

# Problems in Clinical Diagnosis and Therapy in CCHF: Sivas Experience



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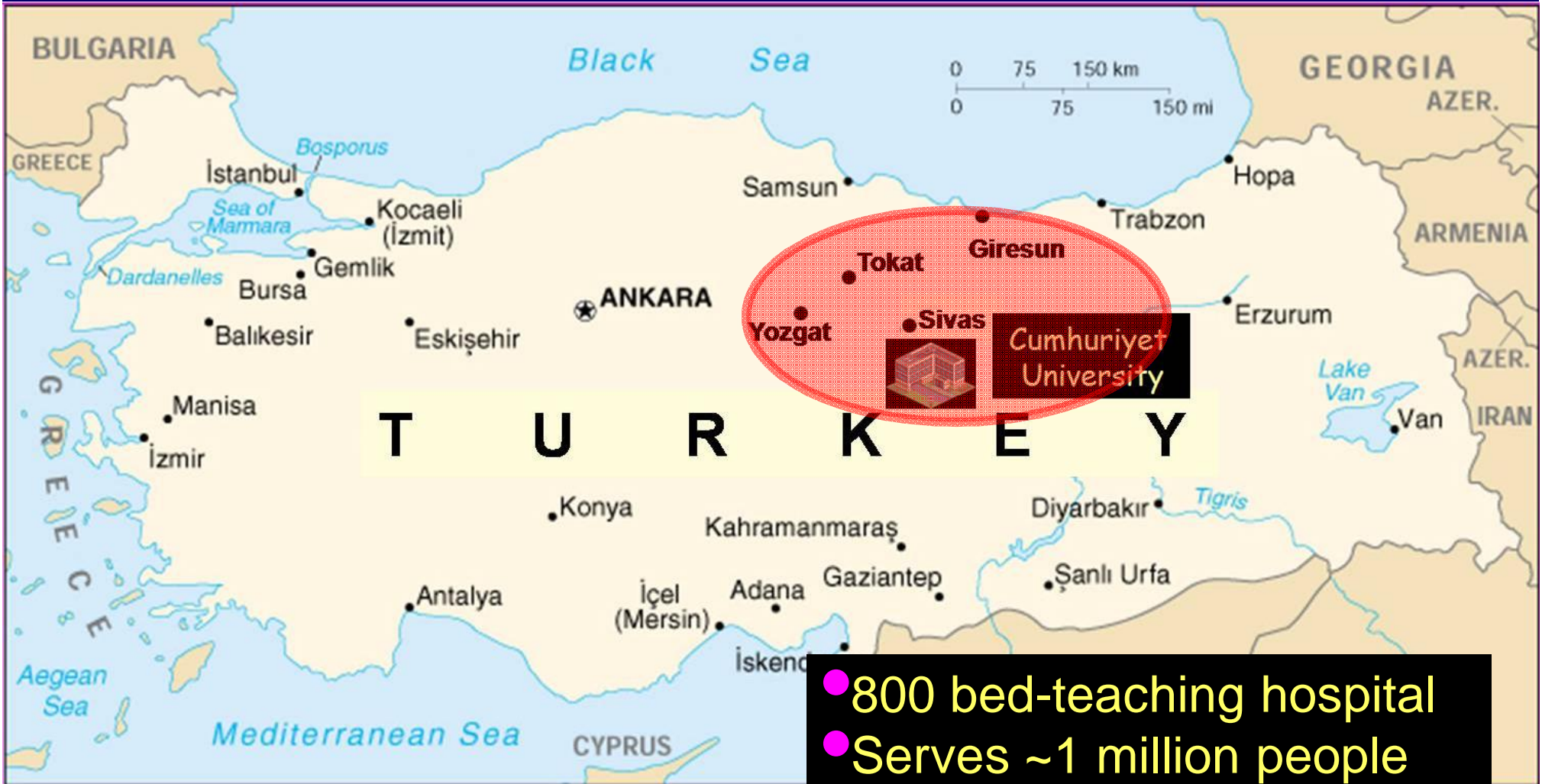
Cumhuriyet University, School of Medicine,

