Rabies virus infection produces encephalitis that is nearly uniformly fatal. It is most commonly transmitted to humans via the bite of an infected animal. The disease causes 60,000 deaths per year in the developing world but remains a rare diagnosis in travellers. However, travellers frequently seek medical advice for animal bites or scratches, sometimes requiring rabies postexposure prophylaxis, which disrupts travel plans. Pre-exposure prophylaxis greatly facilitates postexposure prophylaxis measures. When postexposure prophylaxis is indicated, previously vaccinated people require only 2 doses of vaccine, whereas unvaccinated people require 4 or 5 doses of vaccine in addition to rabies immune globulin. The latter is often not easily available in the region where the injury occurs. In fact, only a small proportion of travellers receive rabies immune globulin with postexposure prophylaxis in the country of exposure. The Canadian Immunization Guide, produced by the National Advisory Committee on Immunization for the Public Health Agency of Canada, recommends pre-exposure prophylaxis for people at high risk of close contact with potentially rabid animals, including travellers to endemic areas with poor access to medical care and timely postexposure prophylaxis.

Two rabies vaccines are licensed in Canada: Imovax Rabies (Sanofi Pasteur), a human diploid cell vaccine, and RabAvert...
experienced a shortage of rabies vaccine in 2008–2009, stocks
response, were explained to travellers. Although Canada
and need for postvaccination serologic testing to verify
intradermal and intramuscular routes of administration. Fac-
sexposure rabies prophylaxis were offered the options of
characteristics of the proposed travel, such as destination, dura-
indication for pre-exposure rabies prophylaxis based on char-
administration. People who presented for pretravel assess-
staffed by nurses trained and experienced in intradermal
rabies prophylaxis was introduced by offering a weekly clinic
December 2008, intradermal vaccination for pre-exposure
years of
experience with intradermal pre-exposure rabies vaccination,
with 4 objectives: 1) to evaluate the impact of the introduction
of intradermal vaccine administration on the proportion of
travellers who accepted pre-exposure prophylaxis, 2) to docu-
menition the seroconversion rate among travellers who received
intradermal vaccination for pre-exposure prophylaxis, 3) to
describe and compare the characteristics of travellers who
received any pre-exposure prophylaxis to those who did not
and 4) to compare the characteristics of travellers who chose
intradermal delivery to those who received the vaccine
intramuscularly.

Methods

Setting and sources of data
The Clinique Santé-voyage de la Fondation du Centre hos-
pitalier de l’Université de Montréal is one of the largest
travel clinics in Quebec. It received about 20 000 visits per
year for pretravel assessment between 2007 and 2017. In
December 2008, intradermal vaccination for pre-exposure
rabies prophylaxis was implemented at the Clinique Santé-voyage de la Fondation du Centre hospitalier de l’Université de Montréal. We reviewed data from 6 years of experience with intradermal pre-exposure rabies vaccination, with 4 objectives: 1) to evaluate the impact of the introduction of intradermal vaccine administration on the proportion of travellers who accepted pre-exposure prophylaxis, 2) to document the seroconversion rate among travellers who received intradermal vaccination for pre-exposure prophylaxis, 3) to describe and compare the characteristics of travellers who received any pre-exposure prophylaxis to those who did not and 4) to compare the characteristics of travellers who chose intradermal delivery to those who received the vaccine intramuscularly.

Design
This was a retrospective cross-sectional study using data from
December 2008 through December 2014. We retrieved data
for all travellers who presented for pretravel assessment
from a computerized database, with only 1 pretravel assessment
included per traveller. Variables collected were age, sex,
receipt of any pre-exposure prophylaxis, type and route of
administration where applicable, country and continent of
travel, reason for travel, duration of travel, and whether travel
was alone, in a couple or in a group. We reviewed the number
of travellers who received any pre-exposure prophylaxis
for a 1-year period before implementation of intradermal
vaccination for pre-exposure rabies prophylaxis (December
2006 to December 2007) and compared it to the number of
travellers who received pre-exposure prophylaxis during the
study period.

