Correspondence

Intranasal versus Injectable Influenza Vaccine

Sir—We read with interest the article by Sendi et al. [1] on the safety of intranasal and injectable influenza vaccines in a working Swiss population. They report that, of the 13% of the subjects who wished to be vaccinated, the nasal route was the preferred route of administration for 97%. This is a striking finding, and we would like to know what information was provided to the volunteers for them to make their choices. Indeed, at that time (winter 2000), to our knowledge, there were no published safety data with side-by-side comparisons of the 2 types of vaccines; more importantly, there were no data on immunogenicity (protective antibody titers) and, therefore, on the efficacy for humans of the specific intranasal vaccine used (Nasalflu; Berna Biotech AG). Thus, we wonder on what grounds the subjects mentioned "increased efficacy" as a reason for choosing the nasal spray (23% in table 1 of [1]). Was that information suggested by the information leaflet?

We made an acceptability assessment during the winter season of 1999–2000 in an elderly population attending the Medical Outpatient Clinic, University of Lausanne (Lausanne, Switzerland) as part of a comparative safety and immunogenicity trial. Our findings are very different from those of Sendi et al. [1]. Indeed, only 98 (25%) of 400 elderly persons agreed to be randomized—in other words, to potentially receive the intranasal vaccine (Nasalflu; Berna Biotech AG). The main reasons they gave to potentially receive the mucosal route were "to try" it and because they "don't like injections." The other 75% of persons preferred to receive the conventional injectable vaccine, with the main reasons being "one shot and that's done," "I am used to it," and "I have problems with my nose." Because the subjects were recruited upon usual attendance for flu vaccination, and because the study protocol did not include many constraints (only 1 additional visit and 2 blood draws were required), it is unlikely that participation in the trial was the main reason for the low acceptance of the intranasal vaccine. Moreover, during the subsequent winter season, we let the working personal of the Medical Outpatient Clinic freely choose between the intranasal or the intramuscular vaccine. Among those who accepted vaccination, 19% chose the intranasal route, and 81% chose the intramuscular route, which is very far from the rates of 97% and 3%, respectively, among the employees of the Canton Basel Stadt reported by Sendi et al. [1].

The study by Sendi et al. [1] was aimed primarily at assessing the safety of a new intranasal vaccine. It definitely contributed to the identification of an important severe adverse event (i.e., facial palsy), a finding that was supported by a later study [2]. However, the design was not appropriate to assess subjects' preference for one vaccine or the other, and this may explain the very different findings between 2 young working communities within the same country. Thus, we doubt the authors' conclusions on public preference based on these data. Such variability calls for well-designed studies aimed at specifically assessing vaccine route preference among the public, using standardized information based on published peer-reviewed evidence.

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Conflict of interest. B.G. and V.D'A. were investigators of several clinical studies of vaccines sponsored by Berna Biotech AG; V.D'A. received funding from Berna Biotech AG to travel to an international conference to present study results.

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References

1. Sendi P, Locher R, Bucheli B, Battegay M. Intranasal influenza vaccine in a working population. Clin Infect Dis **2004**; 38:974–80.
2. Mutsch M, Zhou W, Rhodes P, et al. Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland. N Engl J Med **2004**; 350:896–903.

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Reply

Sir—We thank Genton and D'Acremont [1] for their interest in our article. We agree with the authors that no data from a randomized controlled trial comparing the efficacy of the intranasal versus injectable vaccine are available. However, immunogenicity and safety data regarding the virosome-formulated subunit vaccine containing the heat-labile toxin of *Escherichia coli* were published before winter 2000 [2]. In addition, immunogenicity and safety data were available from Berna Biotech AG. It has been argued that the intranasal vaccine would induce secretory IgA antibodies (in addition to IgG antibodies) in the nasopharyngeal cavity, which are able to neutralize influenza viruses [3]. This may suggest a potentially higher efficacy [3], although a head-to-head randomized controlled trial of the injectable versus intranasal vaccine would be needed to verify this. In our study, patients who chose the intranasal vaccine were less likely to develop influenza-like

symptoms [4]. However, this difference was not statistically significant because of a lack of power, because the number of patients who received the injectable vaccine was very low. In addition, the study was not designed to detect differences in effectiveness [4].

