# Intradermal Pre-Exposure Rabies Vaccination: A Six-Year Retrospective Observational Study in a Canadian Travel Clinic

Kong, Ling Yuan, M.D.[1], Vincelette, Jean, M.D.[2,3], Laplante, Gaétan, M.D.[2], Hudon Duchesne, Jo-Anne[2], Michael, Libman, M.D.[1], Barkati, Sapha M.D.[1,2,3]

1. J.D. MacLean Centre for Tropical Diseases, McGill University Health Centre
2. Clinique Santé-voyage de la Fondation du CHUM
3. Centre Hospitalier de l'Université de Montréal (CHUM)

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Corresponding author:

Sapha Barkati

Department of Medical Microbiology and Infectious Diseases

Centre Hospitalier de l'Université de Montréal

1051, Sanguinet Street

Montreal, Quebec, Canada H2X 0C1

Tel: (514) 890-8000

Fax: (514) 412-7412

Email: sapha.barkati.chum@ssss.gouv.qc.ca

## Abstract

### Background

Few travelers receive rabies pre-exposure prophylaxis (PrEP) with vaccination. The intradermal (ID) route for rabies vaccination is endorsed by the Canadian National Advisory Committee on Immunization, and was implemented at a large travel clinic in 2008. We evaluated the effect of ID vaccine availability on PrEP uptake and rates of seroconversion with ID vaccination.

### Methods

A retrospective, observational study using data from December 2008 to December 2014 was conducted. The proportions of travelers receiving PrEP during a one-year period prior to ID PrEP introduction was compared with PrEP given during the study period. Post-vaccination antibody titers were measured for ID PrEP recipients. Demographic and travel characteristics were compared between vaccinated and unvaccinated travelers, and travelers choosing ID and IM PrEP, using univariate and multivariate analyses.

### Results

The proportion of travelers receiving PrEP increased after ID PrEP introduction. Seroconversion occurred in 99.9% of ID PrEP recipients. Travelers receiving PrEP were older and had longer travel duration compared to those not receiving PrEP. Travelers to Asia were more likely to receive PrEP, but those visiting friends and relatives were less likely to be vaccinated. Travelers choosing ID PrEP were younger than those receiving IM PrEP, and were more likely to be traveling for tourism.

**Interpretation**

Introduction of ID PrEP was associated with an increase in vaccination rates. Reduced cost may be responsible for the increased coverage among young travelers and tourists. Seroconversion rate after ID vaccination was 99.9%, supporting ID PrEP effectiveness in immunocompetent travelers.

## Introduction

Rabies virus infection produces a nearly uniformly fatal encephalitis, and 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 travelers[1]. However, travelers frequently seek medical advice for animal bites or scratches, sometimes requiring rabies post-exposure prophylaxis (PEP), resulting in disruption of travel plans[2]. PrEP greatly facilitates PEP measures[3]. When PEP is indicated, previously immunized individuals require only two doses of vaccine, while unimmunized individuals require four to five doses of vaccine in addition to rabies immune globulin (RIG). The latter is often not easily available in the region where the injury occurs[3]. In fact, only a small proportion of travelers receive RIG with post-exposure prophylaxis in the country of exposure[4]. The Canadian Immunization Guide produced by the National Advisory Committee on Immunization (NACI) for the Public Health Agency of Canada recommends PrEP for people at high risk of close contact with potentially rabid animals, including travelers to endemic areas with poor access to medical care and timely PEP[3]. Two rabies vaccine preparations are licensed in Canada: IMOVAX Rabies, the human diploid cell vaccine (HDCV); and RabAvert, the purified chick embryo cell rabies vaccine (PCECV)[3]. Both are inactivated virus vaccines and are only available as 1.0 ml intramuscular (IM) doses. However, ID administration of these vaccines requires only 0.1 ml per dose, thus reducing cost by increasing the number of doses available from a single vial. At our clinic, ID vaccination cost to the traveler was approximately half that of IM. ID vaccination for PrEP has been demonstrated to be safe and immunogenic in immunocompetent individuals[5-8], and is endorsed by NACI for use in PrEP[3]. It is recommended that ID vaccine should only be administered by trained staff,

that a single vial be used within a 6-hour period after opening, that the cold chain should always be preserved, and that post-immunization antibody titres should be determined at least two weeks after completion of the vaccine series[3]. Vaccine costs can be minimized by grouping vaccinee appointment, and using needles and syringes with low "dead space" and consequent vaccine wastage.