Sivas,

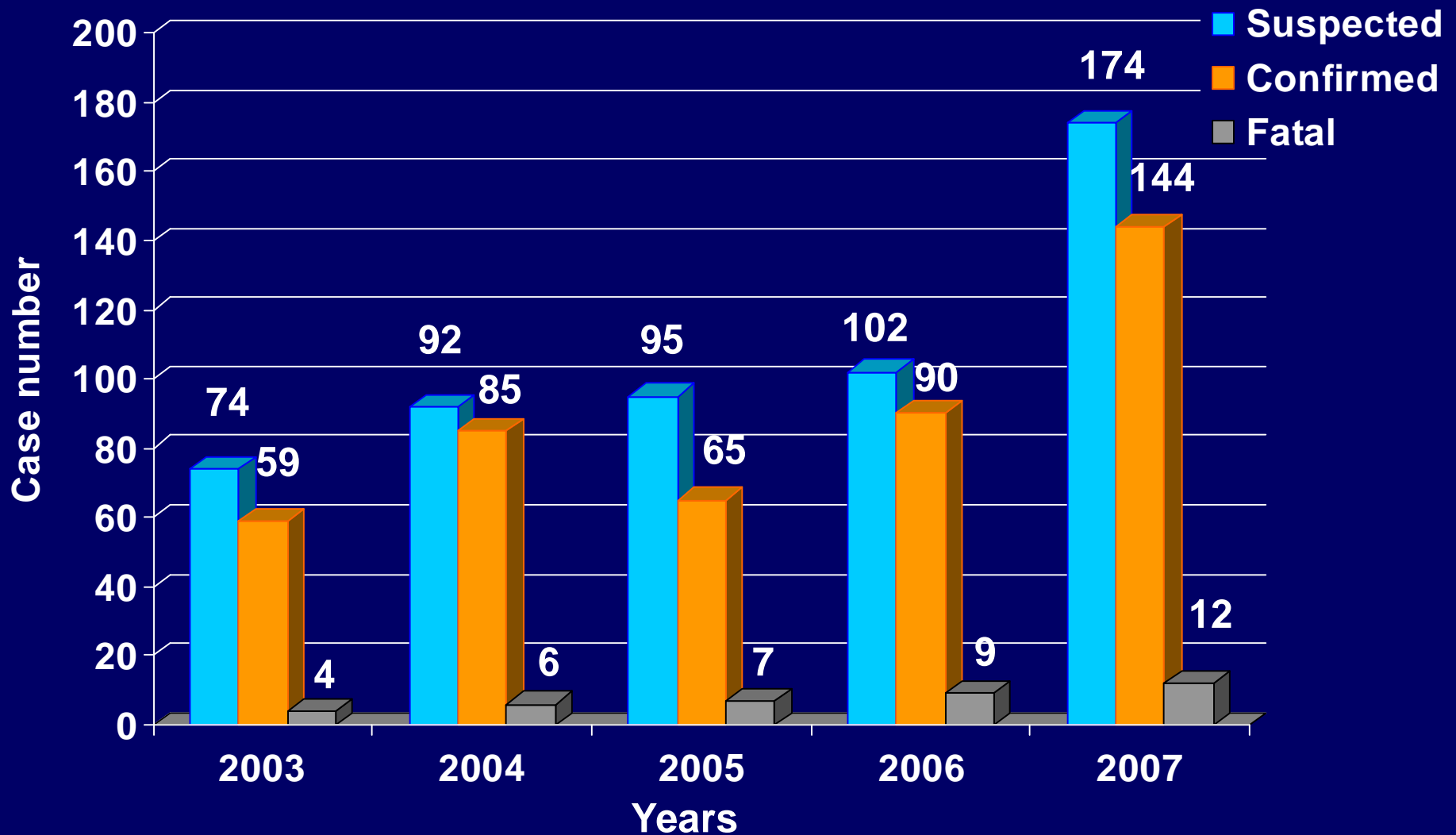
*Turkey*

ESCMID, Viral Hemorrhagic Fevers, Istanbul, 2008





# Distribution of CCHF cases to years (Cumhuriyet University Hospital, Sivas)



# Problems in clinical diagnosis

## Crimean-Congo Hemorrhagic Fever

Fever

