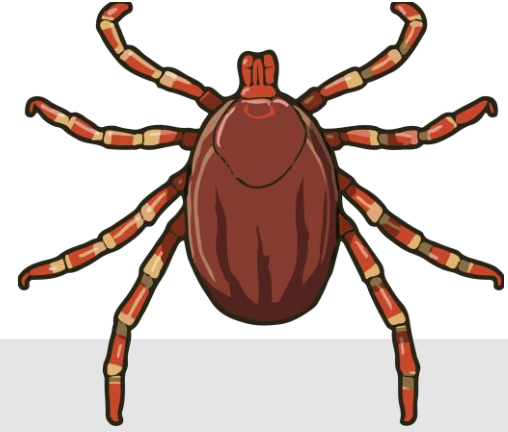


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CENTER FOR INFECTIOUS DISEASES



Crimean Congo Hemorrhagic Fever and Other Viral Hemorrhagic Fever

Önder Ergönül, MD, MPH
Koç University School of Medicine
Infectious Diseases & Clinical Microbiology



Current Treatment of Viral Hemorrhagic Fevers

Viral hemorrhagic fever	Antivirals			Immunomodulator drugs		Monoclonal antibodies
	Ribavirin	Favipiravir	Other antivirals	Steroids	IL-Inhibitors	
Ebola virus disease	No study	Beneficial in a retrospective study; no effect on non-randomized clinical trials [37–39]	Remdesivir in clinical trial; some benefit [33]	No study	No study	mAb114, REGN-EB3 showed survival benefit in clinical trial [32]
Marburg virus disease	No study	No major clinical trial	None	No data	No data	Nothing approved, or on study
Crimean-Congo Hemorrhagic Fever	Observational studies and meta-analysis show benefit, especially when given early [81,82]	Compassionate use only, no RCTs	None	Potential benefit in severe cases [82]; no RCTs	No trials	Human mAbs under study; no clinical trials yet
Lassa fever	Observational studies show mortality benefit, especially when given early [65,66]	Small Phase-II study is conducted; results are pending [69]	None	No data	No data	Promising Arevirumab-3 cocktail, clinical data is needed [71]
Dengue fever	No study	No completed clinical trials; limited data	Celgosivir and balapiravir was tried in RCTs, no benefit [93]	Used in severe dengue; mixed evidence [97–99]	Not routinely used	No approved mAbs
Yellow Fever	No clear benefit	Not studied	None	No data	No data	Demonstrated good tolerance in phase I a/b clinical trial [118]
Rift Valley Fever	No clinical study	Not studied	None	No data	No data	No approved mAbs
Hantavirus	Effective in HFRS, especially when given early [132], not in HPS [134,135]	No data	None	Used in severe HPS; no controlled trials	No trials	No approved mAbs
Other Arenaviruses	No clinical study	No clinical study	None	No data	No data	No clinical mAbs

Güllü D, Keske Ş, Ergönül Ö. Viral hemorrhagic fevers - therapeutic trial advances and challenges. Expert Rev Anti Infect Ther. 2025



Re-purposed Drugs

Ebola

Favipiravir

Brinsidofovir

Remdesivir

CCHF

Favipiravir

Remdesivir

Molnupiravir

Nirmetralvir

Monoclonal antibodies

Evaluation of Antiviral Efficacy of Ribavirin, Arbidol, and T-705 (Favipiravir) in a Mouse Model for Crimean-Congo Hemorrhagic Fever

Lisa Oestereich^{1,2,3}, Toni Rieger^{1,2,3}, Melanie Neumann³, Christian Bernreuther⁴, Maria Lehmann^{1,2}, Susanne Krasemann³, Stephanie Wurr^{1,2}, Petra Emmerich^{1,2}, Xavier de Lamballerie⁵, Stephan Ölschläger^{1,2,4}, Stephan Günther^{1,2,4*}

¹Department of Virology, Bernhard-Nocht-Institute for Tropical Medicine, Hamburg, Germany, ²German Centre for Infection Research (DZIF), Hamburg, Germany,

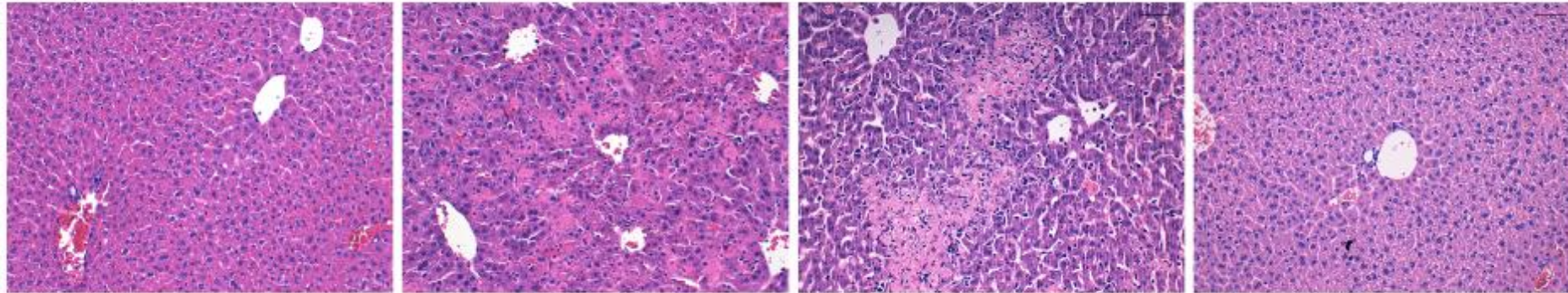
Naïve

Infected

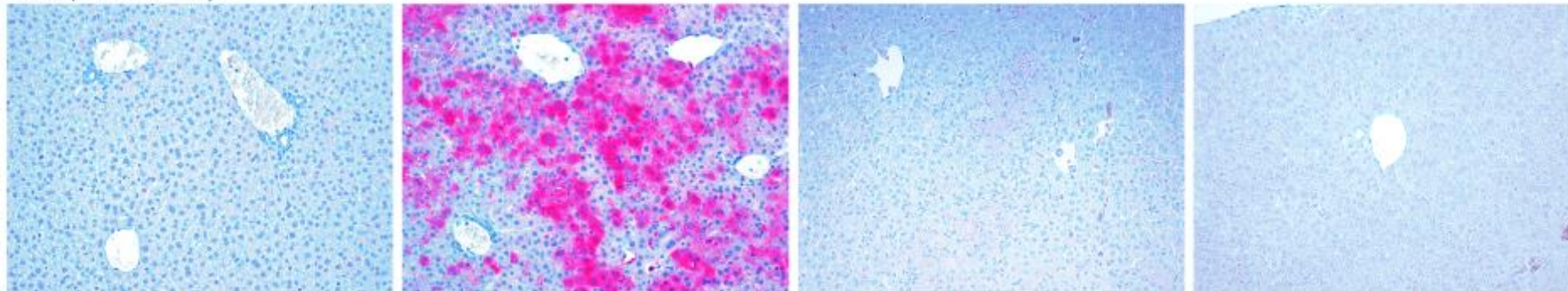
Infected + ribavirin

Infected + T-705

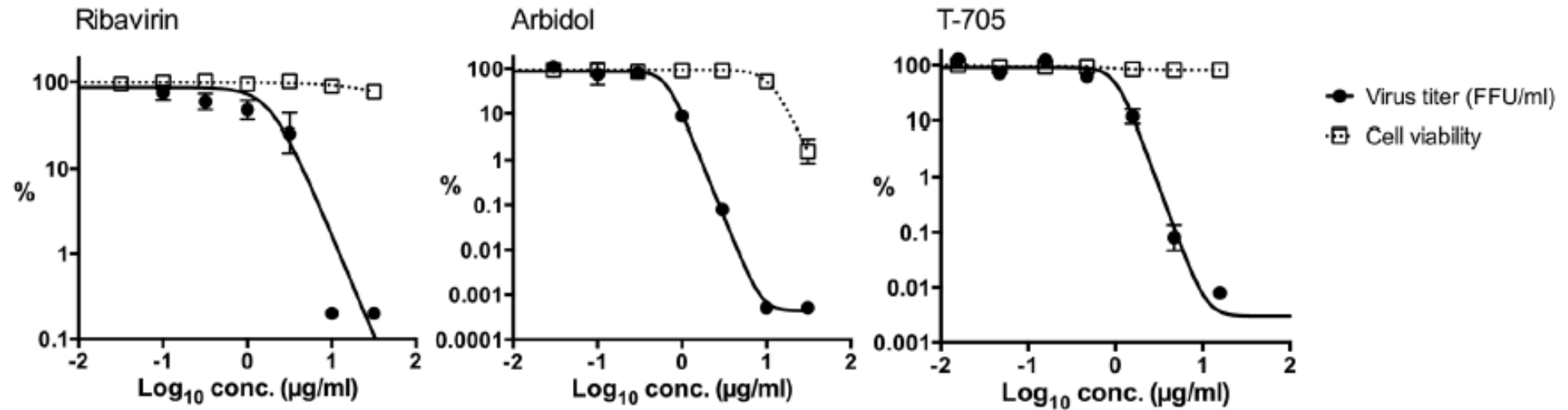
Liver (H&E)



Liver (CCHFV NP)



Favipiravir (T-705) is more effective in vitro and in vivo



	Ribavirin (n=2)	Arbidol (n=3)	T-705 (n=2)
IC ₅₀	2.8 µg/ml (1.9–3.7)	0.6 µg/ml (0.08–1.2)	1.1 µg/ml (1.0–1.1)
IC ₉₀	4.7 µg/ml (4.6–4.8)	1.2 µg/ml (0.2–2.4)	1.6 µg/ml (1.5–1.7)
IC ₉₉	9.5 µg/ml (5.8–13.2)	2.0 µg/ml (0.5–3.8)	2.5 µg/ml (2.0–2.9)



Research paper

Efficacy of favipiravir (T-705) against Crimean-Congo hemorrhagic fever virus infection in cynomolgus macaques