Statistical analysis
To compare characteristics between travellers who received
and did not receive pre-exposure prophylaxis, and between
travellers who received intradermal injections and those who
received intramuscular injections, we expressed categorical
variables as frequencies and percentages, and continuous vari-
able features as means and standard deviations. We compared con-
tinuous and categorical variables using standardized differences
with 95% confidence intervals (CIs) for means and propor-
tions, respectively. We performed the analyses using Stata
version 14.2 (StataCorp). We performed univariate and multi-
ivariate analyses with logistic regression modelling using SPSS
version 20.

Ethics approval
The study was approved by the Centre hospitalier de l’Uni-
versité de Montréal.

Results
From December 2009 to December 2014, an average of
300 travellers were vaccinated annually (Figure 1). In compar-
ison, from December 2006 to December 2007 (before the
implementation of intradermal vaccination for pre-exposure
prophylaxis), 183 vaccine series were given. The number of
pretravel visits decreased from 24 022 in 2006–2007 to 14 336
in 2013–2014 (Figure 1).
A total of 37,032 people presented for pretravel assessment between December 2008 and December 2014. Of the 37,032, 1,721 (4.6%) received pre-exposure prophylaxis, and 35,311 (95.4%) did not. Of the 1,721 travellers who received pre-exposure prophylaxis, 941 (54.7%) received intradermal injections, and 780 (45.3%) received intramuscular injections.

Of the 941 people who received intradermal injections, 940 (99.9%) seroconverted, with an antibody titre greater than 0.5 IU/mL when measured 2–4 weeks after completion of the vaccine series. One traveller had not seroconverted by 2 weeks and could not be tested at 4 weeks to assess for delayed seroconversion because of imminent travel. A single booster dose was given intramuscularly to this person before travel.

Travellers who received pre-exposure prophylaxis were older than those who did not (mean age 35.8 yr v. 32.1 yr), although the effect size was small (standardized difference 0.205, 95% CI 0.156 to 0.253) (Table 1). There was no significant difference in sex between the 2 groups. Travellers who received pre-exposure prophylaxis had longer travel duration than those who did not (mean 16.7 wk v. 5.2 wk, standardized difference 0.944, 95% CI 0.893 to 0.996). Fewer vaccinated travellers than unvaccinated travellers had travel duration of less than 4 weeks (602/1560 [38.6%] v. 24,641/32,516 [75.8%]). Travellers to Asia were most likely to have received pre-exposure prophylaxis, and travellers to the Americas were least likely to have received pre-exposure prophylaxis (standardized difference 0.449, 95% CI 0.398 to 0.499). People travelling for work/business, education/research or volunteer/aid work were more likely to be vaccinated, and those visiting friends and relatives were less likely to be vaccinated, but the effect size was small (standardized difference 0.027, 95% CI −0.023 to 0.077). These results were confirmed on univariate and multivariate analyses (Table 2) with the exception of the finding that people travelling for work/business were more likely to be vaccinated than those travelling for other reasons, which did not reach statistical significance in multivariate analysis.

Travellers who received the vaccine intradermally were significantly younger than those with intramuscular delivery (mean age 34.6 yr v. 37.2 yr), although the effect size was small (standardized difference −0.171, 95% CI −0.266 to −0.076) (Table 3, Table 4). There was no significant difference in sex or mean duration of travel between the 2 groups in multivariate analysis. More travellers to Asia than to other continents received intradermal injections (standardized difference 0.274, 95% CI 0.174 to 0.373), but this difference was not significant in multivariate analysis. People travelling for work/business and volunteer/aid work more often received intramuscular vaccination, whereas those travelling for tourism more often received intradermal vaccination, with a small to medium effect size (standardized difference −0.361, 95% CI −0.264 to −0.067).

