Field effectiveness of vaccination against tick-borne encephalitis

Franz X. Heinz a,*, Heidemarie Holzmann a, Astrid Essl b, Michael Kundi c

a Institute of Virology, Medical University of Vienna, Kinderspitalgasse 15, AT-1095 Vienna, Austria
b Fessel GfK Institute-Health Care, Vienna, Austria
c Institute of Environmental Health, Centre for Public Health, Medical University of Vienna, Vienna, Austria

Received 16 May 2007; received in revised form 8 August 2007; accepted 13 August 2007
Available online 31 August 2007

Abstract

Tick-borne encephalitis (TBE) is a vaccine-preventable disease caused by a flavivirus (TBE virus) that is endemic in many European countries and large parts of Central and Eastern Asia. In Europe, highly purified formalin-inactivated whole virus vaccines are in widespread use, but the vaccination coverage differs significantly between countries with TBE endemicity. Austria presents an exceptional situation because 88% of the total population have a history of TBE vaccination, with 58% being regularly vaccinated within the recommended schedule. In this study, we investigated the field effectiveness of TBE vaccination in Austria for the years 2000–2006 in different age groups on the basis of the documented numbers of hospitalized cases in unvaccinated and vaccinated people and the sizes of these population groups as revealed by representative inquiries. We show that the overall effectiveness in regularly vaccinated persons is about 99% with no statistically significant difference between age groups. It is at least as high after the first two vaccinations, i.e. before the completion of the basic vaccination scheme by a third vaccination, but is significantly lower (about 95%) in those with a record of irregular vaccination. Our data confirm the excellent performance of TBE vaccine under field conditions and provide evidence that, in Austria, about 2800 cases were prevented by vaccination in the years 2000–2006.

Keywords: Tick-borne encephalitis (TBE); Vaccine effectiveness; Vaccination coverage

1. Introduction

Tick-borne encephalitis (TBE) virus is one of the major human pathogenic flaviviruses, a group of about 70 viruses that also includes the mosquito-borne yellow fever, dengue, Japanese encephalitis and West Nile viruses [1,2]. TBE virus circulates in endemic regions of many countries of Central, Southern, Northern, and Eastern Europe as well as Central and Eastern Asia including Northern Japan and Northern China [1,3,4]. Based on sequence comparisons, three subtypes can be differentiated – designated European, Siberian, and Far Eastern subtypes – that are antigenically closely related [5,6] and transmitted by the ticks Ixodes ricinus (European subtype) and Ixodes persulcatus (Asian subtypes) [4,7].

Consistent with the overlap of distribution areas for I. ricinus and I. persulcatus in North-Eastern Europe, European and Asian subtype viruses have both been isolated in the Baltics and Finland [8–10].

About 3000 hospitalized cases of TBE are recorded annually in Europe [11] and between about 5500 and 10,000 in Russia [12,13]. After the acute phase of the disease, a significant proportion of the patients (up to 46%) suffers from neurological sequelae for a certain period of time or even lifelong [14]. In Europe, the lethality as a consequence of TBE lies between 1 and 2% [14] but has been reported to reach 20–40% in the Far East [7]. It has to be considered, however, that these comparisons were not made under standardized conditions and may be biased by differences in the rates of laboratory diagnosis and hospitalization of less severe cases. They thus cannot be ascribed solely to the higher pathogenicity of Far-Eastern strains without further scrutiny and data analysis.
Starting with the development of a formalin-inactivated TBE vaccine in 1973 and its further purification [15–19], highly purified inactivated vaccines are now available in Europe from two manufacturers: Baxter (formerly Immuno), designated ‘FSME Immun™’ [15,16,18], using an Austrian isolate (strain Neudoerfl), and Novartis (formerly Chiron, formerly Behring), designated ‘Encepur™’, using a German isolate (strain Karlsruhe) [20,21]. Both of the manufacturing strains belong to the European subtype [5]. In Austria, FSME Immun™ has been in use since 1976, and Encepur™ was introduced in 1999; in this country, these vaccines are currently used at a ratio of ca. 90 to 10, respectively (Institute for Medical Statistics Austria; www.imshealth.at).