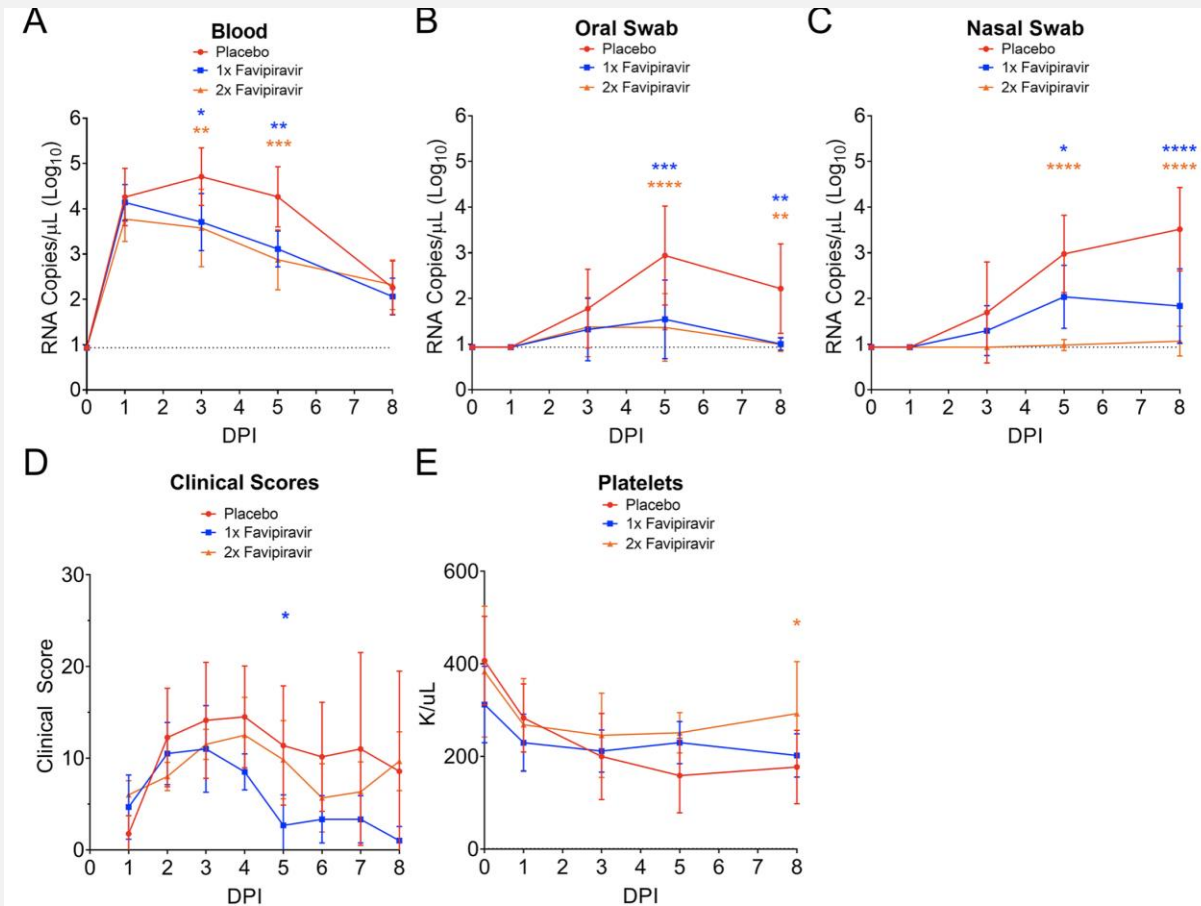
David W. Hawman^a ✉, Elaine Haddock^a, Kimberly Meade-White^a, Glenn Nardone^b, Friederike Feldmann^a, Patrick W. Hanley^a, Jamie Lovaglio^a, Dana Scott^a, Takashi Komeno^c, Nozomi Nakajima^c, Yousuke Furuta^c, Brian B. Gowen^d, Heinz Feldmann^a ✉

Once- or twice-daily favipiravir suppressed viremia and viral shedding in CCHFV infected macaques.

Viral loads within key tissues of favipiravir-treated animals trended lower than in placebo-treated animals.

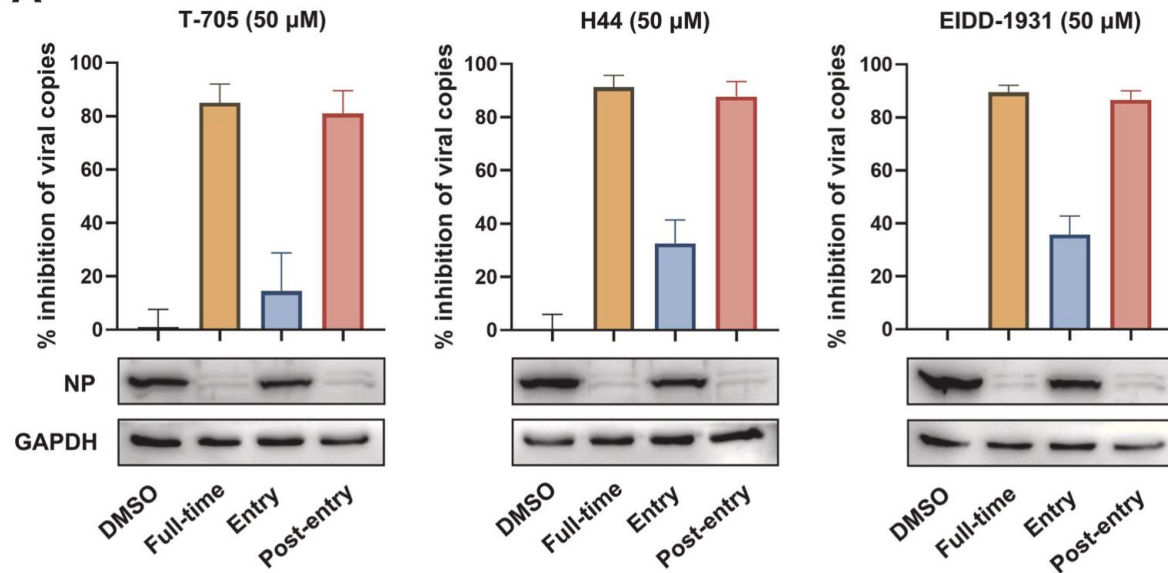
Study highlights the importance of the macaque model of CCHF in evaluating antivirals for human CCHF cases.

Antivir Res 2020

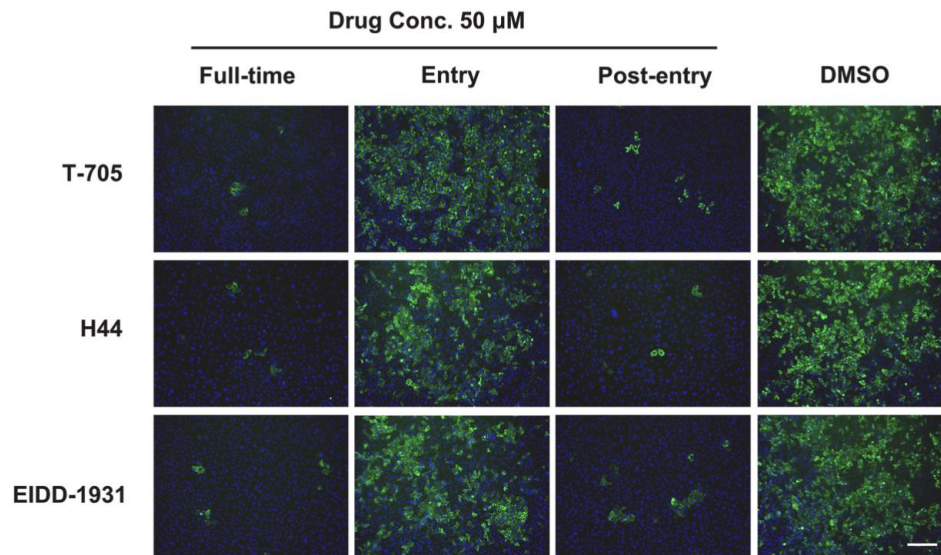




A



B



In vitro and *in vivo* efficacy of a novel nucleoside analog H44 against Crimean–Congo hemorrhagic fever virus

Qianran Wang^{a, d, 1}, Ruiyuan Cao^{b, 1}, Liushuai Li^{a, d}, Jia Liu^a, Jingjing Yang^b, Wei Li^b, Linjie Yan^b, Yanming Wang^b, Yunzheng Yan^b, Jiang Li^a, Fei Deng^a, Yiwu Zhou^c, Manli Wang^{a, 2}, Wu Zhong^{b, 2}, Zhihong Hu^{a, 2}

H44: modified Favipiravir

T-705: Favipiravir

EIDD-1931: Remdesivir

EIDD-2081: Molnupiravir

- H44, T-705, and EIDD-1931 inhibited CCHFV infection at the “post-entry” stage.

- EIDD-2081, the EIDD-1931 prodrug, did not protect IFNAR^{-/-} mice from CCHFV infection.

- **H44 protected IFNAR^{-/-} mice from lethal CCHFV challenge as efficiently as T-705.**

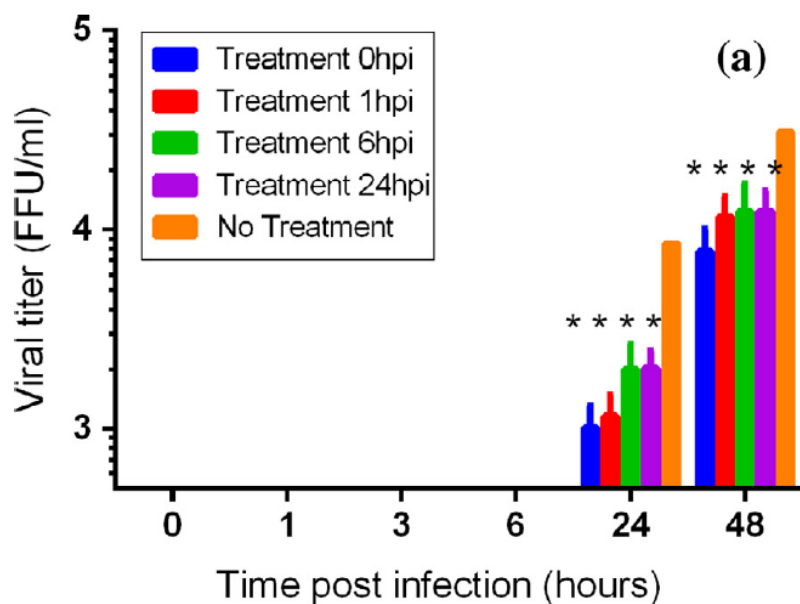
Evaluation of Crimean-Congo hemorrhagic fever virus *in vitro* inhibition by chloroquine and chlorpromazine, two FDA approved molecules

O. Ferraris^a, M. Moroso^b, O. Pernet^{c,1}, S. Emonet^a, A. Ferrier Rembert^a, G. Paranhos-Baccalà^b, C.N. Peyrefitte^{a,b,*}