In December 2008, ID PrEP was implemented at the Clinique Santé-Voyageur de la Fondation du Centre Universitaire de l'Université de Montréal (CHUM). We reviewed data from six years of experience with ID PrEP from 2008 to 2014, with four objectives. Firstly, we evaluated the impact of ID PrEP introduction on the proportion of travelers accepting PrEP. Second, we documented the seroconversion rate among travelers receiving ID PrEP in our clinic. Third, we described and compared the characteristics of travelers who received PrEP to those who did not. Finally, we compared the characteristics of travelers who chose ID PrEP to those who received IM PrEP.

## Methods

The Clinique Santé-voyage de la Fondation du CHUM is one of the largest travel clinics in the province of Quebec and received approximately 20 000 visits per year for pre-travel assessment over the last 10 years. In December 2008, ID PrEP was introduced by offering a weekly clinic, staffed by nurses trained and experienced in intradermal administration. Patients presenting for pre-travel assessment with an indication for rabies PrEP were offered the options of ID and IM routes. Factors associated with ID vaccination, such as decreased cost, potential increased local injection reaction, and need to do post-vaccination serology to verify response, were explained to the patients. Although Canada experienced a shortage of rabies vaccine during 2008-2009, stocks were sufficient to continue offering a free choice or IM or ID administration. All vaccines were given on days 0, 7, and 21 or 28. Groups of three or more patients were booked per intradermal vaccination clinic to minimize vaccine wastage. Post-vaccination antibody titers were measured two to four weeks after the last dose for all recipients. Serum samples were sent to the National Microbiology Laboratory (NML) and tested for rabies antibody levels using a modified Fluorescent Antibody Virus Neutralization (FAVN) assay. An adequate response after vaccination was defined as $\geq 0.5$ IU/ml.

A retrospective, observational study was conducted using data from December 2008 through December 2014. Data on all travelers presenting for pre-travel assessment were retrieved from a computerized database, with only one pre-travel assessment included per traveler. Variables collected were age, gender, receipt of PrEP, 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. The number of travelers receiving PrEP was reviewed for a one-year period prior to implementation of ID PrEP (December 2006 to December 2007) and compared with the number of travelers vaccinated during the study period.

To compare traveler characteristics between non-vaccinated patients and vaccinated patients, and between patients receiving ID PrEP and patients receiving IM PrEP, categorical variables were expressed in frequencies and percentages and compared using a chi-square test. Continuous variables were expressed as means and standard deviations and compared using ANOVA. Univariate and multivariate analyses were performed. Statistical analyses were carried out using SPSS version 20.

## Results

The implementation of ID PrEP in December 2008 was followed by a shortage of rabies vaccine in 2008-2009. From December 2009 to December 2014, an average of 300 travelers were vaccinated annually (Figure 1). In comparison, from December 2006 to December 2007, prior to the implementation of ID PrEP, only 183 vaccine series were given. The number of pre-travel visits decreased from 24022 to 14336 from 2006 to 2014 (figure 1).

Of the 941 recipients of ID PrEP, 940 (99.9%) seroconverted with an antibody titer above 0.5 IU/ml when measured two to four weeks after completion of the vaccine series. One single traveler did not seroconvert at two weeks and could not be tested at four weeks to assess for delayed seroconversion because of imminent travel. A single booster IM dose was given to this patient.

Examining data from December 2008 to December 2014, a total of 37032 travelers presented for pre-travel assessment during the study period (Figure 2). A total of 1721 (4.6%) travelers received PrEP, while 35311 (95.4%) did not. Among those who received PrEP, 941 (54.7%) received ID PrEP, while 780 (45.3%) received IM PrEP. In particular, among travelers to Asia and Africa, 8.9% and 3.9% respectively received PrEP.

Comparing travelers receiving PrEP with those not receiving PrEP (Table 1), we found that travelers receiving PrEP were older with 94.6% of PrEP recipients being over 18, compared to 82.2% in those not receiving PrEP. There was no significant difference between genders.

Travelers receiving PrEP had longer travel duration compared to the non-vaccinated group (mean duration of 16.7 weeks versus 5.2 weeks), and a lower proportion of vaccinated travelers had travel duration of less than four weeks (38.6% versus 75.8%). Travelers to Asia were most likely to be vaccinated, whereas travelers to the Americas were least likely. Vaccinated travelers more often were traveling for work/business, education/research or volunteer/aid work, while travelers visiting friends and relatives (VFR) were less likely to be vaccinated. Those traveling in groups were more frequently unvaccinated. These results were confirmed on univariate and multivariate analyses (Table 2), with the exception of the finding that those traveling for work/business were more likely to be vaccinated, which did not reach statistical significance in multivariate analysis.