Human vaccines are usually licensed and controlled on the basis of seroconversion data, using different assays for measuring the formation of specific antibodies. In the case of TBE virus and other flaviviruses, there is abundant evidence from animal studies that the presence of virus-neutralizing antibodies in serum provides an excellent correlate for protection against virus challenge [22–29]. Nevertheless, the final proof for the success of vaccines depends on the evaluation of their effectiveness in the field. In terms of this field effectiveness, a wide range has been observed for different inactivated vaccines, from 50 to 80% for influenza vaccines [30] to more than 90% for hepatitis B vaccines [31,32] and hepatitis A vaccines [33,34]. The vaccine most closely related to the TBE vaccine investigated here is the inactivated Japanese encephalitis vaccine, which proved to have an effectiveness of 91% under field conditions [35].

With respect to TBE, Austria is an exceptional example because vaccination coverage has been steadily increasing since the 1970s, when the first vaccine (a precursor of the current vaccines [15,16,18]) became available. Today, 88% of the total population in Austria have been vaccinated at least once, with 58% being regularly vaccinated within the officially recommended vaccination schedule. This is in sharp contrast to neighbouring countries with comparable TBE virus endemicity such as Germany and the Czech Republic, where vaccination coverage has reached only 13 and 11%, respectively.

In this work, we have analyzed the field effectiveness of TBE vaccination (i.e. prevention of laboratory-diagnosed cases of TBE virus infections with neurological symptoms causing hospitalization) in Austria for the years 2000–2006 in different age groups and groups with different vaccination histories. The study is based on (1) the annual numbers of hospitalized TBE cases confirmed by laboratory diagnosis, (2) the vaccination history of these cases, (3) the annual population figures in Austria, and (4) the TBE vaccination coverage data in the different groups collected by representative inquiries involving 8500 to 10,000 individuals annually (see Section 2). Our analysis reveals an extraordinarily high degree of protection by TBE vaccination in Austria in the range of 99% which does not exhibit significant differences between age groups. Protection is equally high in the months following the first two vaccinations—i.e. before the third shot of the basic vaccination schedule, but is somewhat lower in persons with an irregular history of vaccination that lies outside the recommended regular scheme. The data presented confirm the excellent protection record of TBE vaccination under field conditions which—when compared to that of other vaccines—is among the best achievable by active immunization against viral diseases [15,30–35].

2. Materials and methods

2.1. TBE vaccination

Like in other European countries, two TBE vaccines are commercially available in Austria, FSME-Immun™ manufactured by Baxter [15] and Encepur™ manufactured by Novartis [21]. Both vaccines are highly purified formalin-inactivated whole virus vaccines adjuvanted with aluminium hydroxide and can be used interchangeably. According to the Institute of Medical Statistics Austria (www.imshealth.at), the market coverage in Austria for the Baxter and Novartis vaccines in 2000 was about 95 and 5%, respectively, and in 2006 about 90 and 10%, respectively. The basic vaccination schedule consists of two vaccinations 1–3 months apart followed by a third vaccination after 9–12 months. Until 2003 in Austria, booster vaccinations have been recommended every 3 years but since 2004 the schedule has been changed and booster intervals of 5 years after the fourth vaccination were introduced. Because of considerations related to the ageing of the immune system, however, the 3-year interval was maintained for the age group 60 years and older.

2.2. Documentation of TBE cases and their vaccination status in Austria

The case definition of TBE in Austria includes (1) hospitalization because of central nervous system disease and (2) confirmation of infection with TBE virus by laboratory diagnosis, usually by the demonstration of specific IgM and IgG antibodies in ELISA [36]. In ambiguous cases, the laboratory diagnosis is supplemented and confirmed by the demonstration of an increase in virus-neutralizing antibody titers. In addition to the reporting of clinical cases of CNS infection (including TBE) being mandatory in Austria, the Institute of Virology in Vienna together with the Institutes of Hygiene in Graz and Innsbruck have established a collaboration network that covers the complete annual documentation of TBE cases in all federal states of Austria. These data are reported annually in the ‘Virusepidemiological Information’ published bi-weekly by the Institute of Virology, Medical University of Vienna. For every single patient with a confirmed TBE virus infection, a questionnaire is sent to the hospital in order to obtain a precise documentation of her/his vaccination history. By this means, the vaccination status of most of the patients could be recorded.
precisely and grouped into the following categories: (1) unvaccinated, (2) regularly vaccinated (including those with completed basic immunization scheme of three doses and those with one or more booster dose within the officially recommended schedule), (3) vaccinated two times but not yet having received the third dose of the basic immunization scheme, and (4) irregularly vaccinated (including those with one vaccination or more but not within the regular scheme). Out of a total of 494 confirmed cases of TBE in the years 2000–2006, only 14 (2.8%) could not be classified unequivocally into one of these categories. Among those 14, nine were without any information on vaccination and five with insufficient information to allocate them to one of the different groups.