![Figure 1: Number of series of pre-exposure rabies prophylaxis vaccine administered, by type, and number of pretravel visits, 2006–2014. Note: ID = intradermal, IM = intramuscular.](image)
Table 1: Demographic and travel characteristics of people who presented for pretravel assessment between December 2008 and December 2014, according to pre-exposure rabies prophylaxis coverage

| Characteristic                           | Pre-exposure prophylaxis | No pre-exposure prophylaxis | Standardized difference (95% CI) |
|------------------------------------------|--------------------------|-----------------------------|----------------------------------|
| **No. of travellers (% of category)**    | n = 1721                 | n = 35 311                  |                                  |
| **Age, mean ± SD; yr**                   | 35.77 ± 15.14            | 32.07 ± 18.20               | 0.205 (0.156 to 0.253)           |
| **Age, yr**                              |                          |                             | 0.190 (0.142 to 0.238)           |
| < 18                                     | 94 (1.5)                 | 6286 (98.5)                 |                                  |
| 18–40                                    | 1044 (5.3)               | 18 673 (94.7)               |                                  |
| 41–60                                    | 470 (5.9)                | 7502 (94.1)                 |                                  |
| > 60                                     | 113 (3.8)                | 2835 (96.2)                 |                                  |
| Missing                                  | 0 (0.0)                  | 15 (0.04)                   |                                  |
| **Sex**                                  |                          |                             | –0.023 (–0.071 to 0.026)         |
| Female                                   | 941 (4.7)                | 18 898 (95.2)               |                                  |
| Male                                     | 780 (4.5)                | 16 392 (95.4)               |                                  |
| Missing                                  | 0 (0.0)                  | 21 (0.1)                    |                                  |
| **Travel duration, mean ± SD; wk**       | 16.67 ± 22.81            | 5.18 ± 11.41                | 0.944 (0.893 to 0.996)           |
| Travel duration, wk                      |                          |                             | 1.118 (1.066 to 1.169)           |
| ≤ 4                                      | 602 (2.4)                | 24 641 (97.6)               |                                  |
| 5–12                                     | 385 (6.8)                | 5261 (93.2)                 |                                  |
| 13–24                                    | 253 (14.2)               | 1525 (85.8)                 |                                  |
| 25–52                                    | 248 (21.7)               | 894 (78.3)                  |                                  |
| > 52                                     | 72 (27.0)                | 195 (73.0)                  |                                  |
| Missing                                  | 161 (9.4)                | 2795 (79)                   |                                  |
| **Continent**                            |                          |                             | 0.449 (0.398 to 0.499)           |
| Africa                                   | 274 (3.9)                | 6684 (96.1)                 |                                  |
| Americas                                 | 328 (2.0)                | 15 696 (98.0)               |                                  |
| Asia                                     | 981 (8.9)                | 10 041 (91.1)               |                                  |
| Europe                                   | 14 (3.2)                 | 428 (96.8)                  |                                  |
| Missing                                  | 124 (7.2)                | 2462 (7.0)                  |                                  |
| **Reason for travel**                    |                          |                             | 0.027 (–0.023 to 0.077)          |
| Tourism                                  | 1103 (4.2)               | 25 391 (95.8)               |                                  |
| Work/business                             | 183 (6.4)                | 2665 (93.6)                 |                                  |
| Education/research                       | 56 (5.5)                 | 964 (94.5)                  |                                  |
| Volunteer/aid work                       | 255 (10.1)               | 2268 (89.9)                 |                                  |
| Visiting friends and relatives           | 2 (0.2)                  | 992 (99.8)                  |                                  |
| Adoption                                 | 0 (0.0)                  | 93 (100.0)                  |                                  |
| Missing                                  | 122 (7.1)                | 2938 (8.3)                  |                                  |
| **No. of travellers in group**           |                          |                             | 0.092 (0.041 to 0.142)           |
| 1                                        | 412 (7.4)                | 5158 (92.6)                 |                                  |
| 2                                        | 636 (5.1)                | 11 828 (94.9)               |                                  |
| ≥ 3                                      | 552 (3.4)                | 15 763 (96.6)               |                                  |
| Missing                                  | 121 (7.0)                | 2562 (7.2)                  |                                  |

