Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

1 McKay L, Clery H, Carrick-Anderson K, Hollis S, Scott G. Genital *Chlamydia trachomatis* infection in a subgroup of young men in the UK. *Lancet* 2003; **361:** 1792.
2 Meikle J. Fertility threat to women. http://www.guardian.co.uk/uk_news/story/0,3604,961845,00.html (accessed Sept 8, 2003).
3 Sena AC, Miller WC, Hoffman IF, et al. Trends of gonorrhea and chlamydial infection during 1985–1996 among active-duty soldiers at a United States Army installation. *Clin Infect Dis* 2000; **30:** 742–48.
4 Fenton KA, Korovessis C, Johnson AM, et al. Sexual behaviour in Britain: reported sexually transmitted infections and prevalent genital Chlamydia trachomatis infection. *Lancet* 2001; **358:** 1851–54.
5 Macleod J, Salisbury C for the ClaSS study group. Prevalence of genital Chlamydia trachomatis infection in an UK general population sample. MSSVD/IUSTI Spring meeting, Leeds, June 12–14, 2003.

Treatment of SARS with human interferons

Sir—We agree with J Cinatl and colleagues (July 26, p 293)[1] that effective antiviral agents are urgently needed to treat severe acute respiratory syndrome (SARS).

On the basis of their results, the authors state that interferons inhibit replication of SARS-associated coronavirus (SARS-CoV) in vitro, with interferon beta being the most potent of those interferons tested. However, we are concerned that shortcomings in the methods used to calculate and interpret their results could have led to misleading conclusions.

First, when comparing the antiviral action of different preparations of interferons, the use of antiviral units of measurement, including international units (IU), might be inappropriate. Different preparations can have different specific activities—ie, IU/mg protein—as in the case of interferon beta (32×10^6 IU/mg protein) and interferon alfa ($2{\cdot}0–2{\cdot}4\times10^8$ IU/mg protein). Therefore, for instance, the inhibitor concentration (EC_{50}) value in Vero cells of interferon beta is not 62—ie, 6500/105 IU—times higher than the EC_{50} of interferon alfa, as stated,[1] but only nine times—ie, 29·5/3·2 ng; this difference could be clinically relevant in pharmacokinetic and pharmacodynamic terms.

Second, Cinatl and colleagues calculated the selectivity index, a parameter of fundamental importance from a therapeutic viewpoint, without knowing the cytotoxic concentration (CC_{50}) values of the interferons used. In their calculation, a value of more than 10 000 was assumed. However, when the therapeutic efficacy of different drugs is compared, this assumption might be incorrect: higher than 10 000 might mean 10 001 IU, for example, for interferon beta and 100 000 IU, for example, for interferon alfa. Although such wide variations in the values are highly unlikely, they would imply indirectly that interferon alfa, which has a lower antiviral activity, is more interesting from a therapeutic viewpoint than interferon beta because the selectivity index for interferon alfa is higher.

Finally, the antiviral action of interferons against a specific virus is usually, historically, measured by back titration of the viral yields when the interferon is added some 18–24 h before virus adsorption. The addition of interferon before and after virus infection does not allow a direct comparison of the sensitivity of SARS-CoV with that of other animal viruses, including human coronaviruses.

Cinatl and colleagues have undoubted merit in having addressed promptly the issue of antiviral action of interferons against SARS-CoV. We consider, however, that their calculations could have been made and their general conclusion—that only interferon beta can be used as an antiviral agent after infection—might have been drawn with undue haste, which has led to errors.

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1 Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Treatment of SARS with human interferons. *Lancet* 2003; **362:** 293–94.

Authors' reply

Sir—Guido Antonelli and colleagues are right to point out that different interferon preparations, including those we used, can have different specific activities (IU/mg protein). In clinical practice this difference can be important in pharmacokinetic and pharmacodynamic terms, since interferons with high specific activity can be used at low protein concentrations relative to interferons with low specific activity. However, our data based on the use of IU/mL suggest that even in the case of application of same protein concentrations interferon beta (specific activity $3{\cdot}2\times10^7$ IU/mg) would be better than interferon alfa ($2–2{\cdot}4\times10^8$ IU/mg) in terms of antiviral activity.

To directly address this point we tested different preparations of interferon alfa and interferon beta in Vero cells infected with SARS-CoV. The results (not presented in our research letter) showed higher antiviral potency for interferon beta than for interferon alfa independent of specific activity—ie, interferon beta-1a has a specific activity (2×10^8 IU/mg) similar to interferon alfa-2b, but its antiviral activity was about 40 times higher.

The differences in antiviral activity of both type 1 interferons could result from their ability to differentially influence expression of cellular genes important for antiviral activity. For example, when the human fibrosarcoma cell line HT1080 is treated with 1000 IU/mL of type 1 interferons, more than 20 genes, including double-stranded RNA-activated protein kinase, are induced by interferon beta but not by interferon alfa.[1]

Antonelli and colleagues also argue that selectivity index as a parameter for therapeutic efficacy cannot be ascertained without knowing cytotoxic concentrations (CC_{50}) of the interferon used. 10 000 IU/mL was the maximum concentration we tested, since higher concentrations of interferons are probably not achievable in the infected cells of patients. CC_{50} value higher than 10 000 simply means that antiviral effects in our culture system are not due to non-specific toxic effects. Our initial experiments were undertaken with a range of concentrations that are commonly used in in-vitro investigations. In additional experiments done by us, interferon concentrations up to 10^6 IU/mL were used without increased toxicity of interferon beta versus interferon alfa in confluent layers of Vero cells.

In conclusion, these results do not lend support to the notion that increased antiviral activity of interferon beta is associated with increased toxicity and thus decreasing of therapeutic index relative to interferon alfa as suggested by Antonelli and colleagues. Treatment of patients who have SARS with interferon alfa and restricted use of steroids did not improve clinical symptoms and signs.[2] This finding could be explained at least partly by our observations, indicating an inability of interferon alfa to inhibit SARS-CoV replication when added to cultured cells after virus infection. Therefore, the selective antiviral activity of interferon beta