2.3. Collection of data on vaccination coverage

In Austria, data on the proportion of people with different vaccination statuses in the total population were collected annually by representative inquiries conducted by the Fesssel GfK Institute-Health Care (Vienna, Austria) using postal surveys of 4000 households (8500–10,000 household members). The results of these inquiries were representative in terms of age, region, gender, and for the purposes of this work, were allocated to the age groups 0–15, 16–49, 50–60, and >60. The figures obtained (i.e. vaccination coverage in Austria) are based on written records of the vaccination history in 87% and on memory in 13% of all vaccinated people.

2.4. Calculation of field effectiveness (FE) and statistical analysis

The field effectiveness in a specific group of vaccinees is defined as

\[ \text{FE} (%) = 100 \times \left(1 - \frac{I_v}{I_n}\right) \] (1)

where \( I_v \) and \( I_n \) are the incidences in vaccinated and not vaccinated, respectively.

The definition above is equivalent to defining field effectiveness as the expected proportion of prevented cases in vaccinees, with \( Q_v \) being observed cases in vaccinees and \( E_v \) being expected cases, assuming that the risk for being infected with TBE virus is the same in vaccinated and unvaccinated people.

This is written as

\[ \text{FE} (%) = 100 \times \left(1 - \frac{O_v}{E_v}\right) \] (2)

Although the total number of people in the groups with different vaccination statuses can easily be determined by multiplication of the population size (from official annual population statistics) with the respective proportion in the random sample, it should be noted that for estimation of field effectiveness the population size is not necessary (see Eq. (3)):

\[ \text{FE} (%) = 100 \times \left(1 - \frac{O_v}{O_n} \frac{r_n}{r_v}\right) \] (3)

where \( Q_v \) and \( O_n \) are the observed numbers of cases in vaccinated and not vaccinated, respectively, and \( r_v \) and \( r_n \) are the fraction of vaccinated and not vaccinated in the population, respectively.

Since the fractions of the various vaccination categories were determined by a sample, they are subject to random variation. Furthermore, if inferences for vaccination effectiveness should be made from Austria to other countries with the same risk, the observed cases are considered as also being subject to random variation. Therefore, numbers of observed cases were assumed to be Poisson random variables, and proportions of the different vaccination groups were considered to follow a multinomial distribution. Based on these assumptions, approximate confidence intervals for the estimates of field effectiveness were computed.

For significance testing, a Monte Carlo procedure was chosen with 10,000 samples drawn under the zero hypothesis of no difference in vaccination effectiveness. Each simulation result was expressed as the relative difference of vaccination effectiveness and the \( p \) value was calculated as the percentile of the obtained distribution function at the position of the relative difference of vaccination effectiveness observed in the compared groups.

Since the vaccination status remained undefined in 14 of the total of the 494 cases (see above ‘Documentation of TBE cases and their vaccination status in Austria’) we carried out ‘best case’ and ‘worst case’ calculations for vaccine effectiveness. In the ‘best case’ analyses of regularly and irregularly vaccinated people, the 14 undefined cases were omitted; in the ‘worst case’ analyses, these cases were assumed to have been regularly or irregularly vaccinated, respectively. For the ‘worst case’ analysis of the group that received only two doses within the regular scheme, the 14 cases were included at that proportion that corresponded to the overall proportion of those with two doses of the regular scheme among all regularly vaccinated people of the same age group and year.