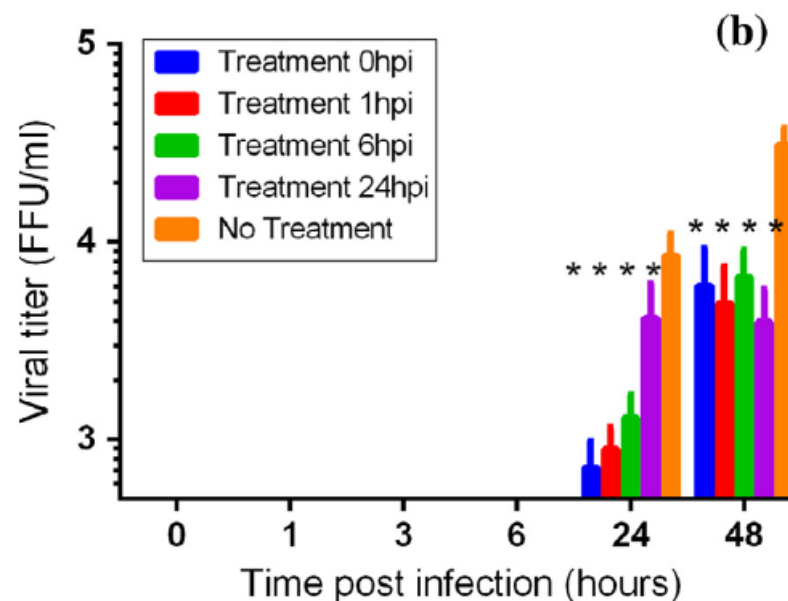
^a Institut de Recherche Biomédicale des Armées, Unité de Virologie, Lyon, France

^b Fondation Mérieux, Laboratoire des Pathogènes Émergents, Lyon, France

^c Unité de Virologie Humaine – INSERM U758, Lyon, France



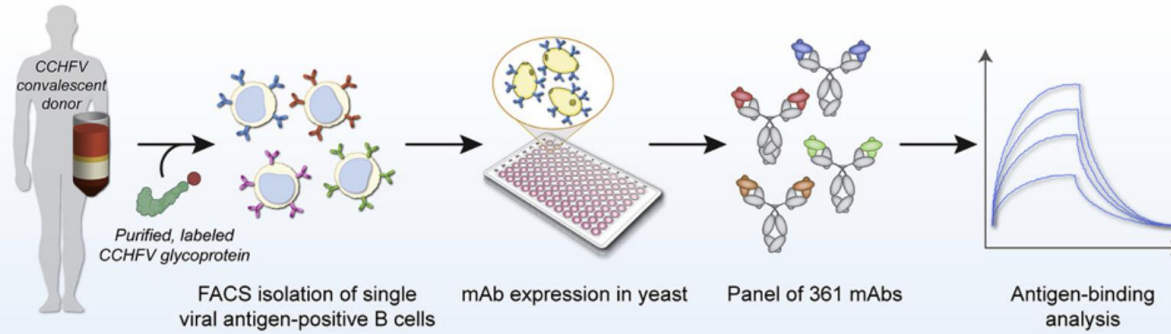
Chloroquine



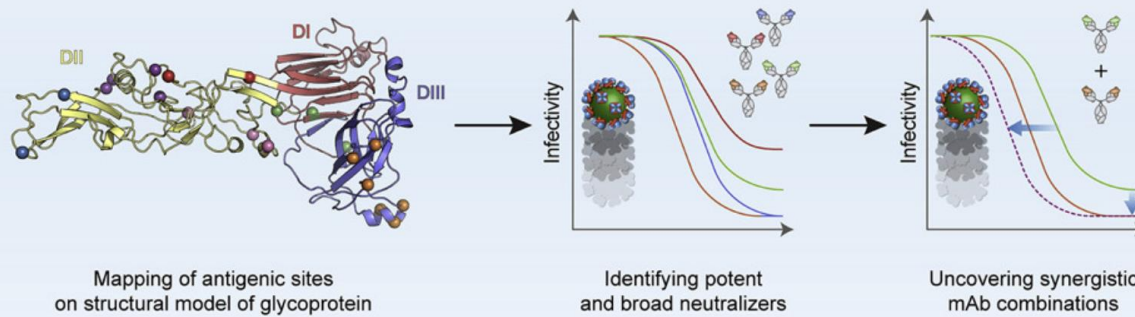
Chlorpromazine



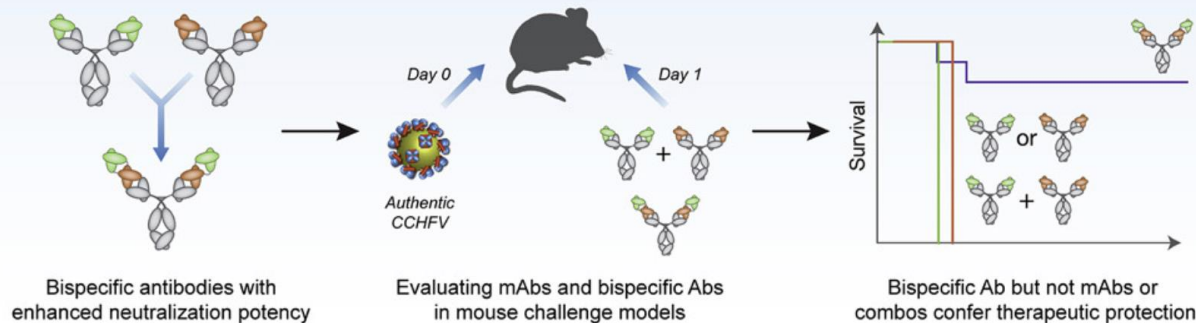
Discovery of CCHFV glycoprotein-specific mAbs from human convalescent donors



Characterization and selection of lead candidate mAbs and mAb combinations



Engineering of highly potent bispecific antibodies and evaluation of therapeutic efficacy



Cell

Volume 184, Issue 13, 24 June 2021, Pages 3486-3501.e21



Article

Protective neutralizing antibodies from human survivors of Crimean-Congo hemorrhagic fever

J. Maximilian Fels^{1, 15}, Daniel P. Maurer^{2, 15}, Andrew S. Herbert^{3, 14, 15}, Ariel S. Wirchnianski^{1, 4}, Olivia Vergnolle^{4, 16}, Robert W. Cross^{5, 6}, Dafna M. Abelson⁷, Crystal L. Moyer⁷, Akaash K. Mishra⁸, Jennifer T. Aguilan¹², Ana I. Kuehne³, Noel T. Pauli², Russell R. Bakken³, Elisabeth K. Nyakatura^{4, 16}, Jan Hellert^{9, 17}, Gregory Quevedo⁴, Leslie Lobel^{10, 18}, Stephen Balinandi¹¹ ... Kartik Chandran^{1, 19, 20} ✉

361 monoclonal antibodies against CCHFV glycoproteins isolated from human survivors

- Potent and broad neutralizers targeting six antigenic sites in Gc identified

- Specific combinations of noncompeting antibodies afford synergistic neutralization

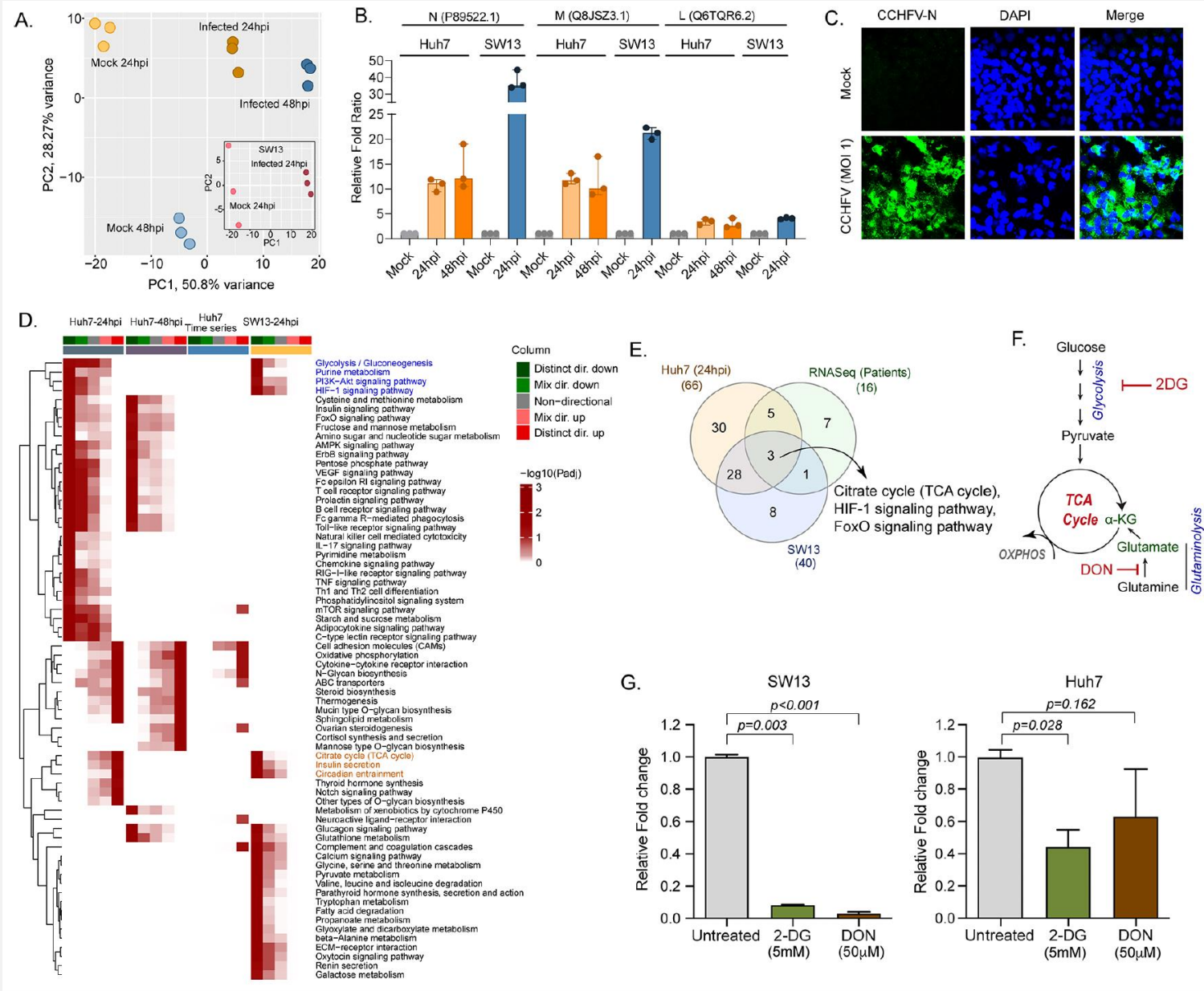
- Bispecific antibody combining synergistic antibodies confers therapeutic protection

