

Original Article

Should travellers to rabies-endemic countries be pre-exposure vaccinated? An assessment of post-exposure prophylaxis and pre-exposure prophylaxis given to Danes travelling to rabies-endemic countries 2000–12

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Abstract

Background: Since 2000, a steady increase of vaccines used for both rabies Post-exposure prophylaxis (PEP) and rabies Pre-exposure prophylaxis (PrEP) given to Danish travellers was observed. This study aims to evaluate whether the increase of PEP and PrEP was due to increased travelling, increased awareness of the need for PrEP, or more animal bites per travel, leading to more PEP being administered, in order to assess the need for changing the recommendations. We also described in which countries Danish travelers most frequently reported possible exposure to rabies, and evaluated the timeliness of rabies PEP, including rabies immunoglobulin (RIG).

Methods: We included all Danes reported to the National Database for Rabies Treatment as having started rabies PEP either abroad or after returning to Denmark, between 2000 and 2012. Data on the yearly number of Danish travelers from 2004 to 2012 to Thailand were collected to calculate the incidence of animal bites at this destination. We also included data on rabies vaccines sold for PrEP or for booster vaccination in Denmark.

Results: PEP after possible exposure to rabies abroad increased yearly by 8.8 %. Likewise vaccines sold for PrEP increased by 8.2% annually. The number of Danish travelers to Thailand increased by 7.3% per year, resulting in a stable incidence of animal bites per 100,000 travelers. Seventy-five % started PEP in the country of exposure, while only 10 % received RIG.

Conclusions: The yearly increase in PEP and PrEP are parallel to the yearly increase in number of travelers, and can thus be explained by the increased rate of traveling, and not by a rise in awareness of rabies risk or more bites per traveler. Even short term travelers should be given the option of including PrEP in their travel immunisation program, as PEP and especially RIG is not always available in rabies-endemic countries.

Key words: Rabies, Postexposure prophylaxis, Rabies exposure

Introduction

Rabies infection is highly preventable with appropriate vaccination, given either as pre-exposure prophylaxis (PrEP) or as post-exposure prophylaxis (PEP). Recommendations for number of vaccines and route of vaccine administration used for PEP differs between countries,^{1–3} and rabies vaccines and rabies immunoglobulin (RIG) might not be available in all endemic areas.⁴

The Danish rabies prophylaxis³ follow WHO recommendations¹ and no human cases have been seen in Denmark for more than 45 years.

Travellers who have started PEP abroad complete the treatment after returning to Denmark. If PEP was not started abroad, the indication for PEP is discussed between the treating physician and the Department of Infectious Diseases Epidemiology at

The Statens Serum Institut (SSI), based on information regarding the circumstances of the exposure. PEP is free of charge for exposed patients.

PrEP is currently recommended to people with occupational risk of rabies exposure, and to people travelling for longer durations to rabies-endemic areas. Booster doses for people with occupational risk are given after serological testing, and otherwise boosters are not recommended unless exposed.

Since 2000, a steady increase of vaccines used for both rabies PEP and rabies PrEP given to Danish travellers has been observed.

Data on international travelling suggest a tripling of international travel from 1980 to 2011,⁵ and internationally there is evidence of an increased number of travellers treated with PEP after travelling to rabies-endemic countries.^{6,7}

The increase in travelling could possibly explain the increased use of PEP and PrEP, but there could hypothetically be other reasons, such as increased awareness of the need for PrEP, or more animal bites per travel, leading to more PEP being administered. If travellers to rabies-endemic countries have become increasingly aware of rabies risk, we would expect the yearly increase in the rate of PrEP sold to exceed the increase in the yearly number of travellers to rabies-endemic countries. If travellers to rabies-endemic countries were being increasingly exposed to rabies, we would expect the yearly increase in the number of travellers who received PEP (in the country of exposure and/or after returning to Denmark) to exceed the increase in the yearly number of travellers to rabies-endemic countries.

