

Ribavirin Experience

2003-06

CCHF Advisory Board

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Ribavirin

- **The mechanism of action is not fully understood**
- **The antiviral activity depend principally on intracellular conversion of the drug to RTP (ribavirin-5'-triphosphate)**
- **RTP competes with adenosine-5'-triphosphate and guanosine-5'-triphosphate for viral RNA polymerase**

- Ribavirin is recommended by World Health Organization (WHO) as a potential therapeutic of CCHF
 - Suppress the viral replication in Vero cells (Watts *et al.*, 1989),
 - Effective in reducing the viral load in an animal model (Tignor&Hanham, 1993).
 - Anecdotal reports (Athar *et al.*, 2003; Fisher-Hoch *et al.*, 1995)
 - Clinical study using a historical control (Mardani *et al.*, 2003)

- **2003** = epidemiology and clinical features
- **2004** = Efficacy of po ribavirin & predictors of mortality
- **2006** = Efficacy of iv ribavirin

2003

Crimean-Congo haemorrhagic fever outbreak in Middle Anatolia: a multicentre study of clinical features and outcome measures

- Case definition = fever + thrombocytopenia
- Definitive diagnosis based on the detection antibody or genomic segments by RT-PCR
- 99 cases

Bakir M, Ugurlu M, Dokuzoguz B, Bodur H, Tasyaran MA, Vahaboglu H. J Med Microbiol 2005;54(Pt 4):385-9.

- **Patients were from the rural areas of 11 cities in Middle Anatolia**



- **low fatality rate (12 %)**

PO Ribavirin 2004

- **Comparison of oral ribavirin treatment in Crimean-Congo hemorrhagic fever: a historical cohort study**
 - Patients admitted to four tertiary care hospitals with a disease resembling Crimean-Congo hemorrhagic fever (CCHF) were treated with oral ribavirin between April and September, 2004.
 - Treated patients who obtained a definitive diagnosis of CCHF (n=126) were compared with a historical cohort (n=92) admitted to the same hospitals in 2003 but who were not treated with ribavirin.

outcome

outcome po ribav	survived	died	
+	117	9	126
-	81	11	92
	198	20	218

Fatality rates = 7.1% / 11.9%

Success rates = 93.8% / 88%

Odds ratio (Bootstrap) OR (95%CI) = 1.75 (0.60 - 4.60)

$p = 0.13$, Exact (Farrington & Manning) test of one sided

Possible reason?

- **Severe cases =**
 - DIC, bleeding in vital organs and circulatory collapse (Swanepoel *et al.*, 1989; Whitehouse, 2004)
- **Decreased bioavailability of the drug**

Predictors of Mortality

- Altered sensorium
 - confusion to drowsiness and coma
- splenomegaly
- INR >1.4

Side effects

- **no serious and persistent side effect has been reported.**

IV Ribavirin 2006

- **Altered sensorium; Splenomegaly;
Prolonged international normalized ratio
(INR>1.4); Hypotension (= <90 mm/Hg [syst]);
Bleeding**
- **IV Ribavirin n=9**
(17 mg/kg IV initial dose; 17 mg/kg IV q 6 h x 4 d; then 8 mg/kg IV q 8 h x 6 d)
- **A total of 24 patients**
- **VLs (RT-PCR) in serially obtained blood
samples were determined**

Outcome (IV Ribavirin)

IV ribavirin \ outcome	Survived	Died	
+	5	4	9
-	9	6	15
	14	10	24

Fatality rates = 44% / 40%

Odds Ratio (95% CL) 0.84 (0.13 - 5.59)