Note: CI = confidence interval, SD = standard deviation.
*Except where noted otherwise.
Overall, a small proportion (4.6%) of travellers seen at our travel clinic received pre-exposure rabies prophylaxis, even among travellers to highly endemic areas where proper post-exposure prophylaxis is often difficult to obtain. The proportion of travellers who received pre-exposure rabies prophylaxis increased substantially after the introduction of intradermal vaccination. During the study period, the number of visits decreased, anecdotally attributed to the worldwide economic recession at the time. Another potential explanation for the decrease is the increasing number of competing private pretravel clinics. The seroconversion rate among travellers who received intradermal vaccination was 99.9%, in keeping with previously reported rates (above 95%). No serious adverse events related to vaccination were reported to the clinic, although there was no active surveillance for such complications. Travellers who received pre-exposure prophylaxis were older and had longer travel duration than travellers who did not receive pre-exposure prophylaxis, presumably owing to the increased perception of risk in these groups; financial resources may also have been a factor. Travellers to Asia were more likely to receive pre-exposure prophylaxis. Travellers visiting friends and relatives were infrequently vaccinated. Travellers who chose to receive the vaccine intradermally were younger than those who received it intramuscularly and were more likely to be travelling for tourism.

The observed low rate of pretravel vaccination is consistent with other studies. Factors contributing to the low uptake of pre-exposure prophylaxis reported in the literature include low perception of benefit, concern about adverse reactions and belief that vaccination is not necessary, but the main barrier to vaccination cited by travellers was cost. Recognized risk factors for animal-associated rabies exposure in travellers include travel to Southeast Asia, India and North Africa, young age and travelling for tourism. Many cases of rabies exposure have occurred early on in the travel period in the setting of short travel duration. However, Dolan and colleagues reported that travellers seeking pre-travel vaccination were more likely to be travelling for longer periods. In our study, younger people were less likely to receive pre-exposure prophylaxis. They were more likely to receive intradermal than intramuscular vaccination.

### Table 2: Univariate and multivariate analyses of demographic and travel characteristics of travellers who received pre-exposure rabies prophylaxis compared to those who did not

| Variable                              | Univariate analysis | Multivariate analysis |
|---------------------------------------|---------------------|-----------------------|
| Age, per year of age                  | 1.011 (1.008 to 1.014) | 1.015 (1.012 to 1.018) |
| Female sex                            | 1.046 (0.950 to 1.153) | 1.082 (0.969 to 1.209) |
| Travel duration, per week of travel   | 1.032 (1.030 to 1.035) | 1.028 (1.026 to 1.031) |
| Continent                             |                     |                       |
| Africa                                | 1.000               | 1.000                 |
| Americas                              | 0.510 (0.433 to 0.600) | 0.613 (0.512 to 0.734) |
| Asia                                  | 2.383 (2.077 to 2.734) | 3.029 (2.585 to 3.549) |
| Europe                                | 0.798 (0.462 to 1.377) | 0.867 (0.487 to 1.542) |
| Reason for travel                     |                     |                       |
| Tourism                               | 1.000               | 1.000                 |
| Work/business                         | 1.581 (1.345 to 1.858) | 1.061 (0.877 to 1.282) |
| Education/research                    | 1.337 (1.015 to 1.762) | 1.386 (1.015 to 1.894) |
| Volunteer/aid work                    | 2.588 (2.244 to 2.986) | 3.906 (3.263 to 4.675) |
| Adoption*                             | --                  | --                    |
| Visiting friends and relatives        | 0.046 (0.120 to 0.186) | 0.030 (0.004 to 0.213) |
| No. of travellers in group            |                     |                       |
| 1                                     | 1.000               | 1.000                 |
| 2                                     | 0.673 (0.592 to 0.765) | 0.994 (0.857 to 1.153) |
| ≥3                                    | 0.438 (0.384 to 0.500) | 0.641 (0.552 to 0.745) |

Note: CI = confidence interval, OR = odds ratio.