When comparing travelers receiving ID PrEP versus IM PrEP (Tables 3 and 4), those receiving ID PrEP were younger with a mean age of 34.6 years compared to 37.2 years in the IM PrEP group. There was no significant difference between genders or mean duration of travel between the two groups on multivariate analyses. More travelers to Asia received ID PrEP, but this was not statistically significant in multivariate analyses. Those traveling for business and volunteer/aid work more often received IM PrEP, whereas those traveling for tourism more often received ID PrEP.

## Interpretation

Overall, few travelers (4.6%) seen at our travel clinic received PrEP, even among travelers to highly endemic areas where proper post exposure prophylaxis is often difficult to obtain. The proportion of travelers receiving a series of rabies vaccine administered increased substantially after introduction of ID PrEP, although the number of patient visits decreased during this period, anecdotally attributed to the worldwide economic recession at the time.

The low rate of pre-travel vaccination is consistent with other studies[9,10] despite that most travelers do not receive optimal prophylaxis including RIG after exposure to a potentially rabid animal[4] . The main barrier cited by travelers against vaccination was cost[9]. As such, ID PrEP has been endorsed as an alternative to IM PrEP that is less costly, while still being immunogenic and safe[11,12].

The seroconversion rate of travelers receiving ID PrEP was 99.9%. Seroconversion rates have previously been shown to be above 95%[13], and our six-year experience confirms this. No significant adverse events related to vaccination were reported to the clinic, although there was no active surveillance for such complications.

Travelers receiving PrEP were older and had longer travel duration, presumably due to the increased perception of risk in these groups, and perhaps financial resources. Travelers to Asia were more likely to receive PrEP. VFR travelers were infrequently vaccinated. Review of confirmed rabies cases among travelers reveals that the VFR population is at heightened risk[14,15].

This confirms previously described problems with the acceptance of preventive measures in this group, despite attendance at a travel clinic. [16] Travelers choosing to receive ID PrEP were younger than those receiving IM PrEP, and were more likely to be traveling for tourism.

Recognized risk factors for animal-associated rabies exposures in travelers include travel to Southeast Asia, India, and North Africa, young age, and traveling for tourism[14]. Many rabies exposures occurred in the setting of short travel duration and early on in travel[1,14]. However, travelers seeking pre-travel vaccination were more likely to be traveling for longer durations[10]. In our study, younger patients were less likely to receive PrEP overall. However, they were more likely to receive ID PrEP than IM PrEP, Tourists, another at-risk group, were also more likely to receive ID PrEP. Those traveling for business and volunteer/aid work more often received IM PrEP, possibly because vaccine-related costs were often assumed by third parties. Our results support the hypothesis that the reduced cost associated with ID PrEP may allow vaccination of younger travelers and tourists, two groups known to be at heightened risk for rabies exposure.

Some limitations of our study include its retrospective nature and absence of information on the reasons for not administering PrEP (e.g. prior immunity, vaccine not indicated, patient preference, medical contraindication, or insufficient time prior to travel).

A strength of the study is the large number of travelers analyzed from a single clinic, minimizing the problem of demographic variablility. No previous study has compared travelers choosing ID versus IM PrEP.

In conclusion, we present our six-year experience with ID PrEP at the Clinique Santé-voyage de la Fondation du CHUM and demonstrate an increase in rabies PrEP vaccine rates given after its implementation. Provision of a weekly clinic where many travelers can be vaccinated during a six-hour period by trained nurses has provided a lower cost alternative for PrEP in our setting. Moreover, ID PrEP appeared to improve PrEP acceptance among younger traveler and those traveling for tourism, possibly because of reduced cost. With a seroconversion rate of 99.9% in our series, ID PrEP is reliable alternative IM PrEP. Promotion of its use should be continued in an attempt to increase PrEP coverage among at-risk travelers.