Cell 2021

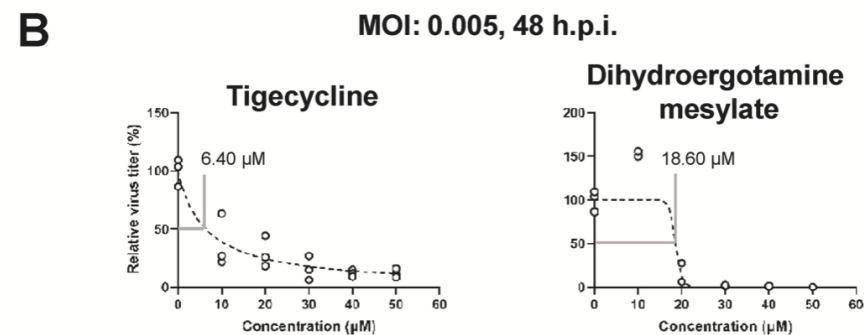
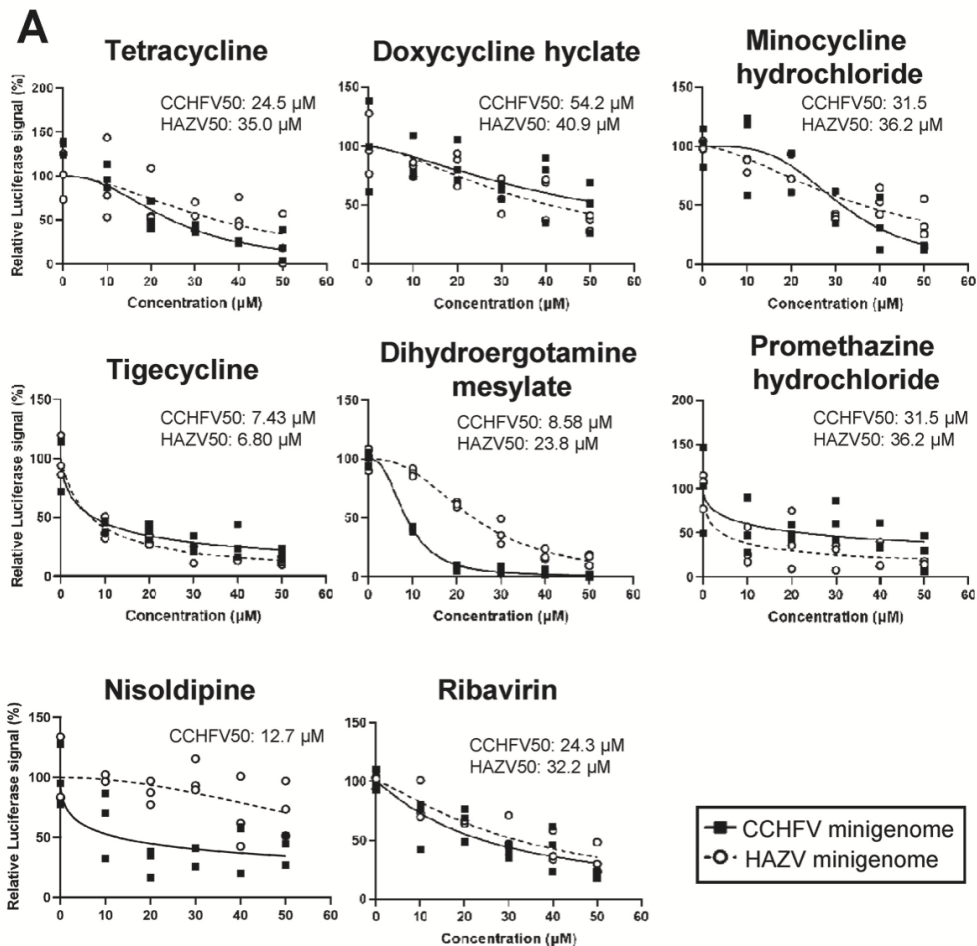


Multi-omics insights into host-viral response and pathogenesis in Crimean-Congo hemorrhagic fever viruses for novel therapeutic target

By blocking the two key CCEM pathways, glycolysis and glutaminolysis, viral replication was inhibited in vitro. Activation of key interferon stimulating genes during infection suggested the role of type I and II interferon-mediated antiviral mechanisms both at the system level and during progressive replication.



Neogi U, Et al. eLife 2022



A screen of FDA-approved drugs with minigenome identified tigecycline as an antiviral targeting nucleoprotein of Crimean-Congo hemorrhagic fever virus

Minato Hirano ^a, Yasuteru Sakurai ^{a, b}, Shuzo Urata ^{a, b}, Yohei Kurosaki ^{a, b}, Jiro Yasuda ^{a, b}, Kentaro Yoshii ^{a, b} ✉

Library screening of FDA-approved compounds identified **ten candidate** compounds.

tigecycline showed inhibition at 10 μM concentration.

Tigecycline treatment dissociated the interaction between CCHFV N protein and RNA: a new target of antiviral development.

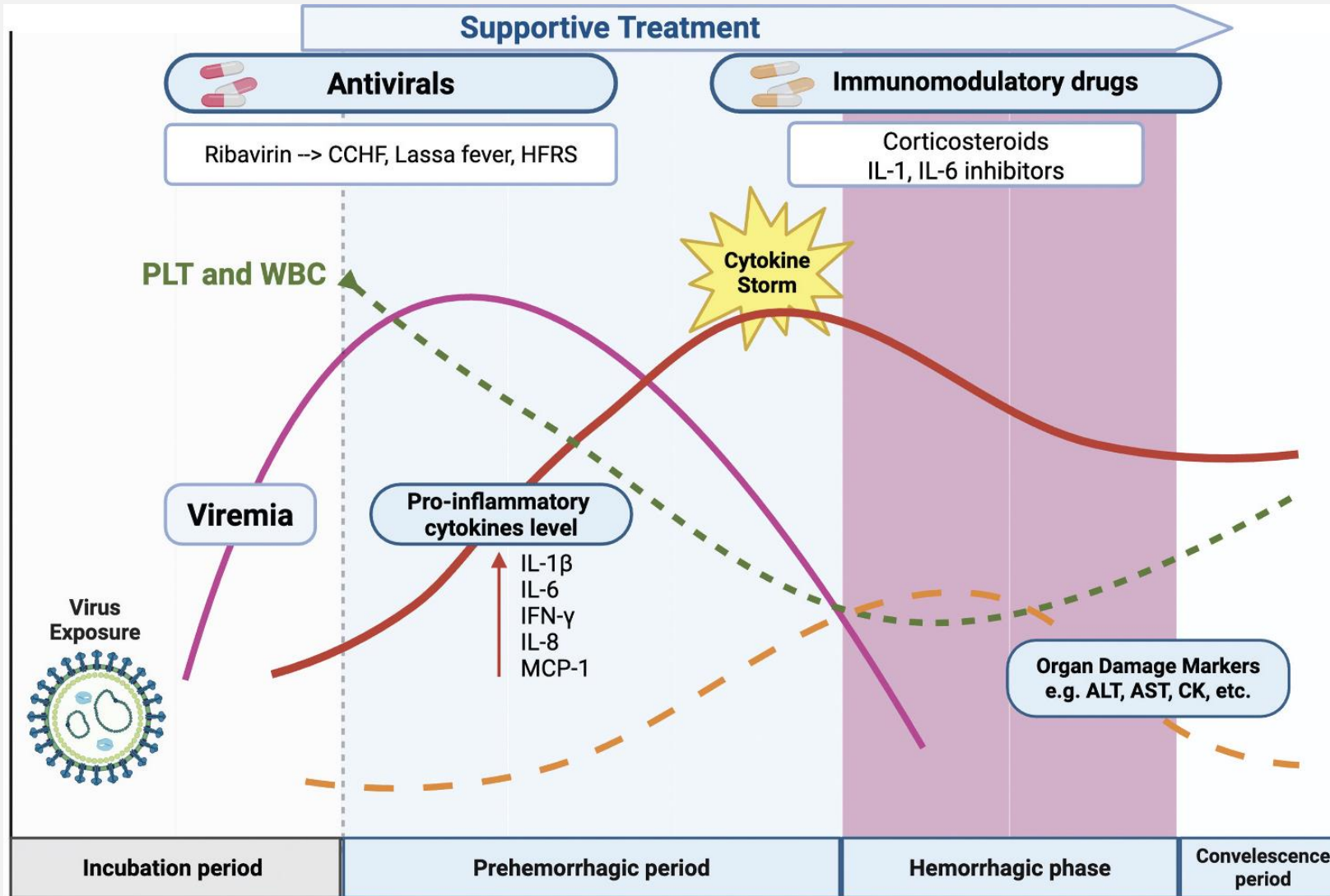


Ribavirin

Arenaviridae
Lassa Fever
South America HF
Bunyavirales
Hanta
Rift Valley
CCHF



Conceptual overview of disease course and therapeutic windows in viral hemorrhagic fevers



Güllü D, Keske Ş, Ergönül Ö. Viral hemorrhagic fevers - therapeutic trial advances and challenges. Expert Rev Anti Infect Ther. 2025



Problems in Study Design: What We Learned?

A. Study Design

1. Inclusion criteria
 1. Severity (Confounding by indication)
 2. Number of days from onset of symptoms
 1. Prehemorrhagic
 2. Hemorrhagic
2. Ineffective application:
GIS symptoms in oral use (hematemesis)
3. Duration of treatment

B. Statistical Analysis

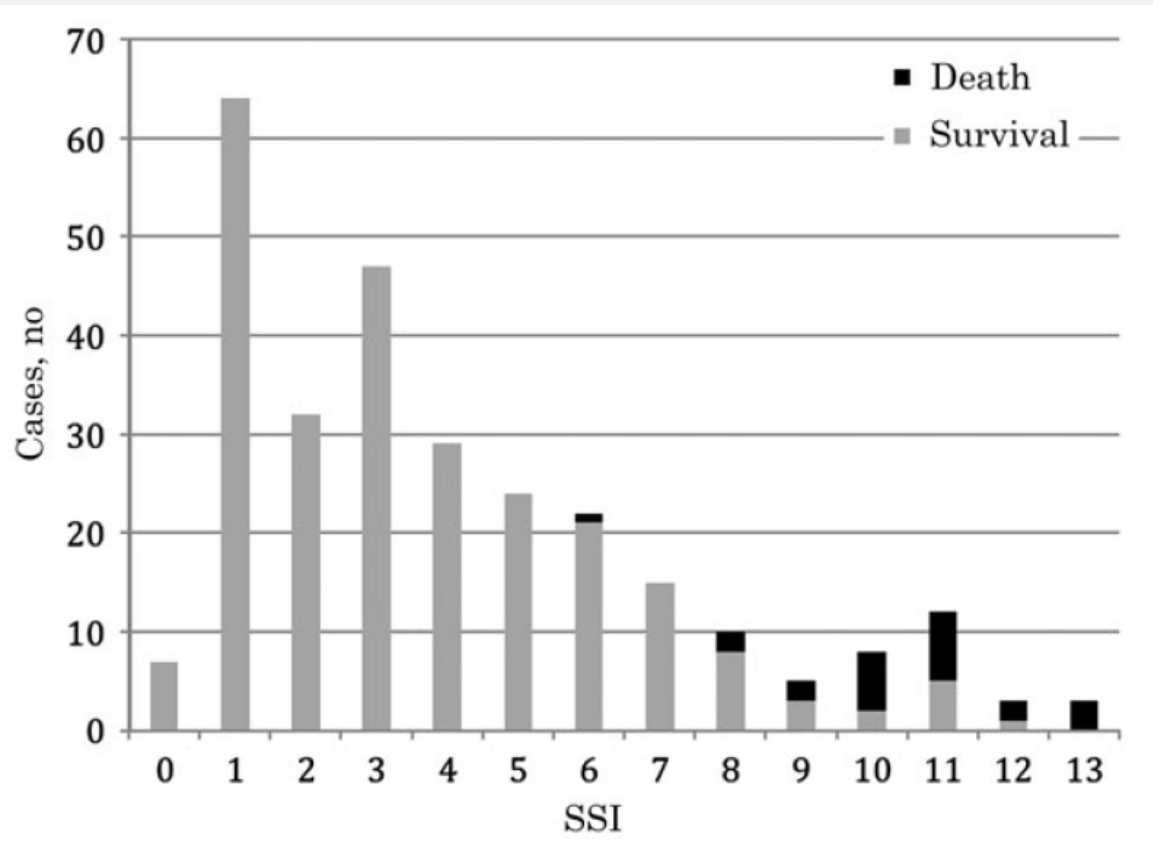
1. P value is not everything; sample size is important
2. Meta-analysis: oranges & apples; early vs late