+

Hemorrhage





# CCHF case definition criteria

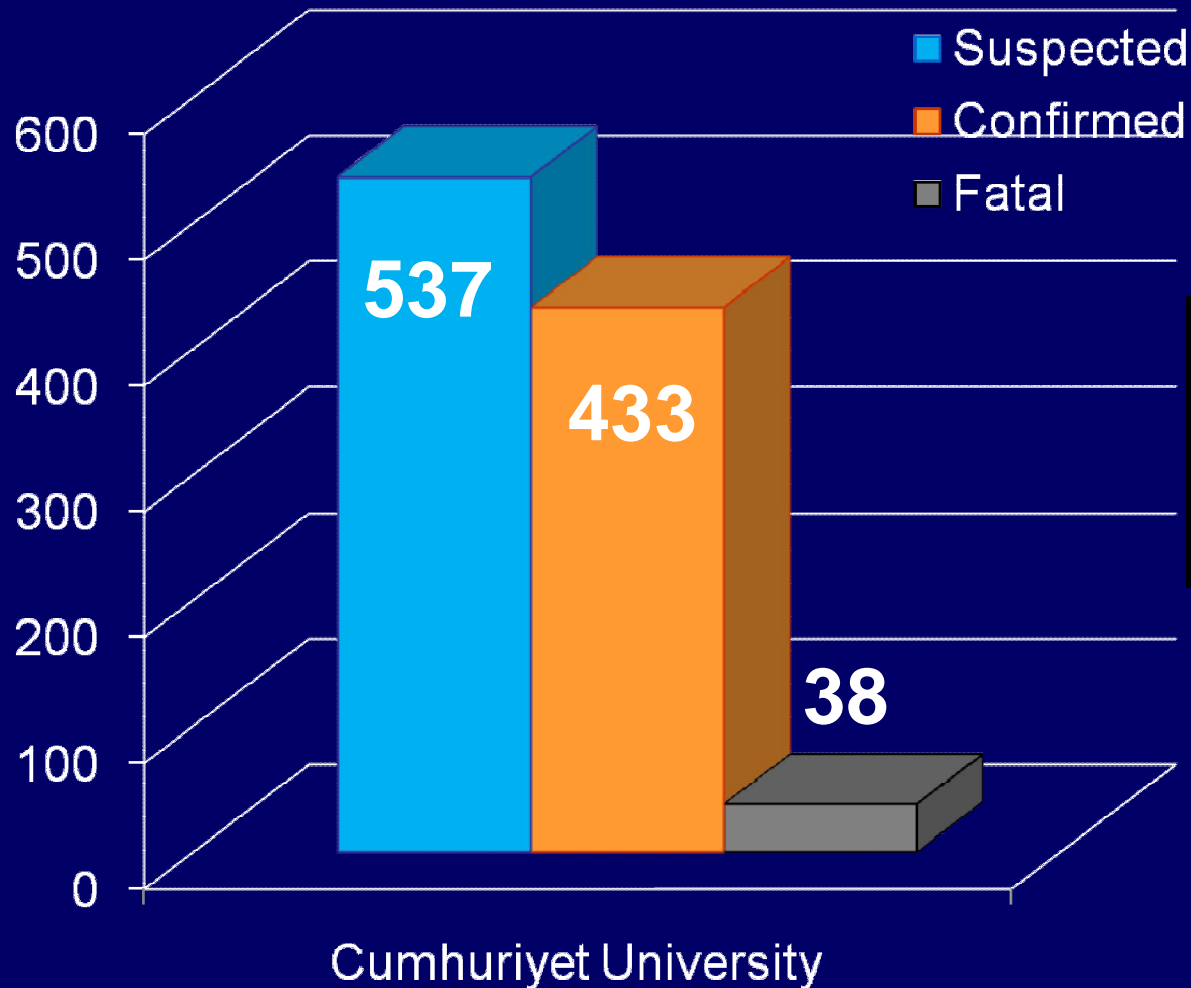
- A patient having an epidemiologic risk factor
  - Tick exposure history and/or
  - Resident in/or traveled to a CCHF epidemic region