In Denmark, data on all returned travellers given PEP is entered into the National Database for Rabies Treatment at SSI. Vaccines sold for PrEP are also registered at SSI. The Danish data have a high degree of completeness, and, together with data on Danes travelling to rabies-endemic countries, can therefore add new information on the background for the increased use of PEP and PrEP.

The main objective of this study was to evaluate which factors contribute to the increase of PEP and PrEP. This knowledge can be used to assess the need for changing the recommendations for rabies prophylaxis for travellers.

We also aimed to describe in which countries Danish travellers most frequently reported possible exposure to rabies (referred to as 'exposure' in the rest of this article) and to evaluate the timeliness of rabies PEP, including RIG, given to Danish travellers.

Methods

We included all Danes reported to the national database for rabies PEP at SSI as having started rabies PEP either abroad or after returning to Denmark, between 2000 and 2012.

We used PEP as a proxy for being bitten by an animal in a rabies-endemic country.

Data on the yearly number of Danish travellers to Thailand from 2004 to 2012 were collected from the Tourism Authority of Thailand in Stockholm (personal correspondence Jan 2014) and used to calculate the yearly incidence of animal bites per 100 000 travellers, used as a proxy for possible exposure to rabies, associated with this particular destination. We assumed that the incidence of animal bites was similar to that of Thailand in other rabies-endemic countries.

We also included data on rabies vaccines sold for PrEP or for booster vaccination in Denmark. We excluded PrEP vaccines sold to the military.

We assumed that obtaining PrEP before travelling to a rabies-endemic country was a sign of awareness of rabies risk. To assess awareness, we therefore calculated the yearly number of vaccines used for PrEP.

The duration of each individual travel was not known. We assumed that most trips were of about a month's duration, so we could compare our results to that of other articles where duration of travel was included.

Yearly incidences were estimated using a Poisson regression.

Data were analysed using STATA 12.

Results

The number of Danish travellers who had received PEP after exposure increased steadily from 55 in 2000 to 156 in 2012 (Figure 1). This is an 8.8% yearly increase (95% CI [6.8–10.9]).

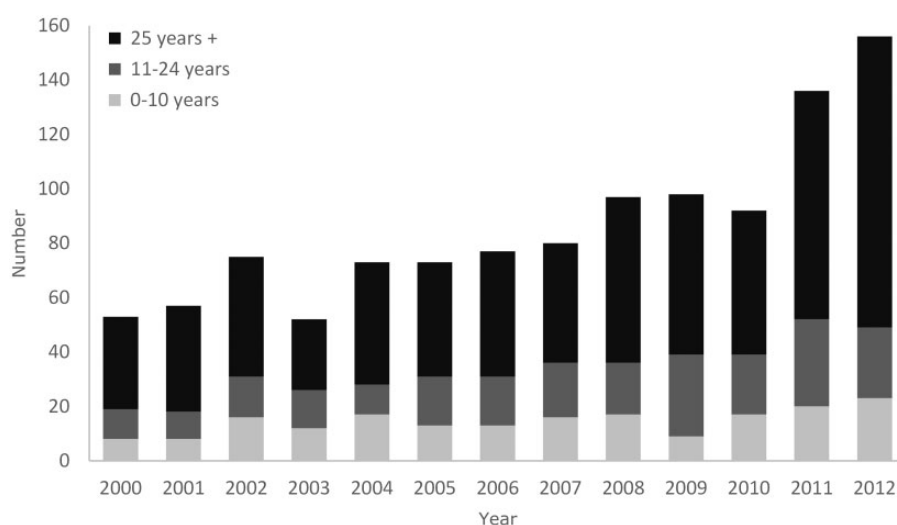
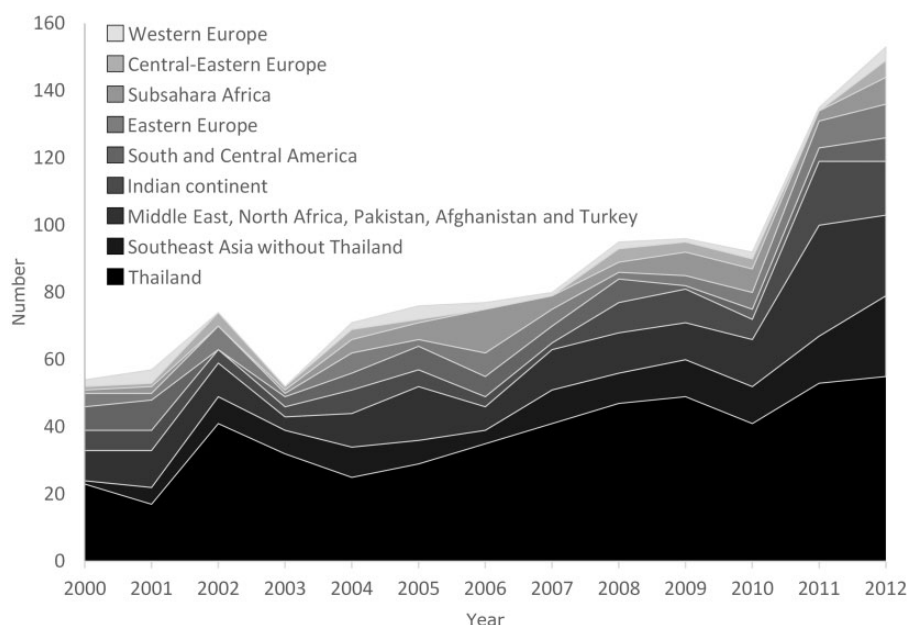