Severity Scoring Index for Crimean-Congo Hemorrhagic Fever and the Impact of Ribavirin and Corticosteroids on Fatality

Başak Dokuzoguz,¹ Aysel Kocagül Celikbas,¹ Şebnem Eren Gök,¹ Nurcan Baykam,¹ Mustafa Necati Eroglu,¹ and Önder Ergönül²

¹Clinical Microbiology and Infectious Diseases Clinic, Ankara Numune Education and Research Hospital, Ankara, and ²Infectious Diseases and Clinical Microbiology, Koç University, School of Medicine, Istanbul, Turkey



Clin Infect Dis 2013

Table 1. Characteristics of SSI Parameters for Crimean-Congo Hemorrhagic Fever

SSI Parameter	Score
Platelet count, $\times 10^3$ platelets/mm³	
>150	0
150–50	1
49–20	2
<20	3
aPTT, sec	
≤ 34	0
35–45	1
46–59	2
>60	3
Fibrinogen level, mg/dL	
≥ 180	0
179–160	1
159–120	2
<120	3
Bleeding	
No	0
Petechia	1
Ecchymosis	2
Bleeding	3
Somnolence	
No	0
Yes	1



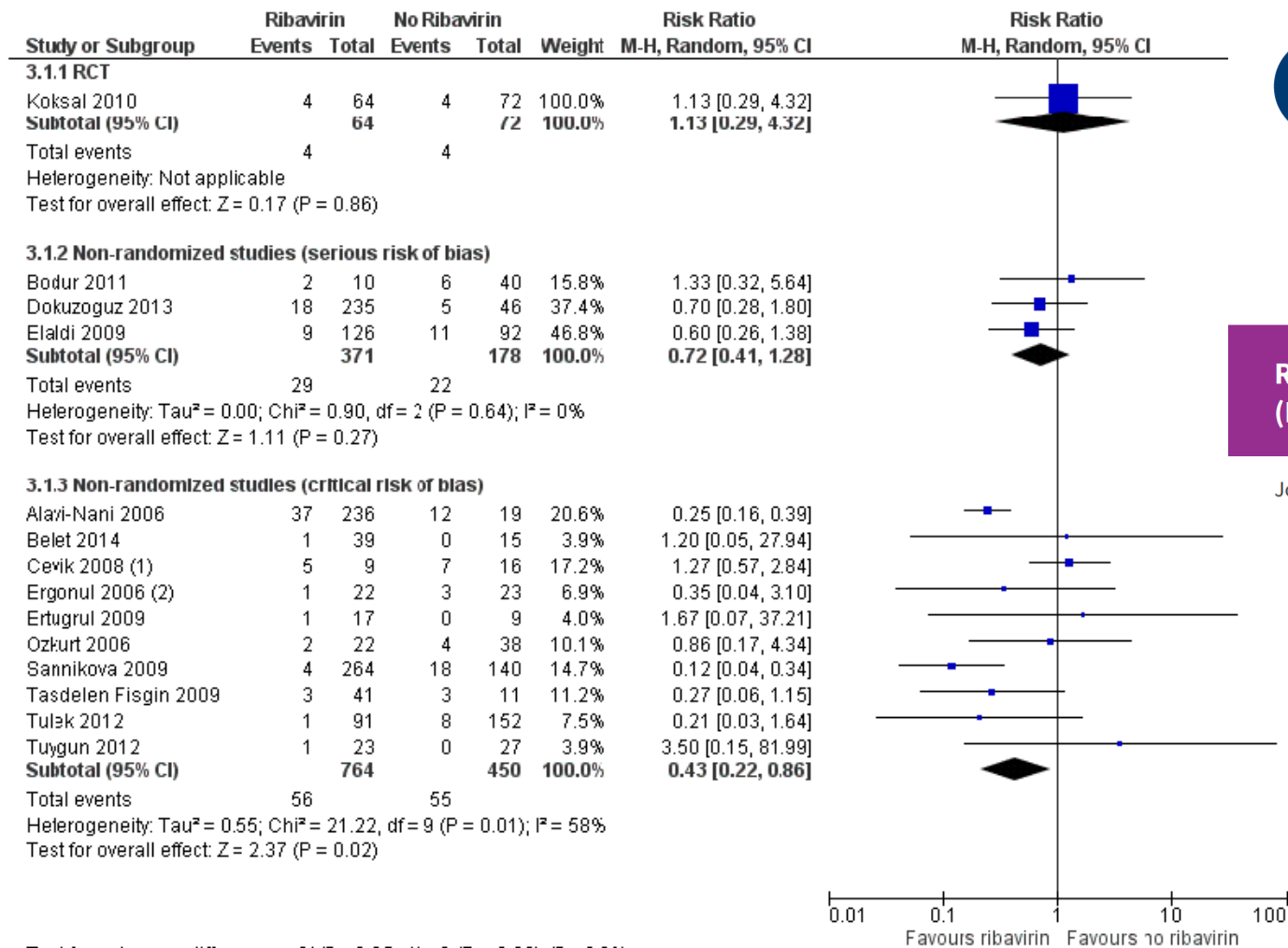
Table 3. Univariate and Adjusted Analysis for Prediction of Death

Factor	Univariate Analysis		Adjusted Analysis	
	OR (95% CI)	<i>P</i> Value	OR (95% CI)	<i>P</i> Value
SSI	2.49 (1.82–3.41)	<.001	3.27 (2.09–5.13)	<.001
Ribavirin use	0.68 (.23–1.93)	.470	0.04 (.004–.48)	.01
Corticosteroid use	5.65 (2.31–13.77)	<.001	0.22 (.039–1.27)	.092

Abbreviations: CI, confidence interval; OR, odds ratio; SSI, severity scoring index.



Figure 7. Forest plot of subsidiary descriptive analysis: ribavirin versus no ribavirin, outcome: mortality



**Cochrane
Library**

Cochrane Database of Systematic Reviews

Ribavirin for treating Crimean Congo haemorrhagic fever (Review)

Johnson S, Henschke N, Maayan N, Mills I, Buckley BS, Kakourou A, Marshall R

Test for subgroup differences: Chi² = 2.05, df = 2 (P = 0.36), I² = 2.3%

Footnotes

(1) Severe cases

(2) Severe cases



PAPER

A randomised controlled trial of ribavirin in Crimean Congo haemorrhagic fever: ethical considerations

B Arda,¹ A Aciduman,¹ J C Johnston^{2,3}

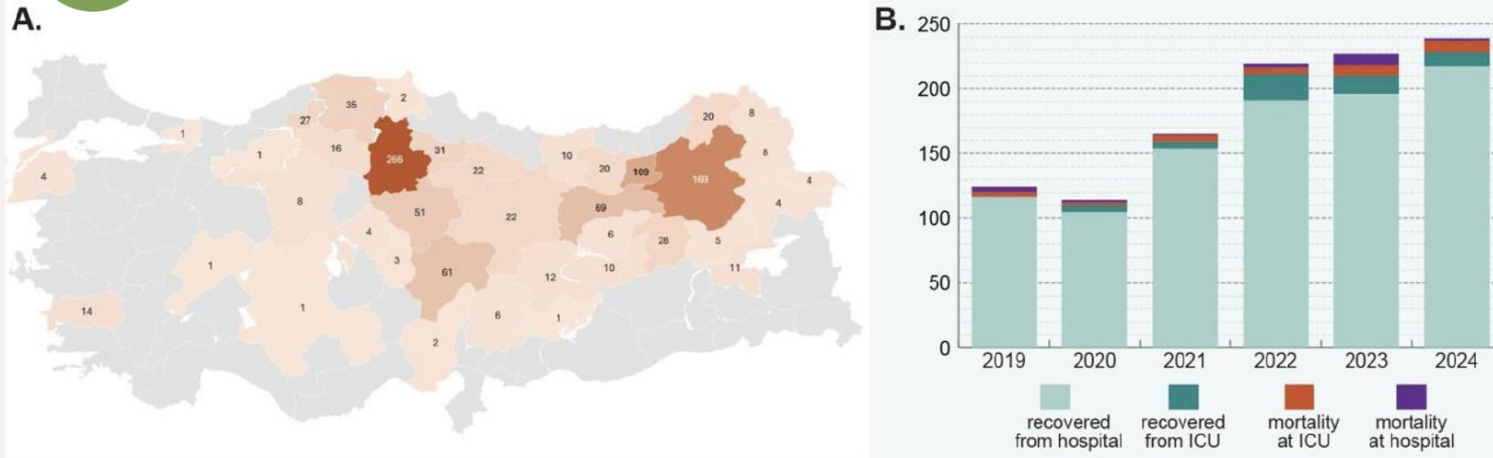
CONCLUSION

There is universal agreement that placebo-controlled trials should be prohibited in life-threatening conditions if an existing treatment is effective at prolonging or preserving life. The available literature provides convincing evidence that CCHF may be effectively treated with prompt administration of ribavirin. It is the standard of care in several nations, and ratified by the Centers for Disease Control and WHO. Therefore, it would be decidedly unethical to conduct an RCT of ribavirin in patients harbouring this life-threatening disease.

