clinical significance versus statistical significance. That is, when evaluating efficacy, the magnitude of the difference in response rate between 2 therapies is at least as important as the *P* value derived from the formal statistical analysis and, thus, should be carefully examined for clinical importance. On the other hand, here we want to present our thoughts on an article published in *Clinical Infectious Diseases,* as an example that reminded us how important it is to also carefully interpret the type 1 error level before introducing a finding for the widespread use of clinicians.

Like anyone who has been interested in Crimean-Congo hemorrhagic fever during their career, we read the manuscript by Ergönül et al [1] with interest. This paper presented important results from the experience of a well-known hospital and research center in Turkey. The main finding presented in this manuscript is that ribavirin therapy was associated with a decrease in mortality among patients with Crimean-Congo hemorrhagic fever. This observation was based on the comparison of the point estimates of the overall case-fatality rate (involving patients with mild and severe disease) with the case-fatality rate among the patients with severe disease who did not receive ribavirin (case-fatality rate, 2.8% vs 4.5%). The point estimate of 2.8% is clouded by the fact that it includes the patients with mild disease; for this comparison, the better estimate of 3.3% could have been used. More importantly, one can easily calculate that the observed difference of 1.2% in case-fatality rate will return a *P* value very close to 1.0 ($P > .99$). Furthermore, when the result of the Fisher's test comparing proportions of patient fatalities is statistically analyzed (0 of 8 patients treated with ribavirin died vs 1 of 22 patients without ribavirin), it reminds us that, in real life, the risk of this therapy being ineffective may be as high as 100%, which is in direct contrast to the findings and interpretation of this study.

The design of the Ergönül et al [1] study was not as ideal as an epidemiologist would like; however, this is relatively acceptable given the nature of this disease and the circumstances surrounding the time at which the paper was published. Our main concern was to express that, although studies with small numbers of subjects may not necessarily have to use the conventional type 1 error level of 5% [2], we do have to carefully consider the effect of chance when presenting findings that will affect clinical practice. This study, which presents a main finding with a *P* value very close to 1.0, does not remove our concerns that, although ribavirin may be safe and possibly an option for the treatment of Crimean-Congo hemorrhagic fever, the seemingly increased efficacy of ribavirin therapy may still be totally attributable to chance.

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References

1. Ergönül Ö, Çelikbaş A, Dokuzoğuz B, Eren Ş, Baykam N, Esener H. Characteristics of patients with Crimean-Congo hemorrhagic fever in a recent outbreak in Turkey and impact of oral ribavirin therapy. Clin Infect Dis **2004**; 39: 284–7.
2. Committee for medicinal products for human use (CHMP): guideline on clinical trials in small populations. European Medicines Agency, London, 2006. Available at: http://www.emea.europa.eu/pdfs/human/ewp/8356105en.pdf. Accessed 13 April 2009.

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Ribavirin in Crimean-Congo Hemorrhagic Fever: Primum Non Nocere

To the Editor—We read the comment about our manuscript that was published 5 years ago, which was the first report on Crimean-Congo Hemorrhagic Fever (CCHF) from Turkey [1]. We hope to correct the point of view presented by Hayran and Aşçıoğlu, to avoid any misinterpretation.

Hayran and Aşçıoğlu criticized our manuscript because of the lack of statistical inference. In this study [1], we did not declare that the ribavirin was effective in the treatment of CCHF with statistical significance. However, it is known that type I error is closely related to the sample size of the study. Thus far, no studies of CCHF have had a sample size sufficient to reach statistical significance; in other words, the sample size has been such that the role of chance cannot be minimized to an acceptable level, such as a type I error level of 5% with a power of 80%. One of the earliest reports on the benefits of ribavirin in CCHF only included 3 severely diseased health care workers, and there was no control group [2]. The report of Mardani et al [3] supported the beneficial use of ribavirin. The results of our study [1] were also consistent with these previous reports.

In our study [1], we included 35 patients with CCHF; 30 cases were severe, and 5 were mild. The overall fatality rate was 2.8% (1 of 35 patients died). Among these, 27 patients were not given ribavirin, because the diagnosis of CCHF was not possible historically. Only 8 patients with severe CCHF received ribavirin. The group of patients who received ribavirin were compared to the group who did not in terms of fatality rate. To overcome the case-mix problem, we grouped the mild and severe cases separately; we did perform the comparison among patients with severe CCHF, then we compared fatality rate for the group that received ribavirin (0 [0%] of 8 patients died) with that for the group that did not receive ribavirin (1 [4.5%] of 22 patients died). We preferred not to provide a *P* value for this comparison because of small sample size and because there was only 1 outcome. The *P*

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value of this comparison would be >.05. However, just by looking at the *P* value one cannot state that ribavirin was not effective in the treatment of CCHF. The lack of the statistical significance could be related to small sample size. Therefore, before making such a statement, a sufficient sample size must be achieved. Obviously, we prefer to stay on the safer side when treating our patients. Accordingly, the comment of Hayran and Aşçıoğlu regarding the lack of statistical inference in this example is not relevant in clinical practice, particularly for the example of CCHF; rather, it might mislead practitioners.