Figure 1. Danish travellers exposed to rabies abroad, divided by age groups and year of exposure, 2000–12

Table 1. Number (%) of Danes exposed to rabies abroad, who received any vaccine, in selected countries/regions of exposure or after return to Denmark, and all travellers possibly exposed, 2000–12

Country/region of exposure	Total number exposed	Number of persons (%) treated with vaccine given in country/region of exposure	Number of persons (%) initiation of PEP after return to Denmark
Thailand	488	418 (86%)	70 (14%)
Turkey	136	126 (93%)	10 (7%)
India	70	59 (84%)	11 (14%)
South East-Asia (except Thailand)	120	84 (70%)	36 (30%)
Central and East-Europe(including Russia)	88	46 (52%)	42 (48%)
South America	64	30 (47%)	34 (53%)
Sub-Sahara Africa	58	20 (34%)	38 (36%)
All travellers possibly exposed	1126	849 (75%)	277 (25%)

**Figure 2.** Continent of possible rabies exposure in Danish travellers, 2000–12

In total, 1126 persons were treated from 2000 to 2012, (Table 1). Among those 584 were female and 538 male; the gender was unknown for four persons. The age ranged between 1 and 87 years (median 29), and there were 189 (17%) children between 1 and 10 years.

South East Asia was the region where most Danish travellers were exposed (Figure 2). Thailand accounted for 488 (43%) of the cases, followed by Turkey and India with 137 (12%) and 70 (6%) exposures, respectively.

The majority, 848 (75%), started vaccination in the country of exposure. There was no significant increase in this proportion during the study period (Figure 3).

The highest percentages of Danish travellers starting PEP with vaccines in the country of exposure were in Turkey (93%) and Thailand (86%) (Table 1). In contrast, only 34% of Danish travellers started PEP with vaccines in African countries (Table 1).

Most of the 848 Danish travellers who started the vaccination course abroad were vaccinated in a timely manner; 93% were vaccinated within 2 days of exposure, 4% within 3–7 days, and 3% were vaccinated more than 7 days after exposure.

For 278 Danish travellers, PEP treatment was initiated after returning to Denmark, here the interval from the exposure to the first vaccine was within 1 week for 47%, 8–14 days for 21% and from 15 to 413 days for 31% of the travellers. Two persons had rabies PrEP vaccination. None of the travellers who received PEP subsequently acquired rabies.

Among all the travellers who were exposed, 116 (10%) got RIG abroad and 468 (42%) received RIG after returning to Denmark.