J Med Ethics 2011



Predictors of ICU Admission



- 18 centers, 1103 lab confirmed cases (2019-2024)
- ICU Admission 8%
- Case fatality rate 5.1%

Table 3

Time-dependent Cox regression model evaluating the effect of early ribavirin administration on in-hospital mortality truncated at 30 days

Variables	aHR	95% CI	p value
Being a female	0.611	0.323–1.153	0.128
Age (≥ 50 y)	2.565	1.241–5.301	0.011
Being a farmer	0.604	0.328–1.114	0.106
Diabetes mellitus	2.708	1.278–5.739	0.009
Chronic heart disease	1.242	0.481–3.208	0.654
Hypertension	0.951	0.404–2.239	0.909
Ribavirin initiation within ≤ 96 h	0.214	0.066–0.694	0.010

Güllü D, Yigci D, Baykam N, Çelikbaş AK, Yapar D, Akdoğan Ö, Özden K, Sarıkaya Rİ, Hasanoğlu İ, Güner R, Doğan E, Karakeçili F, Alay H, Yüce ZT, Eren EE, Erbay A, Gök ŞE, Kader Ç, Kalın GÜ, Yetişgen A, Özgüler M, Şenol A, Gündag Ö, Özer MÇ, Soyak F, Tanır B, Alırvacı ID, Çınar G, Öztürk B, Gürbüz E, Özbay BO, Pınarlık F, Kuşkucu M, Ergönül Ö. **Key predictors of mortality in Crimean-Congo haemorrhagic fever: a retrospective multicentre cohort study.** *Clin Microbiol Infect.* 2025



Evaluation of epidemiological characteristics of Crimean-Congo haemorrhagic fever patients reported to the National Surveillance System in Türkiye, 2011-2024




Selda Şahan ^{a,*} , Seher Topluoğlu ^a , Fehminaz Temel ^b, Yasemin Coşgun ^c, Erdoğan Öz ^d , Muhammed Emin Demirkol ^d, Şuayıp Birinci ^e

Table 3

Logistic model for predictors of fatality[†].

Variables	OR _{adj} ‡ (95 %CI)	p
Age (year)	1.034 (1.029–1.040)	<0.001
Gender (M/F) §	1.3 (1.1–1.6)	0.009
Splenomegaly	2.0 (1.5–2.7)	<0.001
Haemorrhagic findings¶	2.4 (2.0–3.0)	<0.001
Platelet count (↓20,000)	10.3 (6.7–15.7)	<0.001
(20,000–49,000)	4.6 (3.0–7.0)	<0.001
(50,000–99,000)	1.5 (1.0–2.2)	0.086
(100,000–149,000)	1.5 (1.0–2.3)	0.053
Elevated AST and ALT	1.5 (1.1–2.0)	0.007
Ribavirin	1.5 (1.2–2.0)	0.001

Şahan S, Topluoğlu S, Temel F, Coşgun Y, Öz E, Demirkol ME, Birinci Ş. Evaluation of epidemiological characteristics of Crimean-Congo haemorrhagic fever patients reported to the National Surveillance System in Türkiye, 2011-2024.

Acta Trop. 2025



Blood Products in Viral Hemorrhagic Fevers

Blood Products	Primary indications	Standard regimen/considerations	Expected outcomes	References
Packed Red Blood Cells (PRBCs)	Severe anemia (Hb \leq 6 g/dL), acute hemorrhagic shock with tissue hypoxia, increase oxygen-carrying capacity.	Dosage adjusted based on clinical response and ongoing/anticipated blood loss. Restrictive transfusion thresholds (Hb 7–8 g/dL) often supported.	Prevent tissue hypoxia. Rarely the primary cause of death is direct blood loss in VHF.	[8,12,13]
Fresh Frozen Plasma (FFP)	Documented coagulation factor deficiencies, abnormal coagulation tests (prolonged aPTT) with active bleeding, liver disease, DIC.	Typically, 10–20 mL/kg (raises factor levels by \approx 20%).	Restores coagulation factors. Contraindicated for simple volume expansion, protein supplementation, or coagulopathy without active bleeding/impending procedure.	[8,13,14]
Platelets	Significant thrombocytopenia (PLT \leq 20,000/ μ L is predictor of fatal CCHF outcomes) to prevent spontaneous bleeding or stop active hemorrhage.	Guided by careful clinical assessment of bleeding, not solely platelet counts. It can increase the platelet count by approximately 30,000–60,000/ μ L per apheresis unit or a pool of 4–6 units	Improves platelet count and hemostatic function. Routine prophylactic platelet transfusion is generally NOT recommended (e.g. in Dengue) due to limited efficacy and side effects.	[8,13,15–17]
Cryoprecipitate	Fibrinogen replacement (hypofibrinogenemia or dysfibrinogenemia) in actively bleeding patients or high hemorrhage risk.	Fibrinogen \leq 2 g/L in life-threatening bleeding; \leq 1 g/L with microvascular bleeding. Typical dose: 1 unit per 10 kg (approx. 10 units for adult) to increase fibrinogen by \approx 0.5 g/L.	Provides fibrinogen, Factor VIII, vWF, Factor XIII.	[13,18,19]
Balanced Transfusion Strategy (PRBCs, FFP, Platelets)	Massive hemorrhage (loss of > 15% total blood volume or hemorrhagic shock).	Ratios typically 1:1:1 to 2:1:1.	Control life-threatening bleeding.	[8]

Güllü D, Keske Ş, Ergönül Ö. Viral hemorrhagic fevers - therapeutic trial advances and challenges. Expert Rev Anti Infect Ther. 2025



Diagnosis, management, and prevention of Crimean-Congo haemorrhagic fever: a Delphi-based consensus from two decades of experience in Türkiye

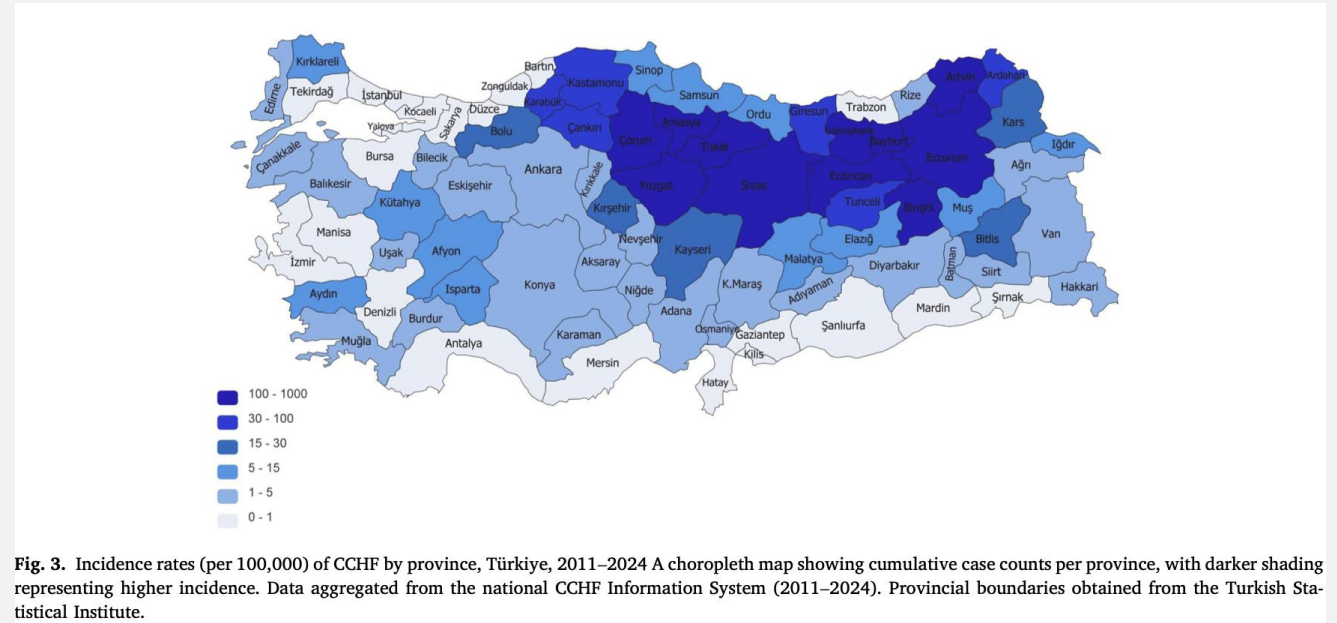
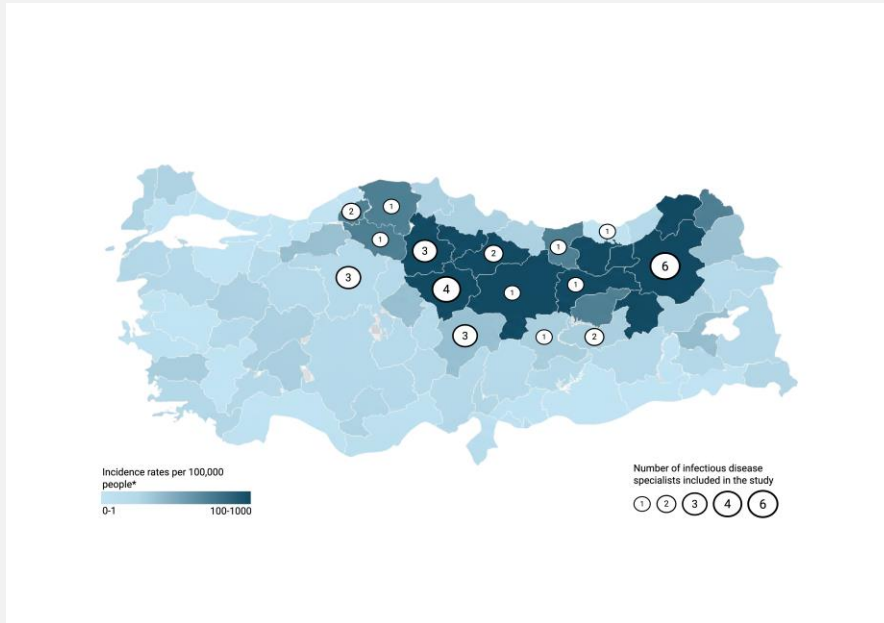
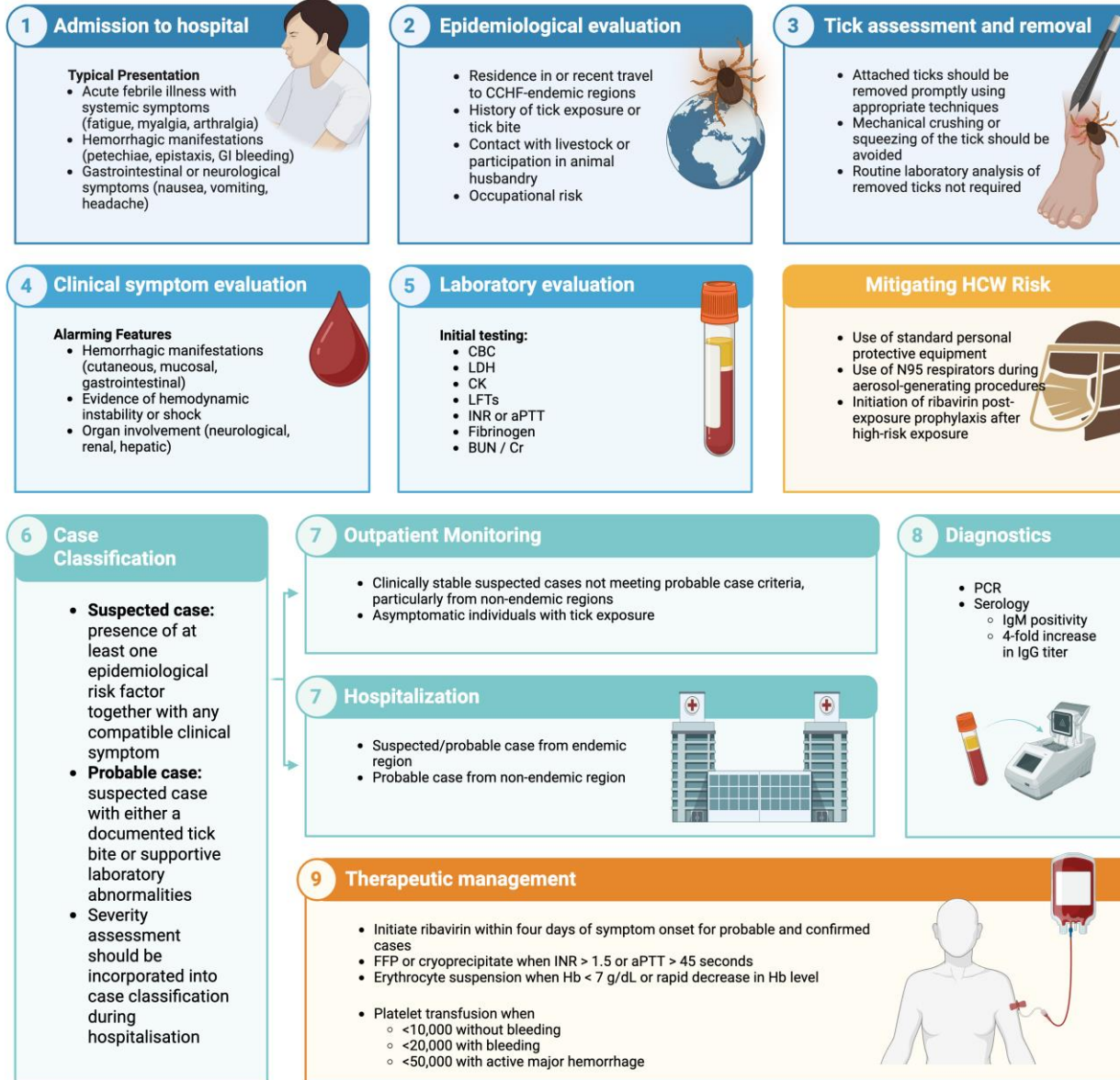


