A Case of In-flight Transmission of Severe Acute Respiratory Syndrome (SARS): SARS Serology Positive

To the Editor:

We reported the first case of in-flight transmission from a passenger with probable SARS to a flight attendant on the flight from New York to Frankfurt/Singapore on 14 March 2003.[1] At the time of admission, the diagnosis was made on epidemiologic and clinical grounds, as diagnostic tests were not yet available. We would like to add that the subsequently performed SARS serology was positive, for both the index passenger and the flight attendant, thus confirming in-flight transmission.

SARS serology was also positive for the wife of the index passenger. However, his mother-in-law had negative SARS serology and was later cleared of having suffered from SARS (Preiser W, personal communication). It remains unclear why the mother-in-law (despite prolonged close contact not only on the long-haul flight but also prior to the flight during their stay in New York and later during the hospitalization in Frankfurt) did not develop SARS, whereas the flight attendant was infected after a very brief contact. Factors determining transmissibility and susceptibility of the SARS coronavirus continue to constitute an important area of research.

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Reference

1. Wilder-Smith A, Leong HN, Villacian JS. In-flight transmission of severe acute respiratory syndrome (SARS): a case report. J Travel Med 2003; 10:299–300.

Hepatitis A+B Vaccine in Elderly Persons

To the Editor:

In the journal *Vaccine*, Wolters et al.[1] published a paper on the immunogenicity of combined hepatitis A + B vaccine in elderly people. In this retrospective study, they measured the anti-HAV and anti-HBs responses in 104 elderly people, mean age 54 years, after application of Twinrix. In short, only 29% of persons older than 40 years exhibited seroprotection against hepatitis B and 65% against hepatitis A. With increasing age, the antibody responses to vaccination were even less pronounced. However, even after what seemed to be a vaccination failure, boosters proved to be very effective. The conclusion was drawn that the application of the combined hepatitis A + B vaccine (Twinrix has been used) is not very effective in elderly persons, and it was recommended to measure antibody responses to both antigens in elderly people to ensure protection. This is particularly important because increasing numbers of elderly people are now traveling to various regions of the world and need adequate protection.

The conclusions drawn are quite alarming and need further scrutiny and interpretation. Changes in the aging immune system have been observed, and impaired antibody responses to tetanus, diphtheria, pneumococcal and tick-borne encephalitis vaccines,[2–5] as well as hepatitis A and B vaccines, as correctly cited by Wolters et al., have been described in elderly people. Determination of antibody levels has been recommended in elderly people after vaccination with new vaccines with which they have had no previous contact. A common basis for this observation apparently lies in the findings that the involution of the thymus is almost complete at the age of 60 years. The host is then dependent on the T cell pool that has been generated in earlier life, and changes in the T cell repertoire can eventually be observed.

Another interesting observation concerns the rate of disappearance of antibodies. Two phases of antibody decline (a fast and a slow phase) have been observed in hepatitis A[6,7] as well as hepatitis B.[8] When antibody responses are being measured, the quantitative results may differ considerably, depending on whether blood samples are being drawn in the middle of the fast phase or only in the slow phase.

After these remarks, it should be stressed that we also have performed a retrospective study of antibody responses against hepatitis B after application of a combined hepatitis A + B vaccine (Twinrix) in comparison with two monovalent hepatitis B vaccines (20 and 10 μg antigen content) in younger and elderly people.[8] We also found that, with increasing age, antibody titers after immunization with hepatitis B antigen tend to be lower. Other results in elderly people were, however, different from those of Wolters et al. In our study, more than 1,000

Table Geometric Mean Titers Against Hepatitis B and 95% Confidence Intervals for the Different Vaccination Groups Stratified for Age

Age (years)	*Hepatitis B (20 μg) n = 155*	*Hepatitis A + B n = 678*	*Hepatitis B (10 μg) n = 256*
15–30	1,437 (647–3,191)	3,162 (2,246–4,451)	918 (420–2,008)
30–50	738 (328–1,660)	1,383 (993–1,927)	158 (87–285)
50–60	451 (156–1,305)	359 (230–561)	117 (63–217)
> 60	96 (23–389)	298 (163–547)	29 (10–81)
Total	523 (320–855)	678 (817–1,243)	142 (98–206)

Subgroup tested within 6 months after booster.

people were included, 49% females and 51% males, of different ages, as indicated in the table. A selected cohort of subjects was followed at fixed times without taking into account mild chronic diseases considering persons as they appeared in clinical praxis. In the table, only results concerning age differences are taken into account.

The differences in titer were statistically significant, with the exception of hepatitis A + B vs. hepatitis B (20 μg) vaccine in the age group 50 to 60 years. Seroprotection rates against hepatitis B with Twinrix (definition ≥ 10 mIU/mL, identical to Wolters et al.) were 97% (15 to 30 years), 93% (30 to 50 years), 89% (50 to 60 years) and 87% (> 60 years).