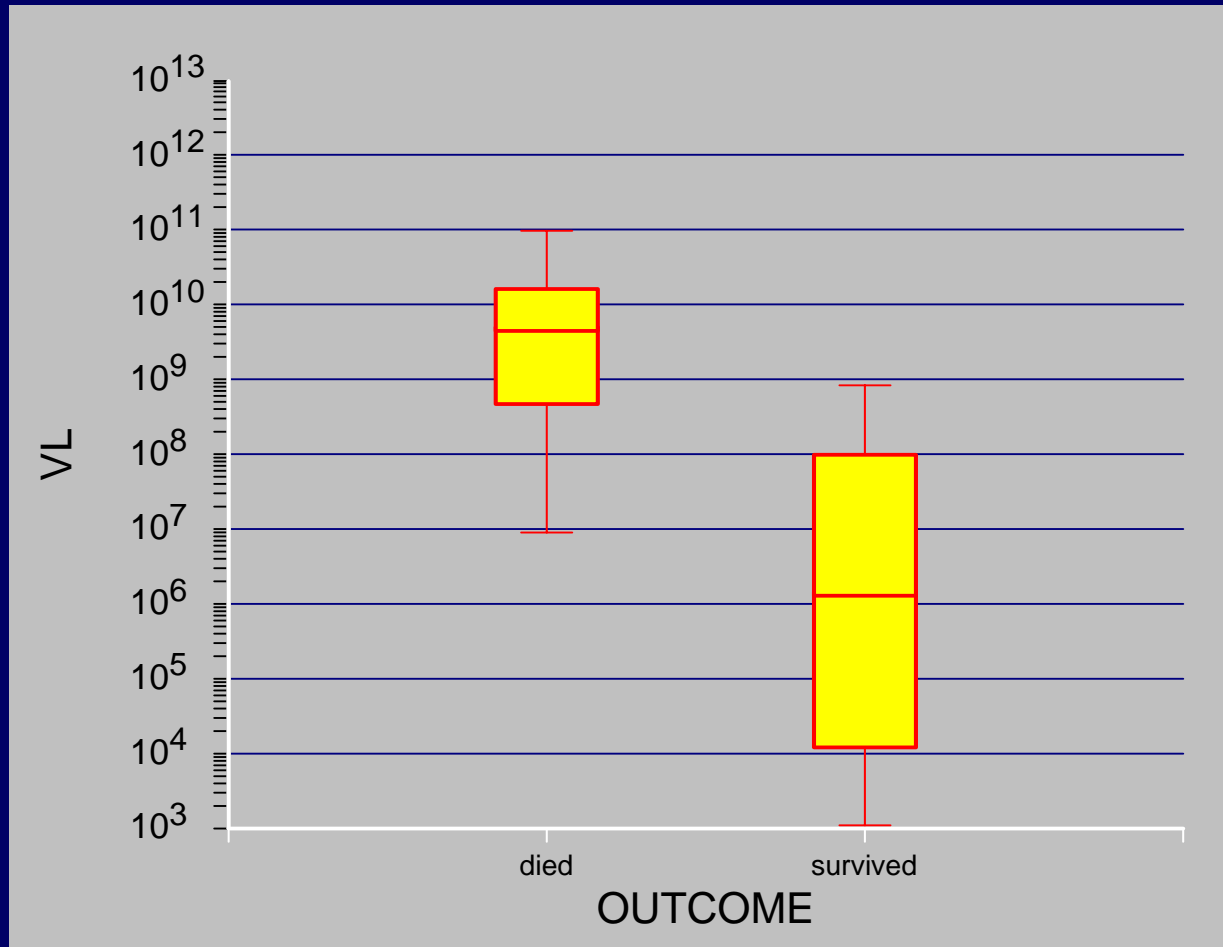
(Bootstrap 3000 samples)

Possible Explanation (?)

Viral yields for strains of CCHF virus from Europe, Asia, and Africa in African green monkey kidney (Vero) cells were markedly reduced by this drug.