There has been a yearly increase of 7.7% (95% CI [2.5–13%]) in the number of travellers treated with RIG after exposure (data not shown) but the proportion of exposed travellers who received RIG has been constant.

The proportion who received RIG in the country of exposure varied from 3% in Sub-Saharan Africa and South America to 13% in South East Asian countries other than Thailand (Table 2).

There was information about seven animals that were examined for rabies, out of which four were positive.

By far the most common country of exposure was Thailand. Thailand was one of the few countries from which we could obtain reliable data on number of Danish visitors during the study

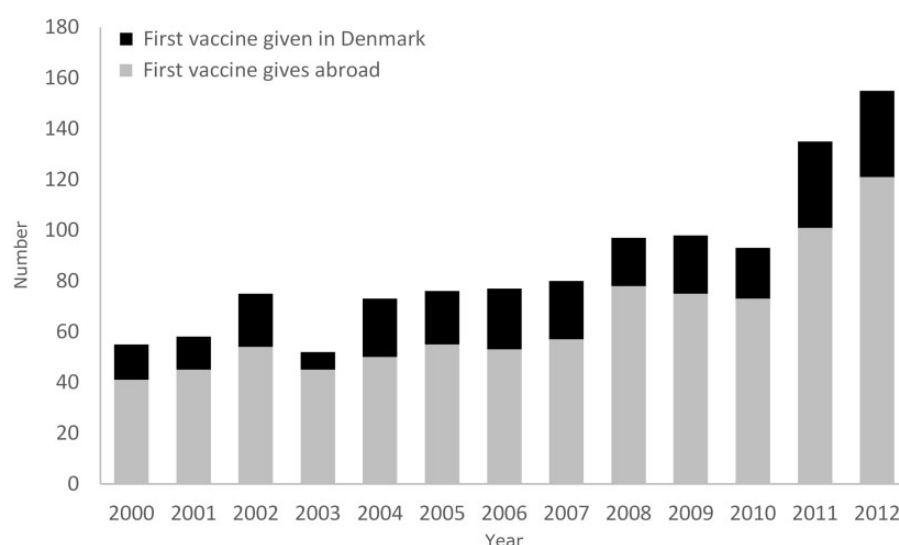


Figure 3. Number of Danish travellers possibly exposed to rabies abroad, who began PEP with vaccines in the country of exposure or after return to Denmark, 2000–12

Table 2. Number (%) of Danish travellers who received RIG in selected countries/regions of exposure or after return to Denmark, and all travellers possibly exposed, 2000–12

Country/region of exposure	Total number exposed	Number of persons (%) treated with RIG given in country/region of exposure	Number of persons (%) treated with RIG given in Denmark	Number of persons not treated with RIG (%)
Thailand	488	55 (11%)	158 (33%)	275 (56%)
Turkey	136	15 (11%)	54 (40%)	67 (49%)
India	70	7 (10%)	28 (40%)	35 (50%)
South East-Asia (except Thailand)	120	16 (13%)	47 (39%)	57 (48%)
Central and East-Europe(including Russia)	88	7 (8%)	57 (65%)	24 (27%)
South America	64	2 (3%)	39 (61%)	23 (36%)
Sub-Sahara Africa	58	2 (4%)	39 (67%)	17 (29%)
All travellers possibly exposed	1124 ^a	116 (10%)	468 (42%)	538 (48%)

^aIn addition to the 1124 exposed travellers two persons had PrEP.