Fig. 3. Incidence rates (per 100,000) of CCHF by province, Türkiye, 2011–2024 A choropleth map showing cumulative case counts per province, with darker shading representing higher incidence. Data aggregated from the national CCHF Information System (2011–2024). Provincial boundaries obtained from the Turkish Statistical Institute.

Turkish Consortium

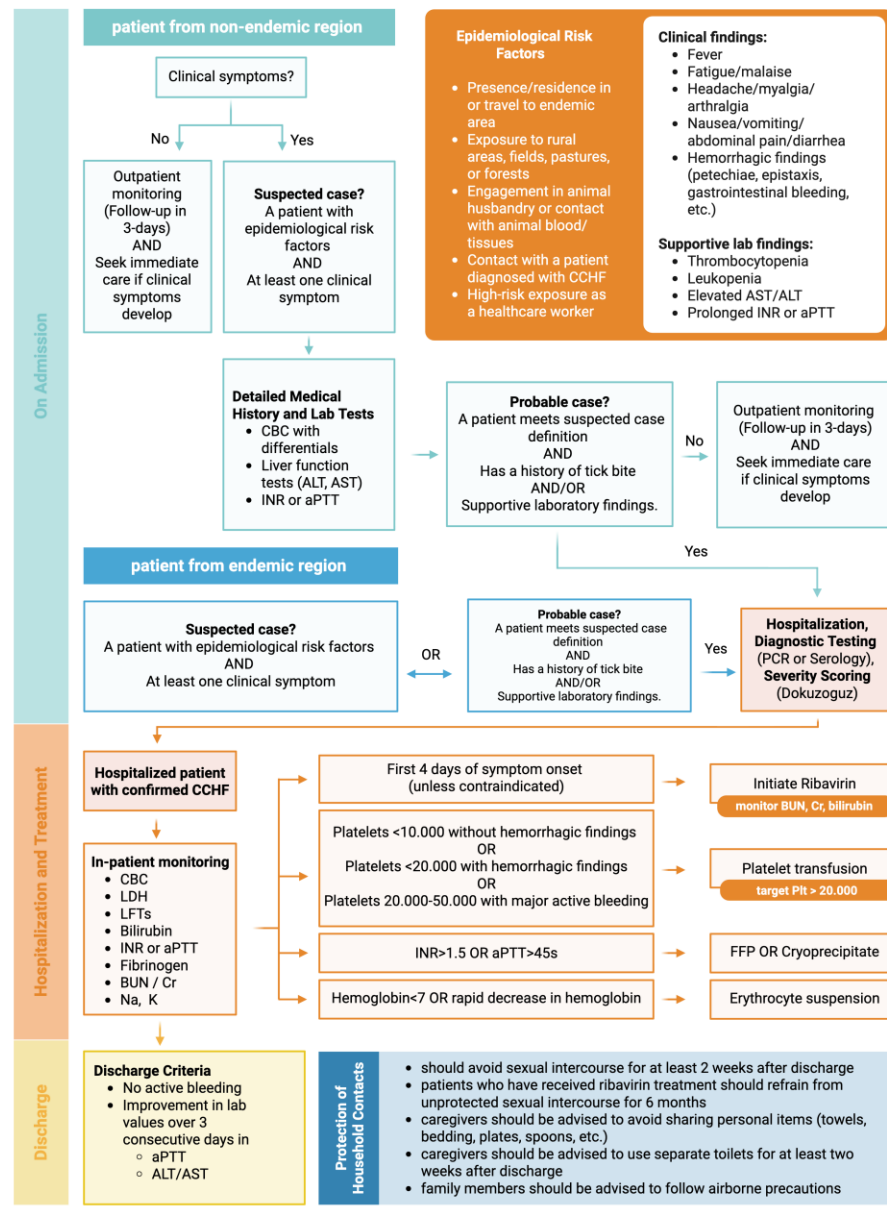
Şahan S, Topluoğlu S, Temel F, Coşgun Y, Öz E, Demirkol ME, Birinci Ş. Evaluation of epidemiological characteristics of Crimean-Congo haemorrhagic fever patients reported to the National Surveillance System in Türkiye, 2011-2024. Acta Trop. 2025



Diagnosis, management, and prevention of Crimean-Congo haemorrhagic fever: a Delphi-based consensus from two decades of experience in Türkiye



Diagnosis, management, and prevention of Crimean-Congo haemorrhagic fever: a Delphi-based consensus from two decades of experience in Türkiye



This flowchart is derived from Delphi consensus statements intended for clinical decision support. Despite reaching consensus, statements concerning corticosteroid therapy were excluded because of limited and low-quality evidence, and to avoid implying a recommendation where evidence is insufficient.



Specific Immunoglobulin Bulgarian Experience

Passive simultaneous transfer of two different specific immunoglobulin preparations,

“CCHF-bulin” (for intramuscular use)

“CCHF-venin” (for intravenous use),

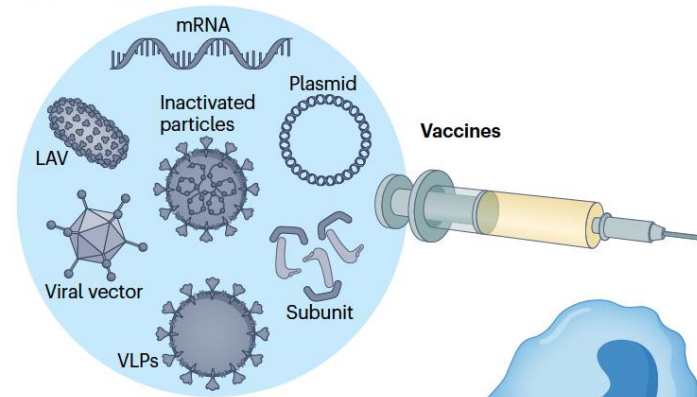
prepared from the plasma of CCHF survivor donors;
applied among 7 patients
(Vassilenko et al., 1990).

Poor data, recently summarized;

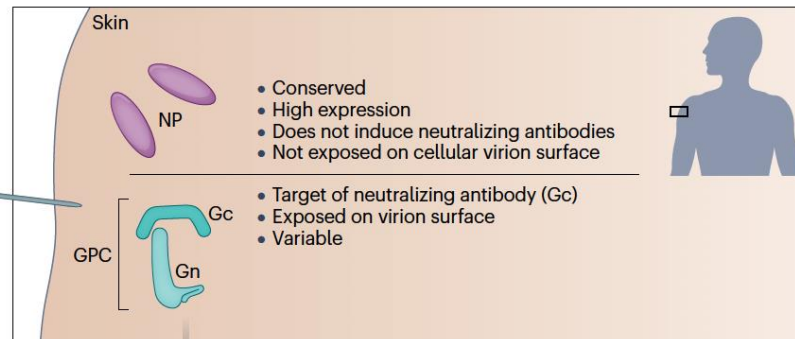
Keshtar Jahromi M, et al. Antiviral Res 2011