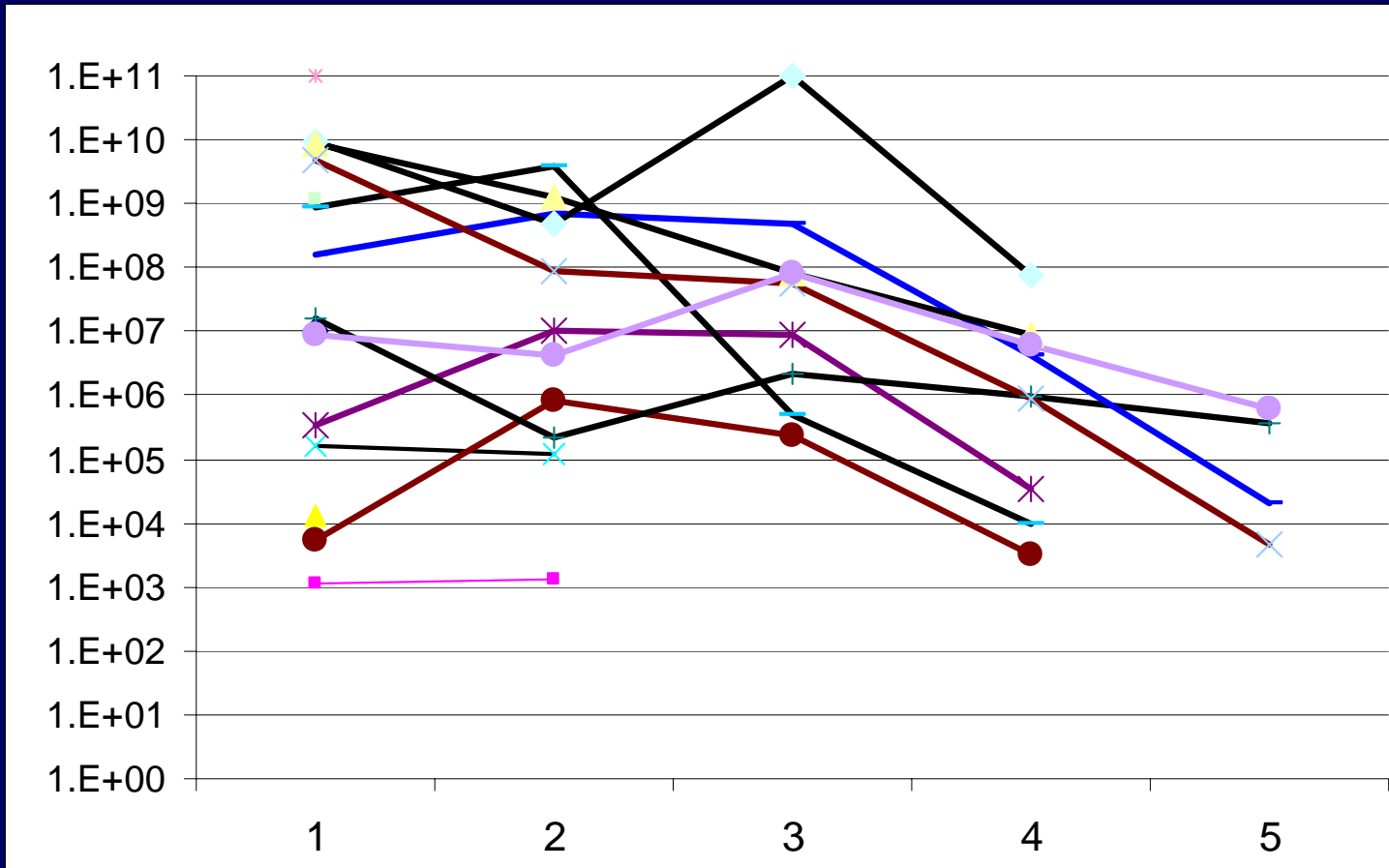
Some CCHF viral strains appeared more sensitive than others

Watts, D. M., M. A. Ussery, et al. (1989). "Inhibition of Crimean-Congo hemorrhagic fever viral infectivity yields in vitro by ribavirin." Am J Trop Med Hyg 41(5): 581-5