The positions of World Health Organization and the European Center for Disease Control and Prevention are clear regarding the beneficial use of ribavirin, and it would be unethical to perform a placebo-controlled, randomized study [4]. Moreover, recent studies have supported the beneficial use of ribavirin, particularly during the early phase of the disease [5]. Besides the small sample size, potential confounders and biases should be controlled precisely in studies on CCHF; these factors have been described in detail elsewhere [4].

In conclusion, ribavirin was found to be effective in vitro and to be beneficial in clinical studies, although the statistical significance of this benefit has not yet been reached [6]. As we stressed in our manuscript 5 years ago, additional studies are necessary.

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References

1. Ergönül O, Çelikbaş A, Dokuzoğuz B, Eren S, Baykam N, Esener H. Characteristics of patients with Crimean-Congo hemorrhagic fever in a recent outbreak in Turkey and impact of oral ribavirin therapy. Clin Infect Dis **2004**; 39: 284–7.
2. Fisher-Hoch SP, Khan JA, Rehman S, Mirza S, Khurshid M, McCormick JB. Crimean Congo-haemorrhagic fever treated with oral ribavirin. Lancet **1995**; 346:472–5.
3. Mardani M, Jahromi MK, Naieni KH, Zeinali M. The efficacy of oral ribavirin in the treatment of Crimean-Congo hemorrhagic fever in Iran. Clin Infect Dis **2003**; 36:1613–8.
4. European Centre for Disease Prevention and Control (ECDC). Consultation on Crimean-Congo hemorrhagic fever prevention and control. Stockholm: ECDC, **2008**.
5. Tasdelen Fisgin N, Ergonul O, Doganci L, Tulek N. The role of ribavirin in the therapy of Crimean-Congo hemorrhagic fever: early use is promising. Eur J Clin Microbiol Infect Dis **2009**; 28:929–33.
6. Ergonul O. Treatment of Crimean-Congo hemorrhagic fever. Antiviral Res **2008**; 78:125–31.

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Subclinical Infection with the Novel Influenza A (H1N1) Virus

To the Editor—On 15 May 2009, an 18-year-old woman was admitted to the Beijing Ditan Hospital because of fever, headache, dyspnea, and a sore throat. The patient is an undergraduate student in the United States, and she arrived in Beijing on 11 May. Two days before admission, the patient developed fever, with temperatures ≤39.4°C. At admission, the temperature was 37.7°C, the blood pressure 110/65 mm Hg, and the pulse 86 beats/minute. A nasopharyngeal swab specimen from the patient was obtained, and real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay confirmed the infection of novel influenza A (H1N1) virus.

On the basis of the local strategy for prevention and control of H1N1 virus infection, the mother of the patient, who had accompanied the patient since her arrival, was quarantined for medical observation. On 17 May, the nasopharyngeal swab specimen from the mother produced positive results for H1N1 by RT-PCR assay. But examination of the mother revealed a temperature of 36.6°C, a blood pressure of 127/80 mm Hg, and a pulse of 72 beats/minute. Moreover, no respiratory symptoms were observed in the mother during the subsequent 1-week medical observation.

Two strains of H1N1 viruses, A/Beijing/01/2009 and A/Beijing/02/2009, were isolated from specimens obtained from the patient and her mother, respectively. Whole-genome sequencing of the 2 isolates revealed that the genomes of the 2 viruses are exactly identical in all segments (GenBank accessions, GQ183617–GQ183632). The result corroborated the epidemiologic evidence that the virus was directly transmitted from the patient to her mother. Furthermore, it's particularly intriguing that the same virus induced severe respiratory symptoms in the patient but caused only inapparent infection in the mother.

More than 70,000 cases of H1N1 virus infection have been confirmed worldwide to date, but very few cases of subclinical infection have been reported. However, a recent statistical study estimated that 23,000 individuals had been infected by the H1N1 virus in Mexico by late April, which doubles the number of cases publicly reported, implying a >50% rate of mild or subclinical infection in the 2009 H1N1 pandemic [1]. The prolonged unawareness of the large proportion of asymptomatic infection is not surprising, because clinical evidence for asymptomatic infection is extremely scarce, and medical resources and surveillance always focus on severe cases in the initial stage of a pandemic. Nevertheless, this unawareness could be detrimental to global disease control. On the one hand, it hampers the reliable assessment, based on public statistics, of the transmissibility of the H1N1 virus and the severity of the pandemic, as exemplified by Fraser et al [1]. On the other hand, the effectiveness of nonphar-

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