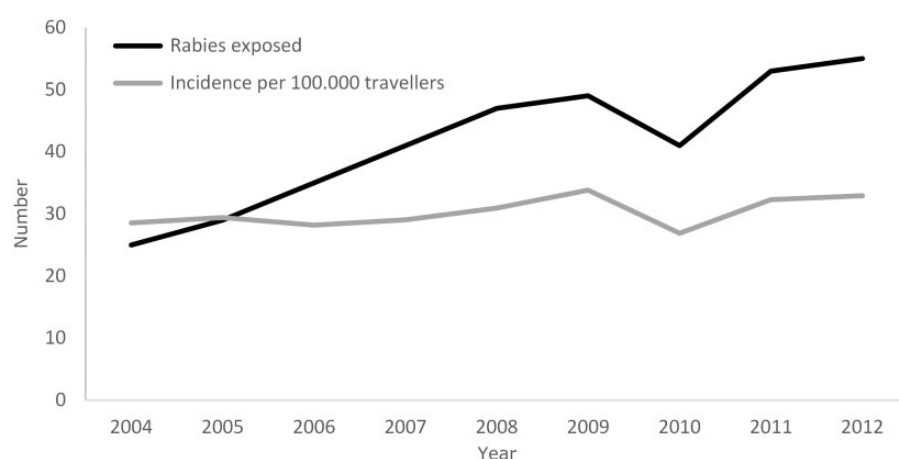


Figure 4. Number of Danish travellers possibly exposed to rabies in Thailand and the incidence of rabies exposure per 100 000 travellers, 2004–12

period. According to the Tourism Authority of Thailand in Stockholm, 1 231 767 Danes travelled to Thailand from 2004 to 2012. In this period, the yearly number of travellers increased on average by 7.3% per year. When using the yearly number of

Danish travellers to Thailand as denominator and number of Danish travellers receiving PEP after exposure in Thailand as numerator, the incidence per 100 000 travellers increased from 29 to 33, which is not statistically significant, (Figure 4).

The vaccines sold for PrEP increased 8.2% annually (95%CI [7.8–8.5]) from 1949 doses in 2000 to 3784 doses in 2012.

Discussion

The strength of this study is the completeness of the national data, both of PEP given and of PrEP sold.

Our study has several limitations. First, the true number of exposures cannot be known, especially since very few of the animals were tested. Second, we do not know how many travellers were bitten while abroad but did not seek medical advice. Third, our study does not include Danes who received the full vaccination course abroad nor travellers who have started PEP abroad but did not complete the vaccinations in Denmark. Fourth, a small proportion of the vaccines sold for other purposes than PEP are used as booster doses, e.g. for occupationally exposed individuals, thus exaggerating the number of PrEP given in our study. However, because only veterinarians and laboratory assistants working with bats or rabies virus are recommended rabies PrEP in Denmark, this proportion is very small, and not thought to have implications for our conclusions. Finally, we had no knowledge on the duration of travel for our study. However, we assumed that most tourists travel for a month or less at a time. Furthermore, it has been reported that more than one-half of exposures took place during the first 10 days of travel,⁸ and among 11 cases of human rabies with known travel-history, five were reported to have travelled ≤ 4 weeks or less.⁹ Therefore, we feel it is justified to calculate the incidence of possible exposure with 1 month as the time-denominator.

The yearly number of PEP treatments given to Danish travellers exposed to rabies abroad almost tripled from 2000 to 2012 with Thailand, Turkey and India as top-three destinations. A recent Dutch study¹⁰ showed that travelling as a tourist to South East Asia carried a higher risk of rabies exposure than travelling to other destinations. This is in line with our findings. Data on international travelling suggest a tripling of international travel from 1980 to 2011.⁵ Although we only have data on Danish travellers to Thailand during the study period, there is no reason to believe that the increase in number of travellers is different for other destinations. The number of PEP treatments given increased at the same rate as the increase in the number of Danish travellers. This suggests that the incidence of bites per travel did not increase.

The increase of vaccines sold for PrEP was also parallel to the increase in number of travellers, indicating that the awareness of rabies risk before travelling had not increased.

Since both the yearly increase in PEP and in PrEP are quite parallel to the yearly increase in number of travellers, we feel it is safe to assume that the increase can be explained by the increased rate of travelling, and not by a rise in awareness or a change in behaviour resulting in more bites per traveller.

