

Original Article

Traveller exposures to animals: a GeoSentinel analysis

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Abstract

Background: Human coexistence with other animals can result in both intentional and unintentional contact with a variety of mammalian and non-mammalian species. International travellers are at risk for such encounters; travellers

risk injury, infection and possibly death from domestic and wild animal bites, scratches, licks and other exposures. The aim of the present analysis was to understand the diversity and distribution of animal-related exposures among international travellers.

Methods: Data from January 2007 through December 2018 from the GeoSentinel Surveillance Network were reviewed. Records were included if the exposure was non-migration travel with a diagnosis of an animal (dog, cat, monkey, snake or other) bite or other exposure (non-bite); records were excluded if the region of exposure was not ascertainable or if another, unrelated acute diagnosis was reported.

Results: A total of 6470 animal exposures (bite or non-bite) were included. The majority (71%) occurred in Asia. Travellers to 167 countries had at least one report of an animal bite or non-bite exposure. The majority (76%) involved dogs, monkeys and cats, although a wide range of wild and domestic species were involved. Almost two-thirds (62.6%) of 4395 travellers with information available did not report a pretravel consultation with a healthcare provider.

Conclusions: Minimizing bites and other animal exposures requires education (particularly during pretravel consultations) and behavioral modification. These should be supplemented by the use of pre-exposure rabies vaccination for travellers to high-risk countries (especially to those with limited access to rabies immunoglobulin), as well as encouragement of timely (in-country) post-exposure prophylaxis for rabies and *Macacine alphaherpesvirus 1* (herpesvirus B) when warranted.

Key words: Bite, rabies, herpesvirus B, pre-exposure, post-exposure, prophylaxis, consultation

Introduction

Animals, and in particular mammals, provide protection, clothing, food, medicine, companionship and entertainment for humans. Consequences of animal domestication, habitat overlap and other forms of contact include harmful exposures, such as bites, scratches, licks and other injuries. Most wounds caused by domestic and wild animals are minor, do not require professional medical attention and go unreported.¹ However, animals are still responsible for many human injuries and deaths annually,² and this is particularly the case for animals accustomed to receiving food from humans.³ Besides risks of trauma associated with physical encounters as well as poisoning and envenomation from certain species, bites from mammals, reptiles, birds and fish can cause infection from bacteria and viruses.⁴

Travellers are at risk of animal bites and other exposures. A relaxed attitude towards safety, including loss of inhibition and situational awareness, when domestic or wild animals are near can result in human morbidity and mortality. Most of these injuries are from domestic animals.⁵ Many travellers who are bitten by animals may not properly wash wounds with soap and water or other disinfectants and may not seek proper treatment.⁶ For example, Bali, Indonesia, was the most common location for travellers visiting a GeoSentinel site to have an exposure to a potentially rabid animal, but very few travellers received rabies immunoglobulin in Indonesia.⁷ To understand the diversity and distribution of animal-related exposures among travellers, we describe the characteristics of travellers with an animal exposure (bite or non-bite) and report which animals were encountered using data from the GeoSentinel Surveillance Network.

Methods

Data source

GeoSentinel is a global, clinician-based sentinel surveillance system, with a network of 68 specialized travel and tropical medicine sites in 29 countries, which monitors travel-related

illness among international travellers and migrants. It was established in 1995 by the International Society of Travel Medicine (ISTM) in collaboration with the US Centers for Disease Control and Prevention (CDC). Data collected include traveller demographics, travel reason and duration, country and region of exposure, clinical visit information and diagnoses. GeoSentinel does not collect data on treatment or clinical outcomes.⁸

The GeoSentinel surveillance system has received a non-research determination from a human subjects advisor at the CDC National Center for Emerging and Zoonotic Infectious Diseases. Additional ethics clearance was obtained by sites as required by their institutions.

Inclusion criteria

Records with a travel-related illness from 1 January 2007, through 31 December 2018, with one or more of the following diagnoses were included: dog bite; monkey bite; cat bite; bat bite; snake bite; other animal bite; dog exposure, non-bite; monkey exposure, non-bite; cat exposure, non-bite; bat exposure, non-bite; other animal exposure, non-bite; rabies post-exposure prophylaxis (PEP); or *Macacine alphaherpesvirus 1* (herpesvirus B) virus PEP. Records were excluded if the region of exposure was non-ascertainable, travellers were travelling for migration purposes only, an additional acute diagnosis not related to the animal bite or non-bite exposure was included, or the diagnosis was 'other' bites or exposures (non-bites) from insects, humans or marine life.

Statistical analysis

Microsoft Access (Redmond, WA, USA) was used for database management, and SAS Version 9.4 (Cary, NC, USA) was used for all analyses. Descriptive frequencies were calculated for type of diagnosis/exposure (bite versus non-bite), country and region of exposure, GeoSentinel site, whether or not travellers were seen during or after travel, whether or not travellers had a pretravel consultation, purpose of travel, gender and age.