**PLUS**

- An acute infectious disease resembling CCHF;
  - Fever ( $>38^{\circ}\text{C}$ )
  - Thrombocytopenia ( $<150 \times 10^3/\text{mm}^3$ ) and/or
  - Hemorrhagic manifestations



# Success of case definition criteria in laboratory diagnosis of CCHF



Success rate  
 $0.88(471/537)$



# The role of thrombocytopenia in the case definition of CCHF

Variable	2003 N=76	2007 N=144	P value
Thrombocytopenia on admission, n (%)	100%	125 (87%)	
Time to hospitalization, mean d (Range)			>0.05

**Repeat CBC test after  
1-2 days of admission**

- Mean time to hospitalization for thrombocytopenic CCHF patients was 2.6 days
- Focus on thrombocytopenia on admission





# Problems in laboratory diagnosis

Serologic and virologic analysis of 31 fatal CCHF cases in acute phase

Variable	No. of (+) / No. of tested (%)	P-value
Anti-CCHFV IgM (+)	12/31 (39)	<0.0001
PCR (+)	21/22 (95)	



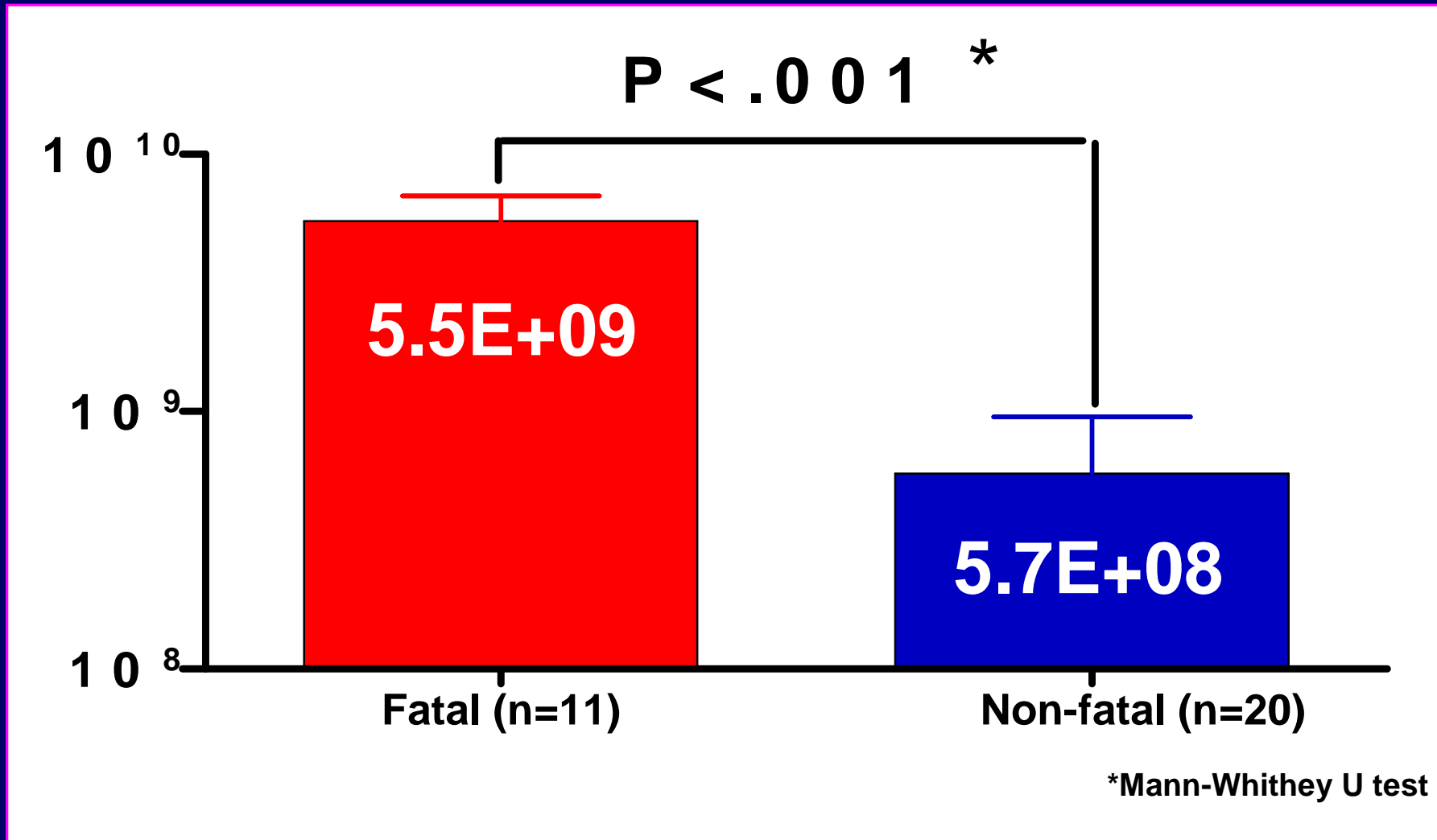
# Problems in CCHF therapy

## Current therapy of CCHF

- Supportive therapy
  - Fluid replacement
  - Blood and blood products
  - Others
- Ribavirin therapy (po, IV) ?
- Immune serum therapy ?



# Why antivirals should be used in CCHF?



# Ribavirin - efficacy reports in CCHF

## Oral ribavirin in confirmed cases

- 80% \*
- 75% \*\*
- 85% (first 5 days of onset) \*\*\*
- 74% (after 5 days of onset) \*\*\*

## Ribavirin (po or iv) in confirmed cases

- 20% (1 of 5) \*\*\*\*

\*Mardani M, et al. CID 2003

\*\*Alavi-Naini R, et al. J Infect 2005

\*\*\*Metanat M, et al. Int J A A 2005 Poster present.

\*\*\*\*Jamil B, et al. Trans R Soc Trop M Hyg 2005



# Efficacy of oral ribavirin in confirmed CCHF in TR (2004)\*

Outcome	Ribavirin N=126	Historical control N=96	P value
Fatal, <i>n</i> (%)	9 (7)	11 (12)	0.243
Non-fatal, <i>n</i> (%)	117 (93)	81 (88)	

- Oral ribavirin was not effective
- Median ribavirin starting time was 5 days after onset symptoms

\* Elaldi N, et al. ECCMID 2007, Munich, GERMANY



# Efficacy of IV ribavirin treatment in severe CCHF cases \*

Variable	Survived	Died
Ribavirin group (n=9)	5	4
Control group (n=15)	9	6

- Fatality rates= 44% / 40%
- OR (95% CI) 0.84 (0.13 -5.59)