3. Results

3.1. Vaccination status of the Austrian population

The percentages of people in Austria in the categories: (1) unvaccinated, (2) regularly vaccinated, (3) vaccinated with two doses only of the basic immunization schedule, and (4) irregularly vaccinated were determined by means of representative inquiries conducted annually (see Section 2). The results generated through these inquiries are displayed in Fig. 1 for the years 2000–2006 with respect to the total Austrian population. For the purposes of this study, these data were further dissected into age groups which were assessed
Fig. 1. Vaccination status (2000–2006) of the Austrian population, estimated from annual representative inquiries in random samples of 8500–10,000 inhabitants. The exact numbers leading to the percentages displayed in the figure are presented in the Supplementary Material (Supplementary Tables 1 to 4).

separately, 0–15, 16–49, 50–59, and >60 years of age. The detailed figures in each of the age groups for all of the four categories listed above are displayed in four tables provided as ‘Electronic Supplementary Material’. As shown in Fig. 1, by the end of 2006 only 12% of the Austrian population had never received a shot of TBE vaccination, and 58% were within the officially recommended regular vaccination schedule.

3.2. Vaccine effectiveness in regularly vaccinated people

On the basis of the information on the TBE-vaccination status of the Austrian population collected by representative inquiries (see also Section 2) and the numbers of cases in unvaccinated and vaccinated people, we first calculated the field effectiveness of vaccination in different age groups for regularly vaccinated people (i.e. those with a documented history of at least three vaccinations within the recommended scheme). The results obtained are shown in Table 1A as the ‘best case’ with respect to vaccine effectiveness (i.e. including only those with an unambiguous vaccination record; see Section 2).

In some of the cases, no clear information on vaccination history could be obtained and therefore we made a second calculation under the assumption that all of the cases with an unknown or undefined vaccination history were properly vaccinated (see Section 2). These figures represent the ‘worst case’ with respect to vaccine effectiveness in this category and are shown in Table 1B. As can be seen from the tables, the overall field effectiveness for all age groups ranges from 98.7 (worst case) to 99.3% (best case), and the differences between the age groups analyzed are statistically not significant. This includes the seemingly lower effectiveness in 0–15 years old children (96% in the worst case, Table 1B) as compared to the other age groups, which is, however, a result of the low number of cases and therefore statistically also not significant (p = 0.063).

3.3. Vaccine effectiveness in irregularly vaccinated people

A significant proportion of those vaccinated at least once (88% of the Austrian population, Fig. 1) have not followed the recommended vaccination schedule. We therefore also calculated the field effectiveness for the pool of people with a specifically documented history of vaccination which, however, lay outside the recommended scheme (‘irregularly’ vaccinated). Again we determined ‘best case’ and ‘worst case’ scenarios, in the latter case including all of those TBE cases into the category of ‘irregularly’ vaccinated people with an unknown or undefined vaccination record (Section 2). The data shown in Table 2 reveal that the FE is still quite high (94.6–96.4%), and – like that in regularly vaccinated people – does not display any significant difference between the age groups analyzed. However, the difference to those within the regular schedule is statistically highly significant with p-values of 0.002 (comparison of worst case ‘regularly vaccinated’ and best case ‘irregularly vaccinated’) and <0.001 (comparison of best case ‘regularly vaccinated’ and worst case ‘irregularly vaccinated’ (Tables 1 and 2)).

3.4. Vaccine effectiveness after only two doses of the basic immunization schedule

As outlined in Section 2, the basic TBE vaccination scheme consists of two vaccinations about 1 month apart followed by a third vaccination after 9–12 months. Theoretically the degree of protection could be lower in the phase of several months between the second and third shot, when basic vaccination is not yet completed. We therefore evaluated our data for this specific group of TBE vaccinated people separately and the results are shown in Table 3A. In all of the years included in this study, there was not a single case of TBE within the first year after a documented history of two vaccinations, and the effectiveness of vaccination was therefore 100%. Even if one would generate a worst case scenario and include a proportionate number of those with unknown/undefined vaccination status into this group, the effectiveness would still be as high as 98.7% and therefore similar to that found in completely vaccinated persons (Table 3B).
3.5. Vaccine effectiveness after change of the intervals for booster vaccinations

In 2003, the Austrian Advisory Board for Vaccination issued a new recommendation to increase the interval for booster vaccinations after the fourth shot from 3 to 5 years, except for those older than 60 years, for whom it remained at 3 years. This recommendation became effective in 2004 and we therefore analyzed the years 2000–2003 and 2004–2006 separately to see whether this change had any effect on the protection rates in the different age groups of regularly vaccinated people. The data obtained (based on the ‘best case’ scenario, see Section 2) are summarized in Table 4. As revealed by statistical analysis, no significant difference in disease incidence was observed for any of the age groups before and after the change of recommendations for booster intervals.