Table 1. Demographic characteristics of travelers with an animal bite or exposure (non-bite) reported to GeoSentinel, 1 January 2007–31 December 2018 (*n* = 6470)

Characteristic	<i>n</i>	%
Median age in years (range)	30 (0–88)	
Gender		
Female	3208	49.7
Male	3250	50.3
Travel reason		
Tourism	4944	76.4
Visiting friends or relatives	694	10.7
Business	446	7.2
Missionary, humanitarian or volunteer	199	3.1
Education or student	113	1.8
Migration	14	0.2
Research	12	0.2
Planned medical care	11	0.2
Migrant worker	9	0.1
Military	8	0.1
Region of exposure ^a		
Southeast Asia	3021	46.7
South Central Asia	1219	18.8
North East Asia	379	5.9
North Africa	342	5.3
South America	334	5.2
Sub-Saharan Africa	284	4.4
Middle East	273	4.2
Western Europe	167	2.6
Eastern Europe	155	2.4
Central America	150	2.3
Caribbean	56	0.9
North America	45	0.7
Oceania	36	0.6
Australia/New Zealand	9	0.1
Hospitalization ^b		
Inpatient	17	6.7
Outpatient	2569	99.3

^aModified UN classification of countries is used in GeoSentinel.

^bAmong 2586 records for which information was available.

Results

From 1 January 2007 to 31 December 2018, 6971 GeoSentinel records met the inclusion criteria, 501 of these records were excluded. A total of 6470 records were analyzed. The median age of travellers included was 30 years (range 0–88 years; interquartile range 23–43); 49.7% were female (Table 1). Children under 18 years of age accounted for 721 (11.1%) records, and almost two-thirds (64.9%) of children were less than 10 years of age; there were three infants <1 year of age. Sixty-nine percent of travellers were seen at a GeoSentinel site after travel. Almost two-thirds (62.6%) of 4395 travellers with information available did not have a pretravel consultation with a healthcare provider. Travellers were most frequently tourists (4944; 76.4%). Only 17 travellers (6.7%) were hospitalized among 2586 records with information available (ten because of dog bites, three because of monkey bites, three for snake bites and one due to a non-bite dog exposure) (Table 2).

All continents except Antarctica had at least one report of an animal bite or non-bite exposure. Most animal bites and non-bite exposures occurred in Asia (Southeast Asia [3021;

46.7%], South Central Asia [1219; 18.5%], North East Asia [379; 5.9%]). Among 6450 records with country of exposure information available, the most frequently reported countries were Thailand (1504; 23.3%), Indonesia (822; 12.7%) and Nepal (664; 10.3%). Overall, travellers who reported bites or other non-bite exposures included visits to 167 countries. Most GeoSentinel records did not specify a particular location of exposure (beyond country or region). However, some of the more frequently reported locations included Ubud in Indonesia (Bali); Bangkok, Chiang Mai, Ko Phi, Ko Samui, Phuket and Prang Sam Yod in Thailand; Beijing in China; Delhi and Goa in India; Ho Chi Minh City in Vietnam; Kathmandu (particularly Swayambhunath) in Nepal; and Lima in Peru.

Among the 6470 records, 11 789 diagnoses were recorded. Of these, 5502 (46.7%) were animal bites and 581 (4.9%) were non-bite animal exposures. The most frequently reported diagnosis was need for rabies PEP (5687; 48.2%); 87.9% of the 6470 travellers in this analysis received rabies PEP. The most frequently reported bites were made by dogs (3141 of 5502; 57.1%), followed by monkeys (1414; 25.7%), cats (581; 10.6%), 'other animals' (255; 4.6%), bats (91; 1.7%) and snakes (18; 0.3%). The most frequently reported non-bite exposures were to monkeys (231 of 581; 39.8%), followed by dogs (157; 27.0%), cats (130; 22.4%), other animals (35; 6.0%) and bats (28; 4.8%). Some records (*n* = 167) had dog (*n* = 75), monkey (*n* = 60), cat (*n* = 29) or bat (*n* = 3) listed in a free text field but did not specify whether these were bites or non-bites.

Among the 255 'other animal' bites and 35 'other animal' exposures (Table 3), all species, except three crocodiles and a turtle, were mammals, ranging from elephants and tigers to squirrels and mice. Out of the 6470, 19 (0.3%) travellers received herpesvirus B PEP, 12 (63.2%) because of monkey bites and seven (36.8%) because of monkey exposures (non-bites).

Discussion

This is the largest report of travellers with animal exposures to date and includes several findings that may be used to improve the education of travellers about animal exposures (bites and non-bites) while abroad.