\* Unpublished data



- Efficacy of ribavirin in CCHF remains to be proven

**Controlled-randomized  
clinical studies needed**

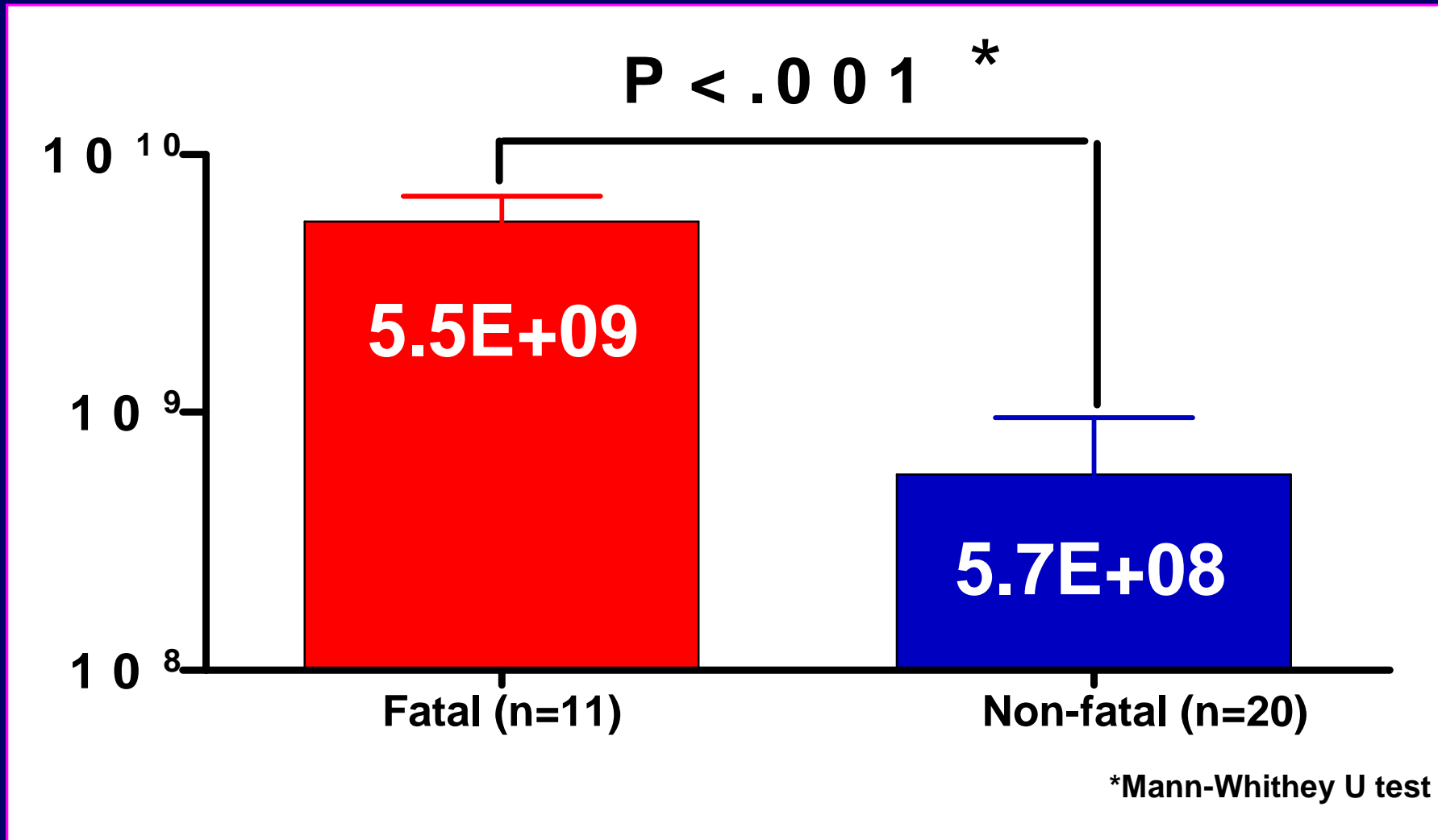