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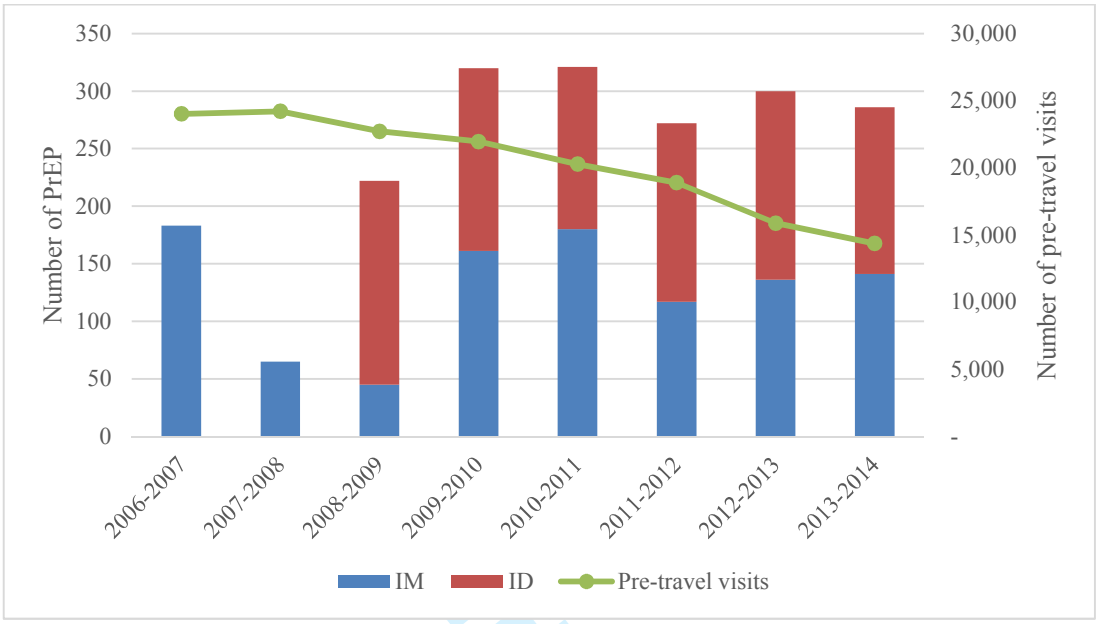
Figure 1. Number of rabies pre-exposure prophylaxis administered, by type, and number of pre-travel visits by year, from 2006-2014




IM: Intramuscular

ID: Intradermal

Figure 2. Study population distribution according to PrEP and route of administration.