In our study, the intranasal vaccine was the preferred route of administration, which is quite different from the findings of Genton and D'Acremont [1]. One reason might be that our study population was rather young, whereas Genton and D'Acremont [1] and others [2, 3] included elderly patients in their studies. Unlike young healthy adults, elderly individuals are more susceptible to serious illness after influenza infection and may therefore rather benefit from influenza vaccination [4]. Elderly individuals may also be less open to novel techniques and might prefer the vaccine that they are used to—that is, the injectable vaccine. In a separate article [5], we analyzed the attitude of the vaccinees towards revaccination in the following winter (2001), given their experience with the influenza vaccine in winter 2000. Our results showed that the decision to get vaccinated against influenza in the winter of 2001 did not depend on the mode of administration (i.e., injectable versus intranasal vaccine) but, rather, on the safety and efficacy of the vaccine experienced by the individuals in the preceding year. This finding is more in line with the findings reported by Genton and D'Acremont [1]. Elderly individuals in whom influenza vaccination is recommended may have had positive experiences with the vaccine in the past and may therefore prefer to be revaccinated using the injectable vaccine that they are used to. Young healthy adults usually know that they are able to better cope with influenza infection than are elderly individuals. They are also less likely to have been vaccinated against influenza in the past. The mode of vaccine administration may therefore be a more important factor for the young population in deciding whether they wish to be vaccinated against influenza for the first time. Finally, we believe that the preferences of the employees of an outpatient clinic, who are mostly health care professionals, may not necessarily coincide with the preferences of the wider working population.

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References

1. Genton B, D'Acremont V. Intranasal versus injectable influenza vaccine. Clin Infect Dis **2004**; 39:754 (in this issue).
2. Gluck R, Mischler R, Durrer P, et al. Safety and immunogenicity of intranasally administered inactivated trivalent virosome-formulated influenza vaccine containing *Escherichia coli* heat-labile toxin as a mucosal adjuvant. J Infect Dis **2000**; 181:1129–32.
3. Glueck R. Review of intranasal influenza vaccine. Adv Drug Deliv Rev **2001**; 51:203–11.
4. Sendi P, Locher R, Bucheli B, Battegay M. Intranasal influenza vaccine in a working population. Clin Infect Dis **2004**; 38:974–80.
5. Sendi P, Locher R, Bucheli B, Battegay M. The decision to get vaccinated against influenza. Am J Med **2004**; 116:856–8.

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Clinical Relevance of Bacteriostatic versus Bactericidal Activity in the Treatment of Gram-Positive Bacterial Infections

In their recent review article, Pankey and Sabath [1] highlight the arbitrariness of the empirical measures used to define bactericidal and bacteriostatic activities and emphasize the importance of multiple factors, such as target organism, organism burden, site of infection, and intrinsic pharmacodynamic and pharmacokinetic properties of individual antimicrobial agents, as potential determinants of the efficacy of specific antimicrobial agents in different clinical circumstances. Their conclusion, that the potential superiority of bactericidal over bacteriostatic activity is of little clinical relevance, however, is built on a specious line of reasoning. The arguments Pankey and Sabath [1] presented simply emphasize both the inappropriate pharmacodynamic *designation* of antimicrobial agents as either "bactericidal" or "bacteriostatic" solely on the basis of their mechanism of action and the notable paucity of clinically validated measures that discriminate bactericidal from bacteriostatic activity [2].

Studies by Scheld and Sande [2] using a rabbit model of pneumococcal meningitis have illustrated the inappropriateness of designating antimicrobials as "bactericidal" or "bacteriostatic" solely on the basis of their mechanism of action. These studies demonstrated that chloramphenicol, an antibiotic generally regarded as bacteriostatic, can in fact achieve bactericidal activity against *Streptococcus pneumoniae* and can achieve microbiologic cure rates comparable to that of ampicillin in the rabbit model of meningitis when mean peak CSF concentrations exceeded the minimum bactericidal concentration for the organism. This study, as well as several others using experimental animal models, also clearly documented the need for bactericidal activity to achieve microbiologic cure of meningitis [3, 4, 5].

Admittedly, little to no suitable *clinical* data exist to address the potential superiority or inferiority of bactericidal versus bacteriostatic activity. Thus, the treatment offered by Pankey and Sabath should motivate a renewed interest in reevaluating this important clinical question. Because of the unavailability of germane data, judgment regarding this issue should be withheld.

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