# Why death occurs in CCHF?

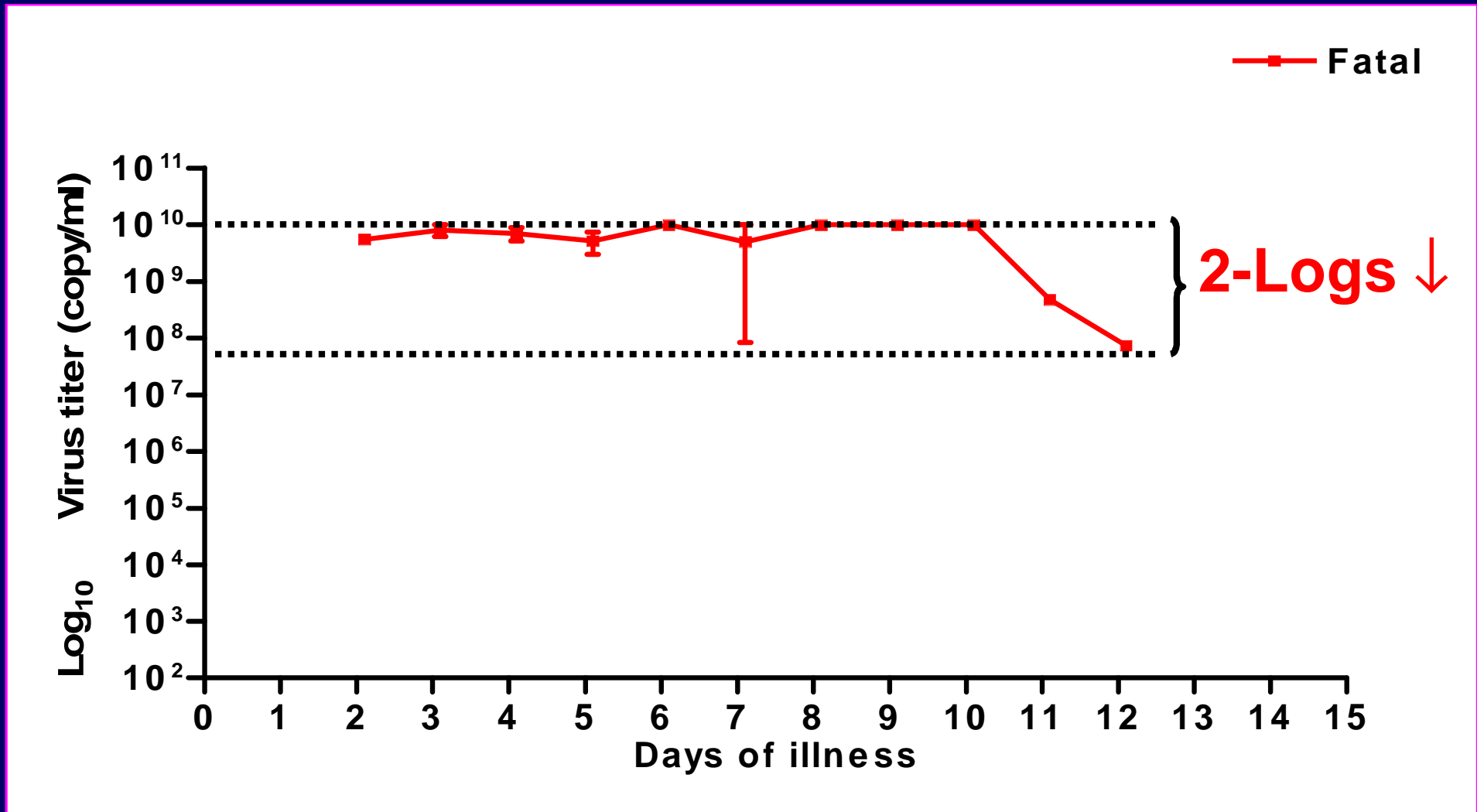




# Serum virus titer on admission (copies/ml)



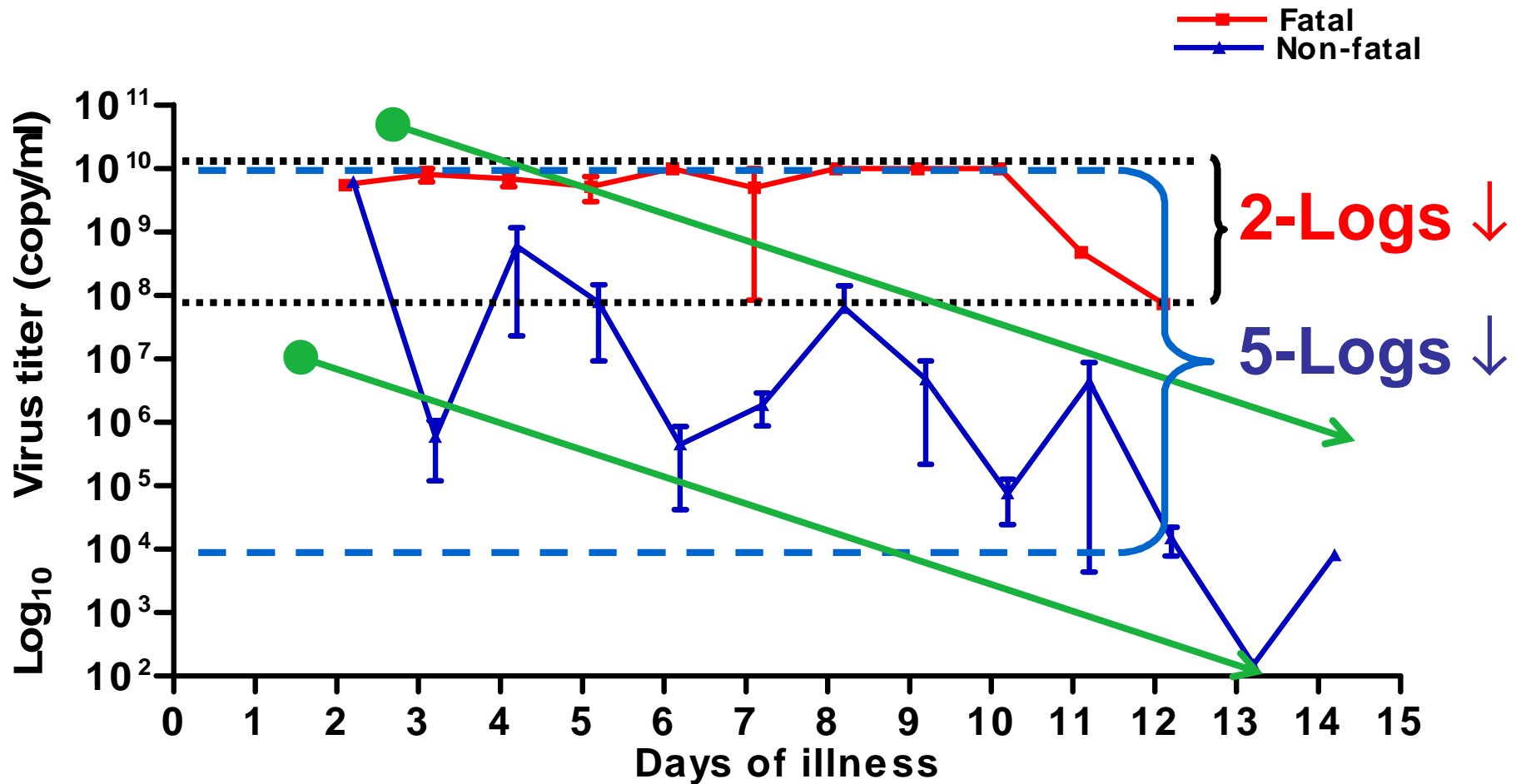
# Kinetic change of serum virus titers in fatal CCHF cases



