- leukopenia, thrombocytopenia in blood

Confirmed case

- Specific clinical and epidemiological data;
- anti-CCHF Ig M titers 1:800 and more, in any IgG titers, detection of RNA of the CCHF virus.

Disadvantage of case definition:
include fever only more than 38,0 C.
Mild cases with sub febrile temperature can be missed
Early autumn season is missed
History of contact with possibly infected animals including agriculture animals is missed

Clinical management

Methodical recommendations for CCHF management were developed by MoH (2007) and National scientific society of infectious diseases specialists (2014).

- It includes above mentioned case definition and recommendation on use ribavirin in daily doses as for treatment HCV-infection (1000-1200 mg). Information about WHO doses exists as international experience.

HCWs in Stavropol treat CCHF patients with small doses of ribavirin, HCWs in Rostov Stavropol treat CCHF patients with WHO doses of ribavirin BUT mortality is the same.
Early address for medical aid and early recognition of CCHF and beginning of supportive treatment is keystone to success

What we have for surveillance, diagnostics and treatment? (3)

Laboratory diagnostics

- PCR AmpliSens® and ELISA (anti-CCHF IgM and IgG) «InterLabService», Moscow; “Vector-Best”, Novosibirsk

Anti-CCHF preventive measures

- several decisions and orders of Rospotrebnadzor regarding CCHF preventive measures (measures in the foci of infection, seasonal anti-tick proceedings of territories in the endemic regions),
- orders of Ministry of Agriculture regarding vector control on animals, anti-tick proceeding of agriculture animals and their places of habitat;
- MoH resolutions regarding stockpiles of blood components, stockpiles of ribavirin for treatment and PEP, annual education of physicians at the beginning of season,

Education of physicians

Short trainings are implemented every year in hospitals and outpatient departments at the beginning of season with the purpose to raise awareness of health care workers

Social mobilization

Information of children and young people in schools, universities via leaflets, lectures; information of population in out-patient departments, markets, supermarkets, banks, hospitals, etc. via leaflets, TV, radio, newspapers.

What we would like to have together with other countries?

- CCHF case definition which allow to suspect all CCHF cases and allow to compare clinical studies in other countries – we need to have common CCHF definition for all countries;

- very desired to have rapid tests for CCHF diagnostics in distinct rural areas, field conditions;

- due to absent of evidence base on ribavirin efficiency we need to have new antiviral drugs for CCHF treatment;

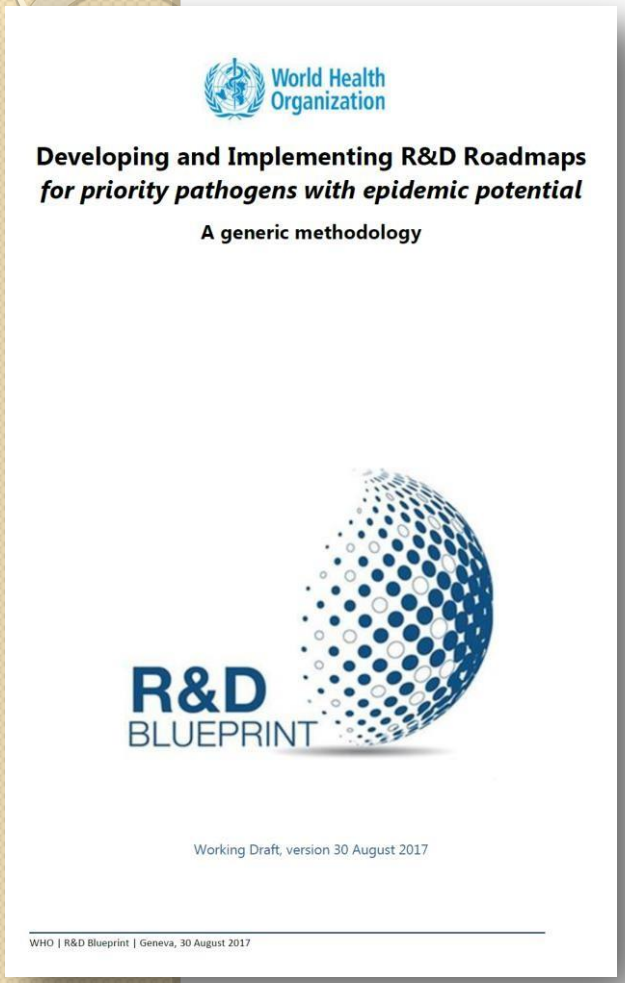
- very desirable to have antivirals which are safe in pregnancy;

- vaccine against CCHF is essential for risk groups in endemic a

- anti-CCHF and anti-tick vaccines are very essential for agriculture and domestic animals to prevent contamination by CCHFv and destroy life circle of ticks or virus replication in ticks;

- very desirable to have pocket-size manual based on WHO CCHF recommendation for case management, IPC, post-exposure prophylaxis, discharge of patients in health care facilities, waste management, isolation room equipment;

Developing & implementing R&D roadmaps



CCHF has been identified as a one the WHO priority disease for which accelerated basic and applied research as well as product development would be beneficial.