Our estimated incidence of 29–33 possible exposures per 100 000 travellers in Thailand is in the low range of that of a large review from 2012.⁹ Here, the incidence of injuries caused by potentially rabid animals was calculated among 1.3 million individuals as 660 injuries per 100 000 tourists per month of stay in high endemic countries (range: 20–2310 per 100 000 travellers). Our estimates were also lower than in questionnaire studies that include travellers who were bitten but did not report

the injuries and/or did not receive PEP.^{11,12} Our study relies on travellers who not only were bitten by animals in a rabies-endemic country but also sought medical advice on the spot or after returning to Denmark. It has been shown that many travellers who are bitten do not seek care; a recent Japanese study showed that only two out of nine travellers who were bitten by a potentially rabid animal sought health care, and only one of the nine received PEP.¹³

A large proportion of the bites were probably sustained from non-rabid animals but it is impossible to know who of the bitten travellers were actually exposed. That travellers do get exposed to rabies is evidenced by several reports on travellers who died from rabies after returning from endemic countries.^{13–15}

RIG injection into wounds can be life saving.^{12,16,17} Failure of PEP is described in several instances.^{18,19} Even though there have been reports of substandard vaccines in use, e.g. in the Philippines,²⁰ most cases with fatal outcome despite PEP were cases where RIG was not given.

Only 10% of the Danish travellers received RIG in the country of exposure. It is possible that in a few instances the exposure was considered as minor scratches, thus assessed as a WHO Category II exposure, and therefore RIG was not given. However, in most instances where RIG was not given, it was probably because it was not available. The unavailability of RIG has been documented by a large number of authors.^{4,9,10,12,16,18} A web-based survey among professionals handling rabies prevention revealed that the major barriers to the availability of RIG were high cost and stock-outs.⁴ One review found that only 9% received RIG in the country of exposure,¹² which corresponds well with our findings. A Dutch study also demonstrated a marked lack of RIG administered in the country of exposure.¹⁰

The availability of RIG is probably not about to change in the near future, given the economic constraints most health care systems suffer in the developing countries.

Most of the travellers to Thailand, Turkey and India started PEP there but less than one-half of the bitten travellers to Sub-Saharan Africa and South American countries received any vaccine in the country of exposure. In spite of the low proportion of exposed travellers receiving PEP in these countries, no cases of travel related human rabies have been diagnosed in Denmark.

Although it is evident that the number needed to treat with PrEP is very high, it is impossible to predict which bites will transfer the virus, and once it is evident that rabies has been transmitted, there is no way back.²¹

In addition, many people who travel to rabies-endemic countries will probably travel again. The long-term risk of rabies exposure in the life cause of such a traveller should be taken into account. Furthermore, it seems that neither duration of travel nor outdoor activities are useful predictors of animal bites.^{9,10}

PrEP is expensive, but imparts long lasting immunity, no boosters are needed until the traveller is exposed, and—most importantly—RIG is not needed if they should be exposed in future. Furthermore, disruption to the travel plans, including expenses, are far greater if the traveller is unvaccinated and needs to go quickly to a facility where both vaccines and RIG can be administered than if only two booster vaccines are needed.

From the results of our study, we conclude that awareness of rabies risk has not changed in the Danish population of

travellers. During the study period, 25% of the travellers only initiated treatment after returning to Denmark, which indicates that knowledge of rabies risk after animal bites is not high enough. Other studies have shown different levels of knowledge in the populations. In a recent study from the Netherlands, knowledge of rabies was generally high; nevertheless, only 6% had gotten PrEP.¹⁰ In a study among foreign backpackers in Bangkok, having sought advice from travel clinic specialists or from friends was associated with a higher vaccination rate than having read about rabies in a book.²² Thus educating the traveller is very much up to the travel health specialist, as not all travellers seem to seek knowledge about risks at the travel destination on their own.

The recommendations for PrEP are mostly directed at long-term travellers and occupational risk.²³ However, in light of the increasing number of travellers to rabies-endemic countries, where RIG and sometimes even vaccines cannot be ensured, and because duration of travel is not a reliable predictor of animal bites, even short-term travellers should be given the option of including PrEP as part of their travel immunization program. Travellers should be educated to avoid animal exposures, and, if bitten, to seek medical care immediately.

Conflict of interest: None declared.

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