\* Elaldi N, et al. ICAAC 2007, Chicago, USA



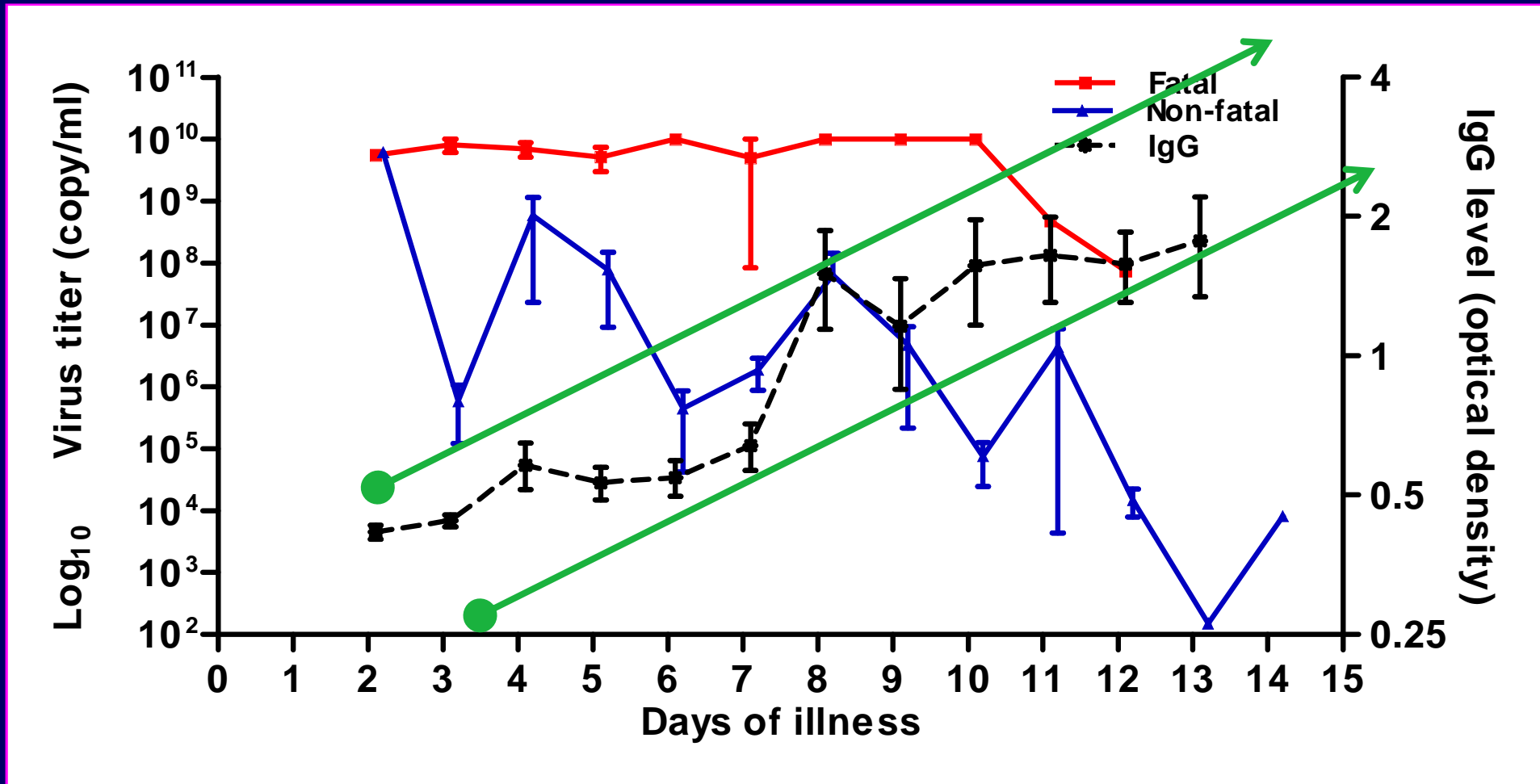
# Kinetic change of serum virus titers in fatal and non-fatal CCHF cases