3.6. Comparison of disease incidence in Austria and the Czech Republic and numbers of cases prevented by vaccination in Austria

Austria and the Czech Republic have in common excellent documentation systems for cases of TBE and – because of their geographic proximity – similar climatic conditions that are known to have a strong influence on the circulation of TBE virus in nature [37,38]. As shown in Fig. 2, the annual numbers of TBE cases in Austria have come down to about 10% compared to those recorded in the pre-vaccination era and the time when vaccination coverage was still low. In contrast, a significant increase has been documented in the Czech Republic in the same time period, with an all-time record of more than 1000 cases in 2006 (National Reference Centre of Epidemiology, Prague). The decrease of cases in Austria parallels the continuous increase in vacci-
Table 3
Incidence of TBE and field effectiveness (FE) of vaccination in people having received only two doses of the basic immunization schedule within the regular interval (Austria 2000–2006)

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>2 doses only of basic schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence/100,000</td>
</tr>
<tr>
<td>(A) ‘Best case’ with respect to vaccine effectiveness, i.e. TBE cases with unknown or undefined vaccination status were not considered to form part of the group</td>
<td></td>
</tr>
<tr>
<td>0–15</td>
<td>0.000</td>
</tr>
<tr>
<td>16–49</td>
<td>0.000</td>
</tr>
<tr>
<td>50–59</td>
<td>0.000</td>
</tr>
<tr>
<td>60+</td>
<td>0.000</td>
</tr>
<tr>
<td>Total</td>
<td>0.000</td>
</tr>
<tr>
<td>(B) ‘Worst case’ with respect to vaccine effectiveness, i.e. a proportionate number of TBE patients with unknown or undefined vaccination status was added to the group</td>
<td></td>
</tr>
<tr>
<td>0–15</td>
<td>0.014</td>
</tr>
<tr>
<td>16–49</td>
<td>0.187</td>
</tr>
<tr>
<td>50–59</td>
<td>0.050</td>
</tr>
<tr>
<td>60+</td>
<td>0.007</td>
</tr>
<tr>
<td>Total</td>
<td>0.079</td>
</tr>
</tbody>
</table>

Table 4
Comparison of the incidence of TBE in different age groups before and after change of booster intervals in Austria (2002–2003 and 2004–2006, respectively)

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>2000–2003</th>
<th>2004–2006</th>
<th>p-Value* (one-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence/100,000</td>
<td>FE</td>
<td>95% CI</td>
</tr>
<tr>
<td>0–15</td>
<td>0.026</td>
<td>98.0</td>
<td>81.56–99.39</td>
</tr>
<tr>
<td>16–49</td>
<td>0.000</td>
<td>100.0</td>
<td>99.76–100.00</td>
</tr>
<tr>
<td>50–59</td>
<td>0.023</td>
<td>99.5</td>
<td>97.57–99.75</td>
</tr>
<tr>
<td>60+</td>
<td>0.029</td>
<td>99.2</td>
<td>97.88–99.53</td>
</tr>
<tr>
<td>Total</td>
<td>0.013</td>
<td>99.6</td>
<td>99.26–99.78</td>
</tr>
</tbody>
</table>


4. Discussion

It was the objective of this study to evaluate the field effectiveness of TBE vaccination in Austria for the years 2000–2006 by making use of the documentation systems for clinical cases of TBE, their vaccination histories and the vaccination status of the Austrian population as determined by representative inquiries. When all age groups are included, our analysis reveals an overall effectiveness of about 99% in persons that had followed the recommended vaccination schedule, with a possible degree of variation from 98.7% (worst case) to 99.3% (best case). The worst case is a the-
respectively; Table 4) revealed that it did not cause a significant drop in vaccine protection and therefore was fully justified.

In the discussions on age-specific recommendations for vaccination intervals, the age limits are ill-defined and therefore taken relatively arbitrarily. In Austria, an age-specific recommendation was issued for those 60 years and older, based on studies that revealed decreased antibody responses in elderly adults after TBE vaccination [41], but also an age limit of 50 years was discussed. In our separate analysis of the group of 50–59-year-old people, we found neither significant differences in protection when compared to younger age groups (sharing the same extension of immunization intervals since 2004) nor to the 60 years old for whom the booster dose schedule remained unchanged (Table 4). Our data thus provide no evidence that would justify a modification of the recommended schedule at the age of 50.