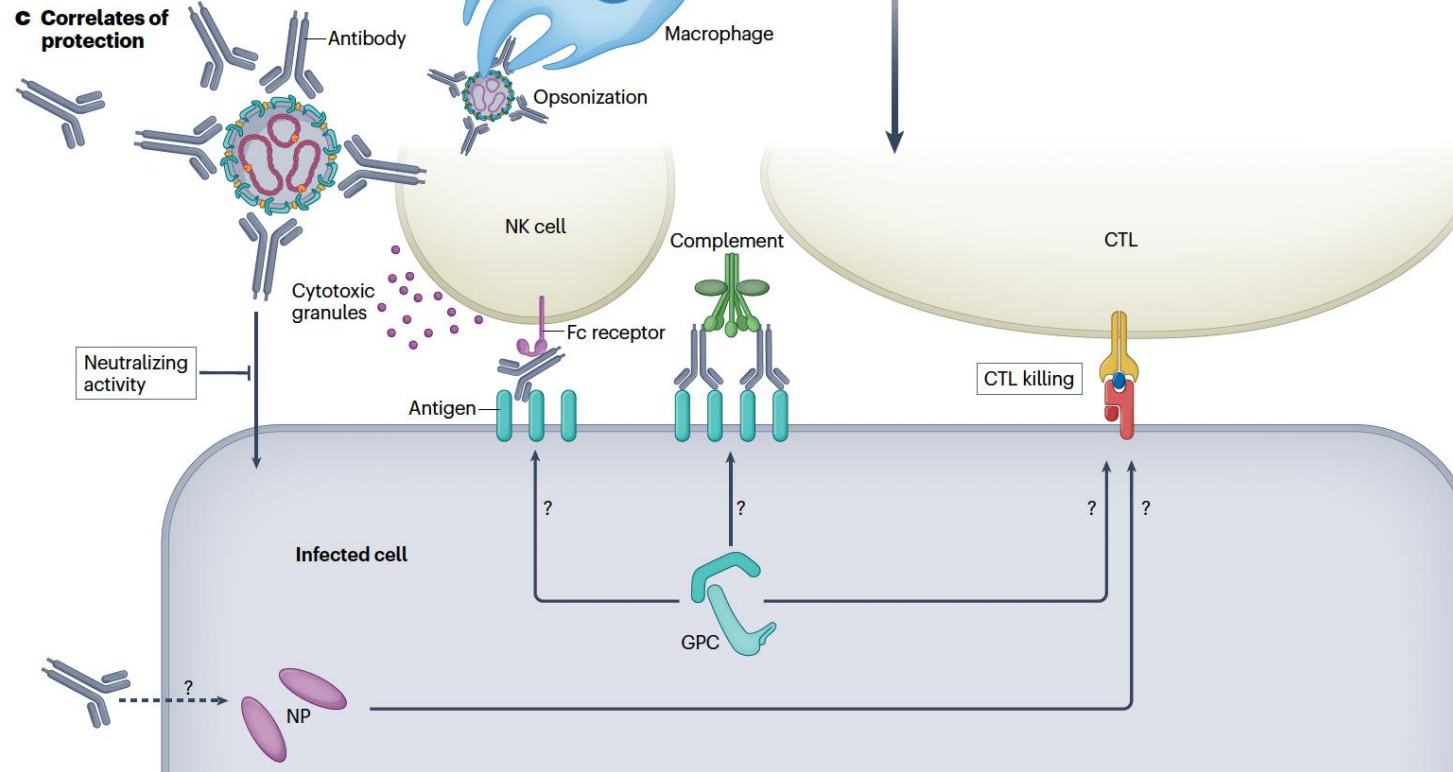
a Vaccine platforms



b Vaccine antigens



c Correlates of protection

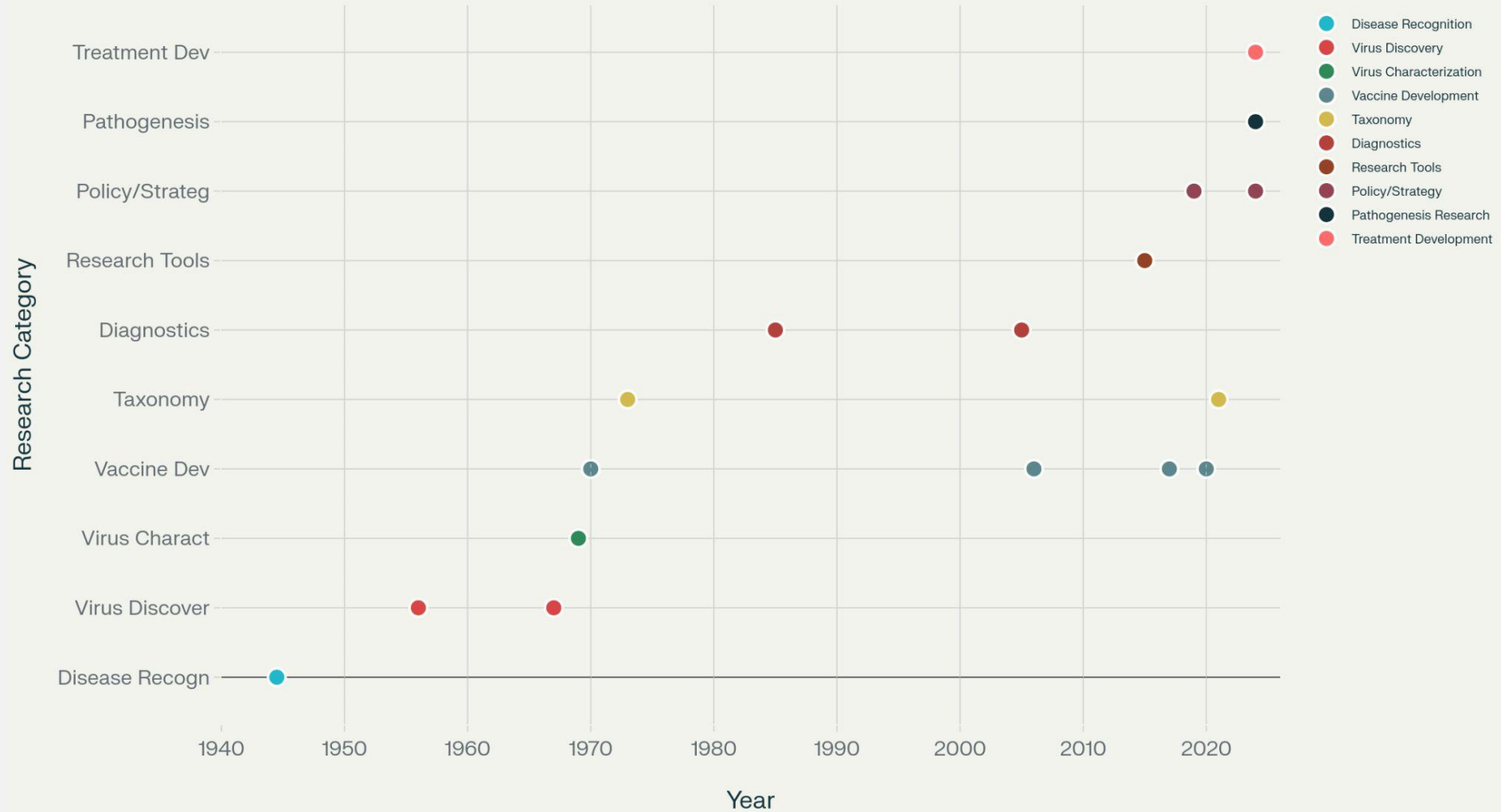


Vaccine Studies for CCHF

Hawman DW & Feldmann H.
Nature Rev Microbiol



CCHF Research Milestones (1944-2024)



By Dennis Bente



Dengue Virus Suppression by Wolbachia-Infected Mosquitoes

A Research Summary based on Lim JT et al. | 10.1056/NEJMoa2503304 | Published on February 11, 2026

WHY WAS THE TRIAL DONE?

Dengue is a growing vectorborne disease globally, yet the arsenal for dengue mitigation remains limited. Preliminary evidence suggests that release of male *Aedes aegypti* mosquitoes infected with *Wolbachia pipientis* bacteria suppresses wild-type mosquito populations and dengue virus transmission to humans.

HOW WAS THE TRIAL CONDUCTED?

Fifteen geographic population clusters in Singapore, comprising some 724,428 residents, were randomly assigned to receive twice-weekly deployments of wolbachia-infected male *A. aegypti* mosquitoes (8 intervention clusters) or no deployments (7 control clusters). Residents with suspected dengue virus infection underwent testing. The primary end point was symptomatic dengue virus infection.

TRIAL DESIGN

- Unblinded
- Test-negative–controlled
- Cluster-randomized
- Location: Singapore

RESULTS

The percentage of residents who had a positive test for dengue virus among those who underwent testing was lower in the intervention clusters than in the control clusters in all exposure periods (6 to 10% vs. 21 to 23%). The estimated overall protective efficacy of the intervention after 3 or more months of exposure was 71 to 72%.

LIMITATIONS AND REMAINING QUESTIONS

- Acquisition of dengue virus infection may have occurred outside designated trial locations.
- The trial was conducted in the context of extensive and integrated vector control, so the results may not be generalizable to other locations.
- Migration of wild-type mosquitoes into trial areas was limited by geographic borders (e.g., major roads and bodies of water) or buffer sites but cannot be ruled out.

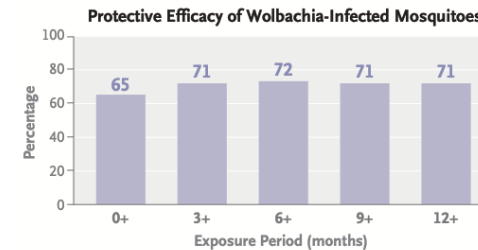
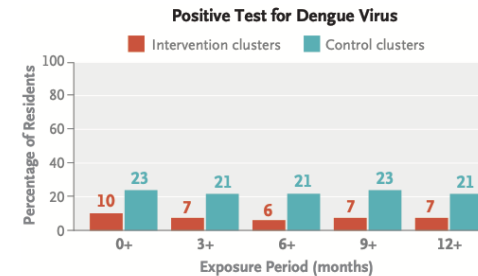
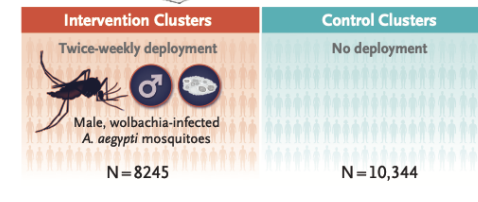
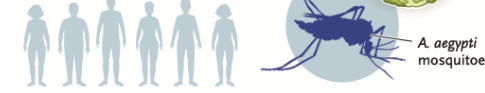
CONCLUSIONS

Release of sterile wolbachia-infected male *Aedes aegypti* mosquitoes reduced the risk of dengue virus infection in Singapore.

NEJM QUICK TAKE

Participants

- 18,589 residents with suspected dengue virus infection included in analysis
- Mean age, 46 years
- Male: 52%; Female: 48%





Summary

In diagnosis, nucleic acid based technology is the most sensitive diagnostic method.

The determination of IgM/IgG antibodies is a reasonable alternative, but cross-reactivity can be a problem in the case of flaviviruses.

Licensed vaccines are available for Yellow Fever, Dengue, and Ebola

Therapy for exotic viral hepatitis is predominantly supportive.

- Corticosteoids and IL inhibitors are in use
- Monoclonal antibodies
- New antivirals

To ensure that preventive measures can be introduced to control possible outbreaks, the timely detection of these viruses is very important.

- Widely used rapid diagnostic tests are needed.



Thank you



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