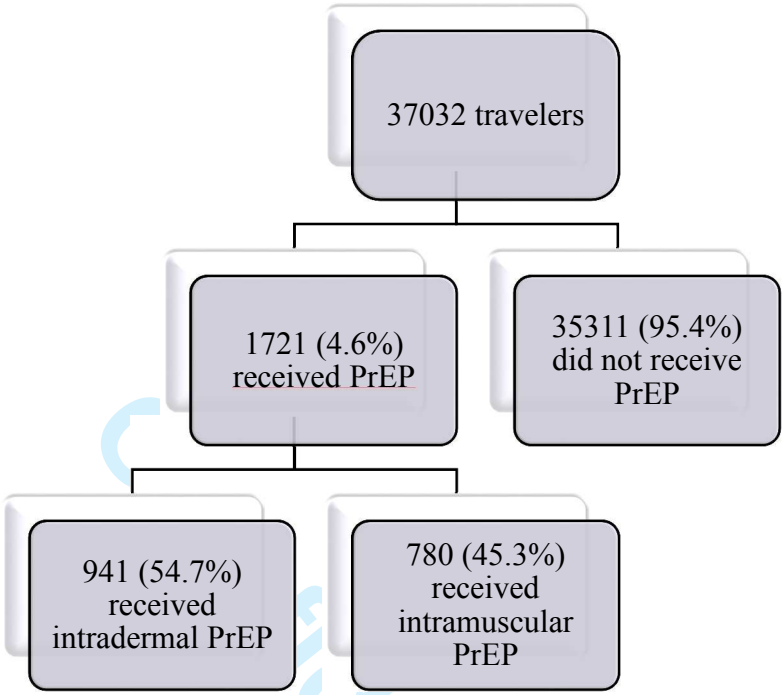


Table 1. Demographic and travel characteristics according to PrEP coverage

| | PrEP | No PrEP | P-value |
|---|---|---|---|
| Continuous variables, mean ± standard deviation | | | |
| Age (years) | 35.77 ±15.14 | 32.07 ±18.20 | <0.0001 |
| Travel duration (weeks) | 16.67 ±22.81 | 5.18 ±11.41 | <0.0001 |
| Categorical variables, n (% of the category) | | | |
| Age (years) | | | <0.0001 |
| <18 | 94 (1.5%) | 6 286 (98.5%) | |
| 18-40 | 1 044 (5.3%) | 18 673 (94.7%) | |
| 41-60 | 470 (5.9%) | 7 502 (94.1%) | |
| >60 | 113 (3.8%) | 2 835 (96.2%) | |
| Travel duration (weeks) | | | <0.0001 |
| ≤4 | 602 (2.4%) | 24 641 (97.6%) | |
| 5-12 | 385 (6.8%) | 5 261 (93.2%) | |
| 13-24 | 253 (14.2%) | 1 525 (85.8%) | |
| 24-52 | 248 (21.7%) | 894 (78.3%) | |
| >52 | 72 (27.0%) | 195 (73.0%) | |
| Gender | | | 0.360 |
| Female | 941 (4.7%) | 18 898 (95.3%) | |
| Male | 780 (4.5%) | 16 392 (95.5%) | |
| Continent | | | <0.0001 |
| Africa | 274 (3.9%) | 6 684 (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%) | |
| Reason for travel | | | <0.0001 |
| Tourism | 1 103 (4.2%) | 25 391 (95.8%) | |
| Work/Business | 183 (6.4%) | 2 665 (93.6%) | |
| Education/Research | 56 (5.5%) | 964 (94.5%) | |
| volunteer/aid work | 255 (10.1%) | 2 268 (89.9%) | |
| Adoption | 0 (0.0%) | 93 (100%) | |
| VFR | 2 (0.2%) | 992 (99.8%) | |
| Number of travelers | | | <0.0001 |
| Solo | 412 (7.4%) | 5 158 (92.6%) | |
| Couple | 636 (5.1%) | 11 828 (94.9%) | |
| Group | 552 (3.4%) | 15 763 (96.6%) | |

*1*

Table 2. Demographic and travel characteristics of travelers receiving PrEP compared with travelers not receiving PrEP: univariate and multivariate analyses

| Variables | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% confidence interval | p-value | Odds ratio | 95% confidence interval | p-value |
| Age (per year of age) | 1.011 | 1.008-1.014 | <0.0001 | 1.015 | 1.012-1.018 | <0.0001 |
| Female gender | 1.046 | 0.950-1.153 | 0.360 | 1.082 | 0.969-1.209 | 0.160 |
| Travel duration (per week of travel) | 1.032 | 1.030-1.035 | <0.0001 | 1.028 | 1.026-1.031 | <0.0001 |
| Continent | | | | | | |
| Africa | 1.000 | - | - | 1.000 | - | - |
| Americas | 0.510 | 0.433-0.600 | <0.0001 | 0.613 | 0.512-0.734 | <0.0001 |
| Asia | 2.383 | 2.077-2.734 | <0.0001 | 3.029 | 2.585-3.549 | <0.0001 |
| Europe | 0.798 | 0.462-1.377 | 0.418 | 0.867 | 0.487-1.542 | 0.627 |
| Reason for travel | | | | | | |
| Tourism | 1.000 | - | - | 1.000 | - | - |
| Work/Business | 1.581 | 1.345-1.858 | <0.0001 | 1.061 | 0.877-1.282 | 0.543 |
| Education/Research | 1.337 | 1.015-1.762 | 0.039 | 1.386 | 1.015-1.894 | 0.040 |
| Cooperation | 2.588 | 2.244-2.986 | <0.0001 | 3.906 | 3.263-4.675 | <0.0001 |
| Adoption | -* | - | - | -* | - | - |
| VFR | 0.046 | 0.12-0.186 | <0.0001 | 0.030 | 0.004-0.213 | <0.0001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Number of travelers | | | | | | |
| Solo | 1.000 | - | - | 1.000 | - | - |
| Couple | 0.673 | 0.592-0.765 | <0.0001 | 0.994 | 0.857-1.153 | 0.935 |
| Group | 0.438 | 0.384-0.500 | <0.0001 | 0.641 | 0.552-0.745 | <0.0001 |