As in other studies (as cited correctly by Wolters et al.), in our experience the immune response to hepatitis A vaccination was good in all age groups up to 65 years (data not shown), which is also in contrast to the results of Wolters et al. As has been shown, however, in our paper[8] the most striking difference from the findings of Wolters et al. concerned our satisfactory results concerning the response to hepatitis B vaccination in the elderly.

The question that should be asked is how these conflicting results might be explained. The existence of different phenotypes of T cells in the two study populations of elderly people can be excluded, because in the Wolters paper, and even more so in our paper, the number of participants was high enough. An incorrectly chosen injection site was denied by Wolters et al. With respect to different vaccine lots, it was stated by Wolters et al. that they found no relationship between particular batches and lack of immune response. No batch was outdated. There appeared to be no reason to assume failure in the production of the vaccine used. Interruptions of the cold chain were not mentioned, and whether, during the relatively long storage of serum samples, electricity blackouts took place was not reported. Low levels of HbsAg carriage were excluded by the authors. With respect to health problems in elderly people, it was reported by Wolters et al. that a considerable proportion of the elderly probands had some kind of chronic disease which significantly influenced the rate of protection against hepatitis B, but not against hepatitis A. In our study, elderly people were included as they appeared in clinical praxis, without registering mild health aberrations. It may be that there were some differences in the quality of the population between the study of Wolters et al. and our study. Also, however, the interval between the booster and the drawing of blood samples was different in the two studies. As shown in the table, the investigated blood samples were obtained in our study within 6 months after the booster, whereas in the study of Wolters et al., the mean time interval between completion of vaccination and measurement of antibody titer was 16.8 months. Since the fast phase of antibody decline lasted for approximately 1.5 years in our study, this might have an enormous quantitative impact. It was also mentioned in the paper of Wolters et al. that people without anti-HBs antibodies had a longer time interval between vaccination and examination of their serostatus than those with protective titers. In the case of vaccination failures, boosters were very effective.

Are, therefore, the data of Wolters et al. more realistic and relevant than ours? We deny the relevance of these data, because, following the consensus statement of the European Consensus Group on hepatitis B immunity, there is no need for booster vaccination after a successful primary vaccination series in healthy individuals, as the maintenance of HBsAg specific memory confers protection against clinical breakthrough infections even in the absence of detectable antibodies.[9] An effective priming apparently took place in the population of Wolters et al., since boosters were very effective. Moreover, in our hands, a follow-up of antibody titers for many years showed that the slow phase of antibody decline still took place in the protective range.

It has further been stated that combined hepatitis A + B (Twinrix) vaccination is not very effective in elderly people. We cannot confirm this. On the contrary, even in elderly people, Twinrix induced a considerably better immune response than two monovalent hepatitis B vaccines (table).

Consequently, it might be concluded that hepatitis B, as well as A, antigens do not compromise the immune

response in elderly people in a clinically alarming way, although a physiological age-dependent decline may be observed, and that vaccination with Twinrix is a very effective means for immunization in this population group.

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References

1. Wolters B, Junge U, Dziuba St, Roggendorf M. Immunogenicity of combined hepatitis A and B vaccine in elderly persons. Vaccine 2003; 21:3623–3628.
2. Grubeck-Loebenstein B. Changes in the aging immune system. Biologicals 1997; 25:205–208.
3. Saurwein-Teissl M, Lung TL, Marx F, et al. Lack of antibody production following immunization in old age: association with $CD8^{+}CD28^{-}$ T cell clonal expansions and an imbalance in the production of Th1 and Th2 cytokines. J Immunol 2002; 168:5893–5899.
4. Schwaiger S, Wolf AM, Robatscher P, et al. IL-4-producing $CD8^{+}$ T cells with a $CD62L^{++(bright)}$ phenotype accumulate in a subgroup of older adults and are associated with the maintenance of intact humoral immunity in old age. J Immunol 2003; 170:613–619.
5. Grubeck-Loebenstein B, Wick G. The aging of the immune system. Adv Immunol 2002; 80:243–281.
6. Wiedermann G, Kundi M, Ambrosch F, et al. Inactivated hepatitis A vaccine: longterm antibody persistence. Vaccine 1997; 15:612–615.
7. Van Damme P, Thoelen S, Cramm M, et al. Inactivated hepatitis A vaccine: reactogenicity, immunogenicity and longterm antibody persistence. J Med Virol 1994; 44:446–451.
8. Rendi-Wagner P, Kundi M, Stemberger H, et al. Antibody-response to three recombinant hepatitis B vaccines: comparative evaluation of multicenter travel-clinic based experience. Vaccine 2001; 19:2055–2060.
9. European Consensus Group on Hepatitis B Immunity. Are booster immunizations needed for lifelong hepatitis B immunity? Lancet 2000; 355:561–565.