An important conclusion of our study is that those who have only received two doses, and not yet completed the basic immunization schedule by a third vaccination, were protected in their first TBE season following the first two shots as good as those with a completed regimen. Not a single case of vaccination breakthrough was recorded in this group from 2000 to 2006 and even under ‘worst case’ assumptions protection would be as good as in those who already have completed their vaccination regime. A subgroup of these vaccinees (about 5% as revealed by representative inquiries conducted in 2004), received the first two vaccinations at a shorter interval of 8–16 days. Such a procedure is usually applied when protection is needed urgently, e.g. when people are about to leave for a vacation in an endemic region and therefore want to be protected as soon as possible. Consistent with previous reports [49], our data do not provide evidence for a lower degree of protection in this subgroup of vaccinees which is probably also due to the fact that TBE has a typical seasonal distribution and occurs only during the warmer months of the year [4]. Protection is therefore necessary for the limited period of time only in which exposure to TBE virus is possible.

Our study also shows that people with an irregular history of vaccination – i.e. outside the officially recommended schedule – have a significantly lower degree of protection than those within the regular scheme. The comparison of the disease incidence in the two different groups of ‘regularly vaccinated’ and ‘irregularly vaccinated’ persons (Tables 1 and 2) reveals that the likelihood to come down

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Unvaccinated cases</th>
<th>Regularly vaccinated</th>
<th>Irregularly vaccinated</th>
<th>Prevented by vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed cases</td>
<td>Expected cases</td>
<td>Observed cases</td>
<td>Expected cases</td>
</tr>
<tr>
<td>0–15</td>
<td>22</td>
<td>3</td>
<td>101</td>
<td>1</td>
</tr>
<tr>
<td>16–49</td>
<td>157</td>
<td>2</td>
<td>1132</td>
<td>11</td>
</tr>
<tr>
<td>50–59</td>
<td>71</td>
<td>3</td>
<td>327</td>
<td>3</td>
</tr>
<tr>
<td>60+</td>
<td>189</td>
<td>6</td>
<td>542</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>439</td>
<td>14</td>
<td>2102</td>
<td>27</td>
</tr>
</tbody>
</table>
with TBE is three- to eight-fold higher in those with an irregular vaccination schedule—depending on worst or best case assumptions. These data corroborate the value of adhering to regular booster vaccinations as recommended.

The increase of vaccination coverage in Austria is paralleled by a continuous decrease in disease incidence, whereas an increase is reported in neighbouring countries such as Germany [50], Switzerland [51], and especially the Czech Republic (Fig. 2), where an all time high of more than 1000 cases was recorded in 2006 (National Reference Centre of Epidemiology, Prague). The disease incidence in unvaccinated Austrians (ca. 6 per 100,000, see Table 1) and people in the Czech Republic (National Reference Centre of epidemiology, Prague), however is similar, consistent with the fact that the reduction of cases in Austria is indeed caused by the high vaccination coverage and not the disappearance of the virus from nature. The year 2006 was exceptional in the Czech Republic with a steep increase of disease incidence to about 10 per 100,000 because of an atypical seasonal distribution with a second peak in autumn that was even higher than that usually observed in early summer (National Reference Centre of epidemiology, Prague). Overall, our analysis clearly shows that the decline of TBE cases in Austria is a result of the exceptionally high vaccination coverage and that, by the effectiveness of this measure, about 2800 cases of neurological disease have been prevented from 2000 to 2006. This includes about 20 deaths, since the average lethality of TBE is about 0.7% in Austria (36 deaths from 5227 cases recorded from 1979 to 2006; previously unpublished data).

Acknowledgements

The authors are grateful for the excellent technical assistance of Silvia Röhne and Jutta Hutecek, to Karin Stiasny for figure design, and to Karin Stiasny and Christian Kunz for critically reading the manuscript (all at the Institute of Virology, Medical University of Vienna, Austria). We also thank Egon Marth and Elisabeth Daghofer (Institute of Hygiene, Medical University of Graz) as well as Manfred Dierich and Gernot Walder (Institute of Hygiene, Medical University of Innsbruck) for their expert contributions to the Austrian TBE surveillance network.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.vaccine.2007.08.024.

References