Turkey, Russia, Iran, Oman, Pakistan will be primary included in R&D roadmaps activity

2 consultations with country representatives and experts in research areas already took place in WHO HQ in 2018

Methodology Synopsis

→ High level summary of principles and concepts to provide an overview and to be used for peer-review publication

Methodology Core Document

→ Outline of the information and elements to understand roadmaps and roadmapping development/process

Appendices

→ Systematic list of detailed instruction/steps to elaborate and to implement R&Droadmaps

World Health Organization

CCHF R&D Blueprint roadmap (1)

Main purpose

- To be able to reduce death and morbidity from CCHF through safe and **affordable effective treatments** informed by **rapid, reliable and easily accessible diagnostics** by 2023, and
- To be able to prevent or mitigate CCHF disease through deployment of safe, **affordable and effective vaccines and other preventive measures** by 2030.

Diagnostic

- **Development and validation of rapid diagnostic tests** for CCHF with high sensitivity and specificity (simple to use, sample-to-answer nucleic acid tests with high sensitivity and specificity and (ii) rapid point-of-care tests (nucleic acid or antigen detection) with minimal requirements for biosafety precautions and staff training (2018-2024).
- By 2020, at least 2 WHO-prequalified, accessible commercial IgM and IgG serology tests available for follow-up of suspected CCHF cases, for epidemiological purposes and for pre-screening volunteers for CCHF vaccine trials.
- Investigate utility of alternative sample types (urine, oral fluid, semen etc) for CCHF diagnosis; this will also provide knowledge about CCHFV persistence in body fluids and may support non-invasive diagnostics.

- Developing «fever panel» – diagnostic tests that use a common platform to distinguish CCHF from related illnesses with similar presentation
- Continue to review the utility of next generation sequencing (especially metagenomics) for CCHF diagnostic use (including contact tracing and epidemiological approaches), particularly using portable solutions e.g. MinIon in the field.

CCHF therapeutics interventions

EDPLN

- Ribavirin: systematic reviews regarding the clinical efficacy of Ribavirin in treatment of CCHF have been published . Both studies agree that current evidence is insufficient and call for a large placebo-controlled trial.
- Favipiravir (T-705) good efficacy in transgenic IFNAR mouse models.
- Intravenous immunoglobulin (IVIG), several studies in Soviet Union, South Africa, Turkey and Bulgaria reported but lack of evidence in absence of proper controls.
- Monoclonal antibodies (Mabs) [similar to Ebola]
- New compounds

CCHF R&D Blueprint roadmap (2)

Therapeutics

- By 2019, produce protocols in consultation with national regulatory authorities for dose regimen and subsequent randomized controlled trials to assess the efficacy and safety of existing therapeutic products (e.g. favipiravir), alone or in combination therapy against CCHF.
- By 2020, initiate first evaluation of the therapeutic potential of antibody therapy in a relevant preclinical model of CCHFV infection.
- **By 2021, start patient enrolment to phase II trials of an existing therapeutic (e.g. favipiravir)** in 2 or more countries to evaluate efficacy against CCHF disease and establish pharmacokinetic data.
- By 2023, take successful therapeutics forward to a phase III randomized controlled trial to establish full efficacy against CCHF disease.
- Development of a standardized case definition for CCHF for clinical trials

CCHF R&D Blueprint roadmap (3)

Vaccines and Vector Control

- Working with the appropriate national regulators, take at least one CCHF vaccine candidate that meets the TPP for CCHF vaccines and with proven efficacy in relevant animal models, into human phase 1 safety and early immunogenicity trails by 2019 and phase II trial by 2023.

- Prioritise and progress 5 early-stage developmental human CCHF vaccines through relevant animal models by 2025.
- By 2025, complete a proof-of-concept study of experimental *Hyalomma*-targeted tick vaccines and/or veterinary anti-CCHF vaccine(s) in relevant animal models.

- By 2025, identify the adaptive immune responses and protective mechanisms in humans and NHPs against CCHF disease and iden the correlates of protection for use in preclinical vaccine studies.

Only together we can find a solution!

Thank you for attention!