Locations of exposure

Exposures reported to GeoSentinel have occurred in major wildlife areas or countries endemic for rabies. Although most exposures occurred in Asia, 167 countries had at least one report, and locations varied from exotic animal parks to major metropolitan areas. Animal exposures can happen anywhere, as demonstrated by the report of exposures (bite and non-bite) on all continents except Antarctica, although travellers to regional hot spots, such as Thailand, Indonesia and Nepal should be specifically informed of risks. Travellers to these and other moderate- to high-risk locations (see CDC recommendations at www.cdc.gov/travel/destinations) should be better informed about risks of animal exposures. Planned travel activities (e.g. outdoor activities, working with animals, etc.) and length of travel (e.g. long trips; see CDC URL above) are additional factors worth discussing with travellers at the pretravel consultation and are factors that could influence the decision to provide rabies pre-exposure prophylaxis (PrEP).

Table 2. Demographics by animal bite or exposure (non-bite) reported to GeoSentinel, 1 January 2007–31 December 2018

	Dog		Monkey		Cat		Other animal		Bat		Snake
	Bite (<i>n</i> = 3143)	Exposure (<i>n</i> = 157)	Bite (<i>n</i> = 1 414)	Exposure (<i>n</i> = 231)	Bite (<i>n</i> = 581)	Exposure (<i>n</i> = 130)	Bite (<i>n</i> = 255)	Exposure (<i>n</i> = 35)	Bite (<i>n</i> = 91)	Exposure (<i>n</i> = 28)	Bite (<i>n</i> = 19)
Median age in years (range)	32 (0–88) ^a	29 (3–67)	27 (0–85) ^f	28 ⁱ (2–82)	30 (1–82) ^l	27 (1–71) ⁿ	32 (1–76) ^p	33 (8–31)	34 (3–72) ^t	35 (4–62)	32 (3–72)
Female gender, <i>n</i> (%)	43.8 ^b	50.3	57.7 ^g	56.7	53.5	56.2	53.5 ^a	51.4	40.7	39.3	57.9
Top 3 travel reasons, <i>n</i> (%)	Tourism 2148 (68.3), VFR 467 (14.9), Business 321 (10.2)	Tourism 122 (77.7), VFR 13 (8.3), Business 13 (8.3)	Tourism 1331 (94.1), VFR 24 (1.7), Business 24 (1.7)	Tourism 212 (91.8), Business M/H/V 5 (2.2)	Tourism 411 (70.7), VFR 100 (17.2), Business 33 (5.7)	Tourism 84 (64.6), VFR 22 (16.9), Business 12 (9.2)	Tourism 198 (77.7), VFR 22 (8.6), Business 22 (8.6)	Tourism 24 (68.6), VFR 6 (17.1), Business 2 (5.7), M/H/V 2 (5.7)	Tourism 68 (74.7), VFR 7 (7.7), Business 6 (6.6)	Tourism 21 (75.0), M/V/R 2 (7.1), Research 2 (7.1), Business 2 (7.1)	Tourism 18 (94.7), Business 1 (5.3)
Top 5 exposure countries, <i>n</i> (%)	Thailand ^c 637 (20.3), Nepal 395 (12.6), China 236 (7.5), India 219 (7.0), Indonesia 156 (5.0)	Thailand 46 (29.3), India 17 (10.8), Nepal 16 (10.2), China 11 (7.0), Indonesia 9 (5.7)	Indonesia ^h 484 (34.4), Thai-land 438 (31.1), Nepal 143 (10.2), India 60 (4.3), Vietnam 48 (3.4)	Nepal 56 (24.2), Thai-land 56 (24.2), Indonesia 48 (20.1), India 16 (6.9), Cambodia 14 (6.1)	Thailand 149 (25.7), Turkey 71 (12.2), Morocco 37 (6.4), Algeria 31 (5.3), Philip-pines 28 (4.8)	Thailand 37 (28.5), Turkey 19 (14.6), Nepal 11 (8.5), pines 8 (6.2), China 7 (5.4)	Thailand ^q 34 (13.4), India 16 (6.3), Indone-sia 15 (5.5), Nepal 14 (5.5), Mexico 13 (5.1)	Indonesia 5 (14.3), Mexico 4 (11.4), Thailand 3 (8.6), China 2 (5.7), Costa Rica 2 (5.7), India 2 (5.7), South Africa 2 (5.7), Taiwan 2 (5.7)	Indonesia ^t 13 (14.4), French Guiana 7 (7.8), Thailand 5 (5.6), Vietnam 5 (5.6), Mexico 4 (4.4), United States 4 (4.4)	Indonesia 4 (14.3), Greece 3 (10.7), Austria 2 (7.1), Chile 2 (7.1), Philip-pines 2 (7.1), Thai-land 2 (7.1), United States 2 (7.1)	Nepal 9 (47.4), Indonesia 2 (10.5), India 1 (5.3), Malaysia 1 (5.3), Philippines 1 (5.3), St. Kitts and Nevis 1 (5.3), Sri Lanka 1 (5.3), Zambia 1 (5.3)
Hospitalization, <i>n</i> (%)	10 (1.0) ^d	1 (1.0) ^e	3 (0.5) ⁱ	0 ^k	0 ^m	0 ^o	0 ^r	0 ^s	0 ^u	0 ^v	3 (50.0) ^w