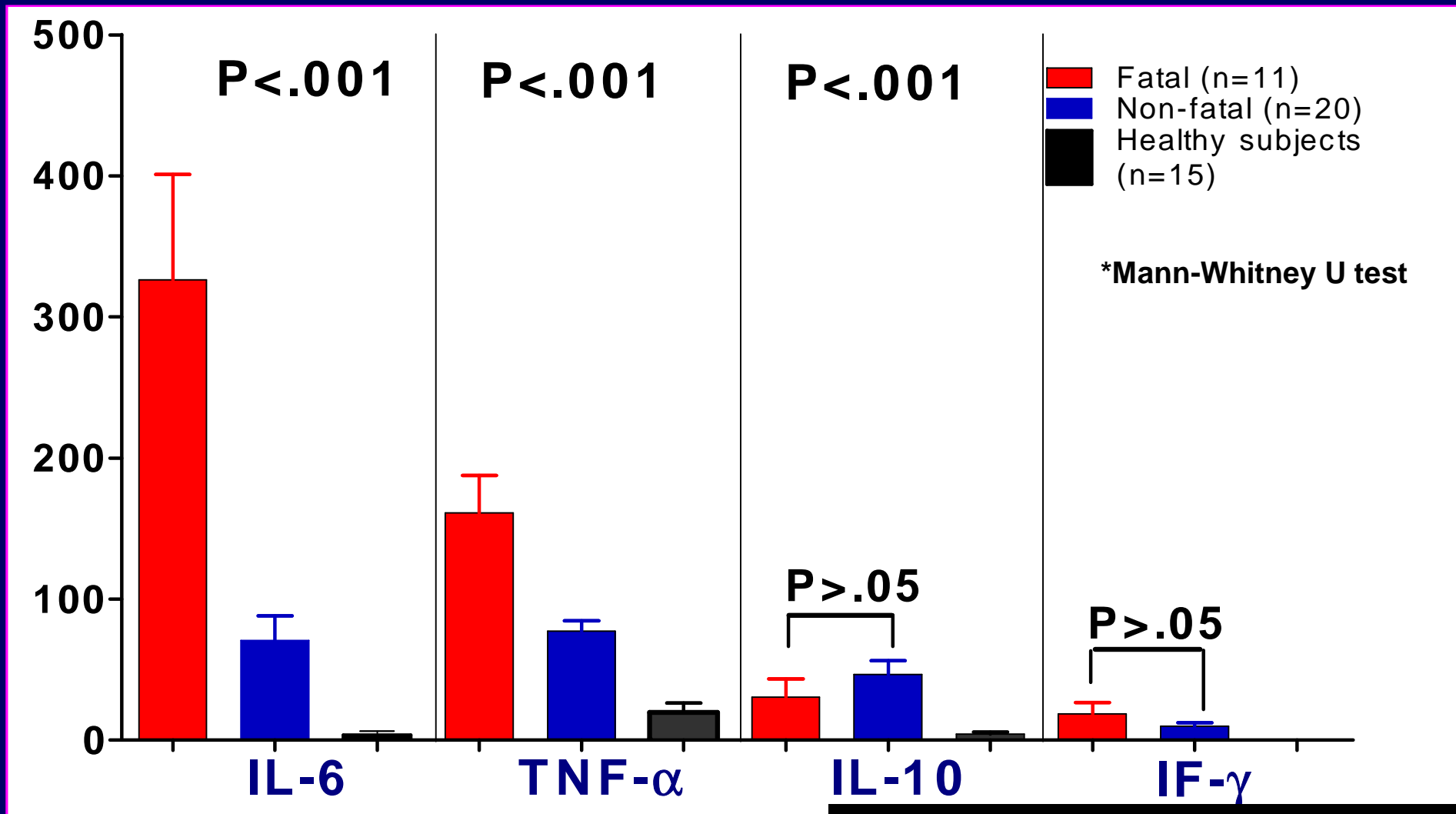
\* Elaldi N, et al. ICAAC 2007, Chicago, USA



# Kinetic change of serum virus titers and specific anti-CCHFV IgG levels



# Serum cytokine levels on admission (pg/ml)\*



\* Elaldi N, et al. ICAAC 2007, Chicago, USA



# Laboratory findings on admission

	Non-fatal (n=20)	Fatal (n=11)	p value	Normal range
WBC (x10 <sup>9</sup> /L)	2.9	5.4	<u>0.04</u>	4.0-11.0
Platelet (x10 <sup>9</sup> /L)	53	29	0.09	150-450
Hb (g/dL)	13.8	12.4	0.07	12-18
ESR (mm/h)	21	27	0.73	
PT (s)	14.0	21.7	< <u>0.001</u>	9.45-13.0
aPTT (s)	34.2	49.7	<u>0.001</u>	25.1-34.7
INR	0.97	1.90	< <u>0.001</u>	
DIC, n (%)	5	11	< <u>0.001</u>	
AST (U/L)	352	1376	<u>0.043</u>	9-36
ALT (U/L)	275	428	0.68	10-28
LDH (U/L)	922	2902	<u>0.004</u>	200-480
CPK (U/L)	956	1341	0.457	20-150
Creatinin (mg/dL)	0.8	2.1	<u>0.000</u>	0.6-1.2
Bilirubin (mg/dL)	0.84	1.35	<u>0.034</u>	0.2-1.6



# Correlation analyzes (Pearson's test) (N=31)

Cytokine, Comparator	<i>r</i>	P
● IL-6, CRP	0.489	<0.01
● IL-6, coagulation test		
PT	0.462	<0.01
aPTT	0.692	<0.01
INR	0.544	<0.01
DIC score	0.626	<0.01
● TNF- $\alpha$ , coagulation test		
PT	0.109	>0.05
aPTT	0.236	>0.05
INR	0.220	>0.05



# Death occurs in CCHF, Because:

- Unchecked viremia
- ↑ Levels of IL-6, TNF- $\alpha$
- Disseminated Intravascular Coagulation
- Absence of specific IgG ab
- SHOCK

**DEATH**





# What can we do?

- Unchecked viremia
  - Ribavirin treatment ?
  - Other antivirals ? (Future treatments?)
    - Interferon (IF)- $\alpha$  treatment ? \*
    - Human Mx proteins \*\*  
(IF-induced GTPases)
  - Hyperimmune serum treatment ?

\* Andersson I, et al *J Virol* 2004

\*\* Andersson I, et al *J Med Vir* 2006



# What can we do?

- ↑ Levels of IL-6, TNF-  $\alpha$  (Future treatments?)
  - Anti-cytokine antibodies ?
  - TNF- $\alpha$  synthesis inhibitors ?
- Fighting against DIC
  - ,Fresh Frosen Plasma
  - Platelet suspension
- Absence of specific IgG ab
  - Immune serum, IVIG?



Thank you very much  
for your attention!