*No person travelling for adoption received pre-exposure rabies prophylaxis.
| Variable                        | Route: no. of travellers (% of category)* | Standardized difference (95% CI) |
|--------------------------------|------------------------------------------|----------------------------------|
|                                | Intradermal n = 941                      | Intramuscular n = 780            |                                  |
| Age, mean ± SD; yr             | 34.60 ± 15.15                            | 37.18 ± 15.02                   | −0.171 (−0.266 to −0.076)       |
| Age, yr                        |                                          |                                  | −0.121 (−0.216 to −0.026)       |
| < 18                           | 60 (63.8)                                | 34 (36.2)                       |                                  |
| 18–40                          | 581 (55.6)                               | 463 (44.3)                      |                                  |
| 41–60                          | 246 (52.3)                               | 224 (47.6)                      |                                  |
| > 60                           | 54 (47.8)                                | 59 (52.2)                       |                                  |
| Sex                            |                                          |                                  | −0.097 (−0.191 to −0.002)       |
| Female                         | 535 (56.8)                               | 406 (43.1)                      |                                  |
| Male                           | 406 (52.0)                               | 374 (47.9)                      |                                  |
| Travel duration, mean ± SD; wk | 16.85 ± 19.70                            | 16.44 ± 26.20                   | 0.018 (−0.082 to 0.117)         |
| Travel duration, wk            |                                          |                                  | 0.153 (0.053 to 0.253)          |
| ≤ 4                            | 302 (50.2)                               | 300 (49.8)                      |                                  |
| 5–12                           | 208 (54.0)                               | 177 (46.0)                      |                                  |
| 13–24                          | 169 (66.8)                               | 84 (33.2)                       |                                  |
| 25–52                          | 156 (62.9)                               | 92 (37.1)                       |                                  |
| > 52                           | 32 (44.4)                                | 40 (55.6)                       |                                  |
| Missing                        | 74 (79)                                  | 87 (11.2)                       |                                  |
| Continent                      |                                          |                                  | 0.274 (0.174 to 0.373)          |
| Africa                         | 129 (47.1)                               | 145 (52.9)                      |                                  |
| Americas                       | 145 (44.2)                               | 183 (55.8)                      |                                  |
| Asia                           | 610 (62.2)                               | 371 (37.8)                      |                                  |
| Europe                         | 6 (42.8)                                 | 8 (57.1)                        |                                  |
| Missing                        | 51 (5.4)                                 | 73 (9.4)                        |                                  |
| Reason for travel              |                                          |                                  | −0.361 (−0.460 to −0.262)       |
| Tourism                        | 696 (63.1)                               | 407 (36.9)                      |                                  |
| Work/business                   | 40 (21.8)                                | 143 (78.1)                      |                                  |
| Education/research             | 38 (67.8)                                | 18 (32.1)                       |                                  |
| Volunteer/aid work             | 101 (39.6)                               | 154 (60.4)                      |                                  |
| Visiting friends and relatives | 0 (0.0)                                  | 2 (100.0)                       |                                  |
| Missing                        | 66 (7.0)                                 | 56 (7.2)                        |                                  |
| No. of travellers in group     |                                          |                                  | −0.166 (−0.264 to −0.067)       |
| 1                              | 212 (51.4)                               | 200 (48.5)                      |                                  |
| 2                              | 388 (61.0)                               | 248 (39.0)                      |                                  |
| ≥ 3                            | 285 (51.6)                               | 267 (48.4)                      |                                  |
| Missing                        | 56 (6.0)                                 | 65 (8.3)                        |                                  |