*No traveler traveling for adoption received PrEP

Table 3. Demographic and travel characteristics according to PrEP route of administration

| | Intradermal | Intramuscular | P-value |
|---|---|---|---|
| Continuous variables, mean ± standard deviation | | | |
| Age (years) | 34.60 ±15.15 | 37.18 ±15.02 | <0.0001 |
| Travel duration (weeks) | 16.85 ±19.70 | 16.44 ±26.20 | 0.730 |
| Categorical variables, n (% of the category) | | | |
| Age (years) | | | 0.079 |
| <18 | 60 (63.8%) | 34 (36.2%) | |
| 18-40 | 581 (55.7%) | 463 (44.3%) | |
| 41-60 | 246 (52.3%) | 224 (47.7%) | |
| >60 | 54 (47.8%) | 59 (52.2%) | |
| Travel duration (weeks) | | | <0.0001 |
| ≤4 | 302 (50.2%) | 300 (49.8%) | |
| 5-12 | 208 (54.0%) | 177 (46.0%) | |
| 13-24 | 169 (66.8%) | 84 (33.2%) | |
| 24-52 | 156 (62.9%) | 92 (37.1%) | |
| >52 | 32 (44.4%) | 40 (55.6%) | |
| Gender | | | 0.046 |
| Female | 535 (56.9%) | 406 (43.1%) | |
| Male | 406 (52.1%) | 374 (47.9%) | |
| Continent | | | <0.0001 |
| Africa | 129 (47.1%) | 145 (52.9%) | |
| Americas | 145 (44.2%) | 183 (55.8%) | |

| | | | |
|---|---|---|---|
| Asia | 610 (62.2%) | 371 (37.8%) | |
| Europe | 6 (42.9%) | 8 (57.1%) | |
| Reason for travel | | | <0.0001 |
| Tourism | 696 (63.1%) | 407 (36.9%) | |
| Work/Business | 40 (21.9%) | 143 (78.1%) | |
| Education/Research | 38 (67.9%) | 18 (32.1%) | |
| Cooperation | 101 (39.6%) | 154 (60.4%) | |
| Adoption | 0 (0.0%) | 0 (0.0%) | |
| VFR | 0 (0.0%) | 2 (100%) | |
| Number of travelers | | | 0.001 |
| Solo | 212 (51.5%) | 200 (48.5%) | |
| Couple | 388 (61.0%) | 248 (39.0%) | |
| Group | 285 (51.6%) | 267 (48.4%) | |

Table 4. Demographic and travel characteristics of travelers receiving intradermal PrEP compared to travelers receiving intramuscular PrEP: univariate and multivariate analyses

| Variables | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% confidence interval | p-value | Odds ratio | 95% confidence interval | p-value |
| Age (per year of age) | 0.989 | 0.983-0.995 | <0.0001 | 0.986 | 0.979-0.993 | <0.0001 |
| Female gender | 1.214 | 1.003-1.469 | 0.046 | 1.069 | 0.857-1.577 | 0.555 |
| Travel duration (per week of travel) | 1.001 | 0.996-1.005 | 0.730 | 1.004 | 0.999-1.009 | 0.130 |
| Continent | | | | | | |
| Africa | 1.000 | - | - | 1.000 | - | - |
| Americas | 0.891 | 0.645-1.229 | 0.481 | 0.834 | 0.584-1.193 | 0.321 |
| Asia | 1.848 | 1.411-2.421 | <0.0001 | 1.258 | 0.907-1.743 | 0.169 |
| Europe | 0.843 | 0.285-2.494 | 0.758 | 0.396 | 0.123-1.274 | 0.120 |
| Reason for travel | | | | | | |
| Tourism | 1.000 | - | - | 1.000 | - | - |
| Work/Business | 0.164 | 0.113-0.237 | <0.0001 | 0.185 | 0.123-0.279 | <0.0001 |
| Education/Research | 1.235 | 0.695-2.192 | 0.472 | 0.909 | 0.496-1.663 | 0.756 |
| Cooperation | 0.384 | 0.290-0.507 | <0.0001 | 0.444 | 0.313-0.629 | <0.0001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Adoption* | - | - | - | - | - | - |
| VFR** | - | - | - | - | - | - |
| Number of travelers | | | | | | |
| Solo | 1.000 | - | - | 1.000 | - | - |
| Couple | 1.476 | 1.149-1.896 | 0.002 | 1.183 | 0.887-1.577 | 0.252 |
| Group | 1.007 | 0.780-1.300 | 0.957 | 1.281 | 0.953-1.723 | 0.101 |

*No traveler traveling for adoption received PrEP

**Only two VFR received PrEP, both via the IM route