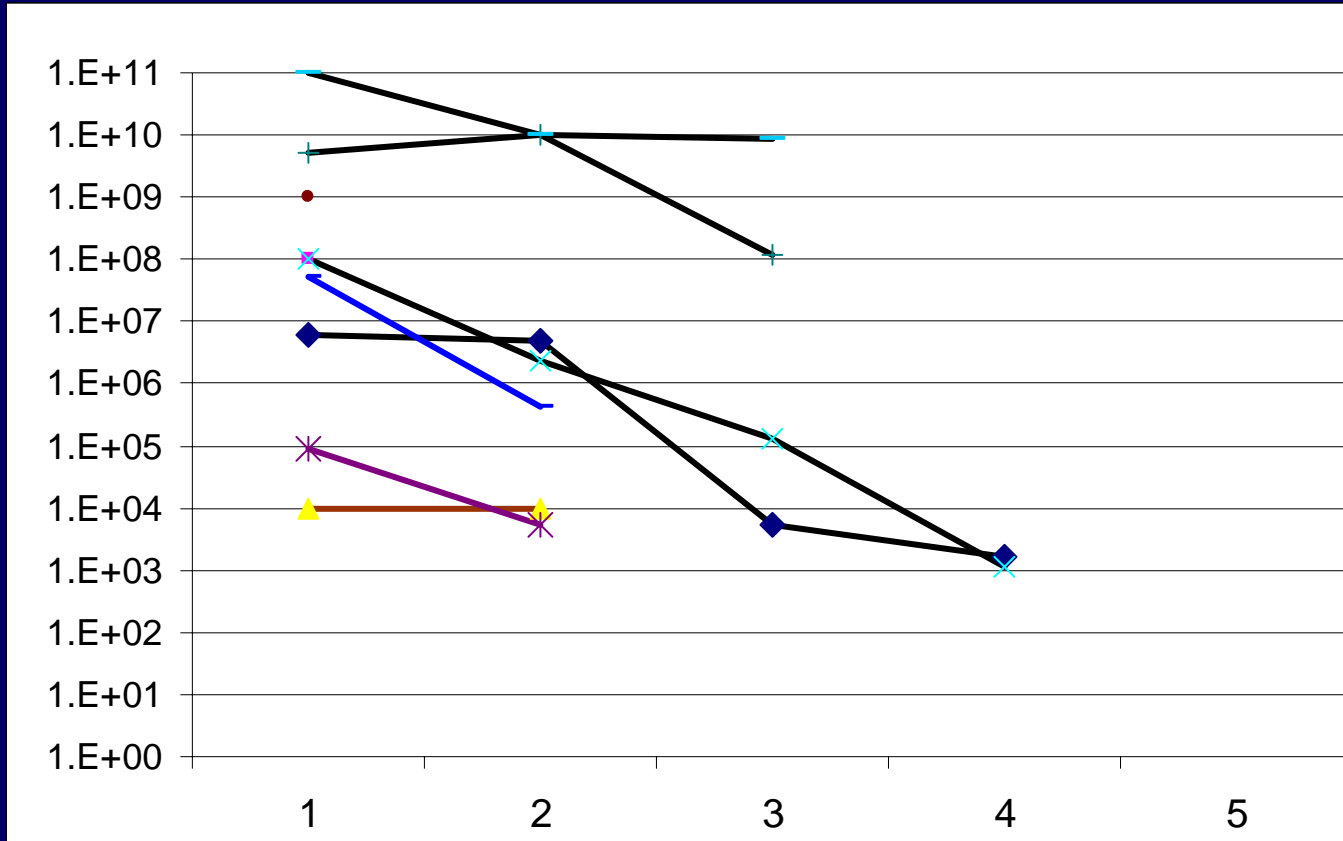


	Count	Mean	
<u>died</u>	<u>10</u>	<u>1.1e+10</u>	<u>p=0.0001</u>
<u>survived</u>	<u>14</u>	<u>8.2e+08</u>	

No ribavirin



IV Ribavirin



Suggestions

- Controlled-randomized clinical study
- Experimental models comparing antiviral activity of Ribavirin with Turkish strains