Note: CI = confidence interval, SD = standard deviation.
*Except where noted otherwise.
confirmed rabies cases among travellers reveals that the population of travellers visiting friends and relatives is at heightened risk.15,16 This confirms previously described problems with acceptance of preventive measures in this group, despite attendance at a travel clinic.17 Tourists, another at-risk group, were also more likely to receive intradermal vaccination in our study. Those travelling for work/business and volunteer/aid work more often received intramuscular vaccination, possibly because vaccine-related costs were frequently assumed by third parties. Our results support the hypothesis that the reduced cost associated with intradermal vaccination for pre-exposure rabies prophylaxis may allow vaccination of younger travellers and tourists, 2 groups known to be at heightened risk for rabies exposure.

Strengths and limitations
A strength of our study is the large number of cases from a single clinic analyzed, which minimized the problem of demographic variability. Limitations include its retrospective nature and absence of information on the reasons for not receiving pre-exposure prophylaxis (e.g., prior immunity, vaccination not indicated, patient preference, medical contraindication or insufficient time before travel). Other covariates of interest that were not available included occupation, income level, comorbidities (e.g., immunocompromising conditions), previous travel to rabies-endemic countries and type of destination (rural v. urban). However, our study included several covariates, such as age, reason for travel, duration and destination of travel, that are recognized as key factors in rabies vaccination uptake.

Conclusion
We found an increase in rates of pre-exposure rabies prophylaxis after the implementation of intradermal vaccination at a large travel clinic. Provision of a weekly clinic where many travellers can be vaccinated by trained nurses during a 6-hour period has provided a lower-cost alternative for pre-exposure prophylaxis in our setting. Moreover, intradermal injection appeared to improve the acceptance of pre-exposure prophylaxis among younger travellers and those travelling for tourism, possibly because of reduced cost. With a seroconversion rate of 99.9% in our series, intradermal vaccination for pre-exposure prophylaxis is a reliable alternative to intramuscular vaccination. Its use should continue to be promoted in an attempt to increase pre-exposure rabies prophylaxis coverage among at-risk travellers.

Table 4: Univariate and multivariate analyses of demographic and travel characteristics of travellers who received intradermal vaccination compared to those who received intramuscular vaccination

| Variable                        | OR (95% CI) | Univariate analysis | Multivariate analysis |
|---------------------------------|-------------|---------------------|-----------------------|
| Age, per year of age            | 0.989 (0.983 to 0.995) | 0.986 (0.979 to 0.993) |
| Female sex                      | 1.214 (1.003 to 1.469) | 1.069 (0.857 to 1.577) |
| Travel duration, per week of travel | 1.001 (0.996 to 1.005) | 1.004 (0.999 to 1.009) |
| Continent                       | 1.00        | 1.00                |
| Africa                          | 0.891 (0.645 to 1.229) | 0.834 (0.584 to 1.193) |
| Americas                        | 1.848 (1.411 to 2.421) | 1.258 (0.907 to 1.743) |
| Asia                            | 0.843 (0.285 to 2.494) | 0.396 (0.123 to 1.274) |
| Europe                          | 1.00        | 1.00                |
| Reason for travel               | 1.00        | 1.00                |
| Tourism                         | 1.00        | 1.00                |
| Work/business                    | 0.164 (0.113 to 0.237) | 0.185 (0.123 to 0.279) |
| Education/research              | 1.235 (0.695 to 2.192) | 0.909 (0.496 to 1.663) |
| Volunteer/aid work              | 0.384 (0.290 to 0.507) | 0.444 (0.313 to 0.629) |
| Visiting friends and relatives* | --          | --                  |
| No. of travellers in group      |             |                    |
| 1                               | 1.00        | 1.00                |
| 2                               | 1.476 (1.149 to 1.896) | 1.183 (0.887 to 1.577) |
| ≥ 3                             | 1.007 (0.780 to 1.300) | 1.281 (0.953 to 1.723) |

Note: CI = confidence interval, OR = odds ratio.
*Only 2 people in this category received pre-exposure prophylaxis, both intramuscularly.
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