^aAmong 3134 records with information available.^bAmong 3139 records with information available.^cAmong 3131 records with information available.^dAmong 1050 records with information available.^eAmong 97 records with information available.^fAmong 1408 records with information available.^gAmong 1411 records with information available.^hAmong 1409 records with information available.ⁱAmong 614 records with information available.^jAmong 230 records with information available.^kAmong 131 records with information available.^lAmong 578 records with information available.^mAmong 233 records with information available.ⁿAmong 129 records with information available.^oAmong 90 records with information available.^pAmong 253 records with information available.^qAmong 254 records with information available.^rAmong 88 records with information available.^sAmong 16 records with information available.^tAmong 90 records with information available.^uAmong 32 records with information available.^vAmong 17 records with information available.^wAmong 6 records with information available.

VFR, visiting friends and relatives

M/H/V, missionary, humanitarian, volunteer

Table 3. 'Other' animals listed by exposure reported to GeoSentinel, 1 January 2007–31 December 2018 ($n = 108$)

Animal	Bite (n)	Exposure (non-bite) (n)	Unknown if bite or exposure (n)	Total
Ape	1	0	1	2
Bear	3	0	0	3
Coati	3	1	2	6
Cow	1	0	1	2
Crocodile	3	0	0	3
Deer	1	0	0	1
Donkey	2	0	0	2
Elephant	1	2	0	3
Fennec	1	0	0	1
Horse	3	0	1	4
Jackal	1	0	0	1
Kudu	0	2	0	2
Lemur	2	1	1	4
Liger	1	0	0	1
Lion	1	1	0	2
Meerkat	3	1	0	4
Mongoose	1	0	1	2
Mouse	4	0	0	4
Rabbit	1	1	0	2
Raccoon	8	2	0	10
Rat	11	2	3	16
Rodent NOS	2	0	0	2
Sheep	1	0	0	1
Sloth	0	1	0	1
Squirrel	23	2	0	25
Tiger	2	0	0	2
Turtle	1	0	0	1
Weasel	1	0	0	1
Total	82	16	10	108

NOS, not otherwise specified.

Species involved

Although the most frequently reported bites were from dogs, monkeys and cats, many different animal species caused concern for consultation or rabies or herpesvirus B PEP. Species extended from squirrels in the Grand Canyon (USA) and white-nosed coatis in Mexico to sika deer in Japan and Indochinese tigers in Thailand. Travellers should be informed of the broad range of potential animals that may cause health risks after exposure, which includes both domesticated and non-domesticated animals. Few travellers are aware that all mammals are susceptible to rabies.⁹ This knowledge gap could be addressed with educational material and information presented at pretravel consultations.

Specific diseases of concern

Rabies. Rabies is a severe illness that results in approximately 60 000 human fatalities annually, mostly in Africa and Asia.¹⁰ The risk of rabies to travellers is difficult to estimate, but potential rabies virus exposure is likely one of the most frequent health threats to international travellers; an average of 3.7 cases of rabies in travellers were documented each year between 2004 and 2012,¹¹ and the incidence of potential rabies virus exposure in travellers has been estimated at 0.4 per 1000 per month of

stay abroad.¹² Although there were no human cases of rabies in the present report, this does not indicate that the risk of rabies exposure among travellers is low.

The Advisory Committee on Immunization Practices recommends rabies PrEP for travellers who may come into contact with rabid animals and for whom immediate access to appropriate PEP (rabies vaccine and rabies immunoglobulin [RIG]) may not be available.¹³ Few people travelling, even to Southeast Asia, receive rabies PrEP.⁹ Most travellers report high cost and insufficient time before departure for why they choose not to receive PrEP,¹⁴ and many travellers simply underestimate their risk of rabies.¹⁵ Even very high-risk groups, such as spelunkers, do not obtain PrEP frequently.¹⁶ However, travellers may consider PrEP since it negates the need for RIG which may be expensive or not available in many countries.⁷ The recent simplification of rabies PrEP with a two-dose regimen (rather than the three-dose regimen), as recommended by the World Health Organization, may make it possible for travel medicine specialists to convince travellers to have this vaccine before international travel.¹⁷ Some countries in Australia and Europe are already using the simplified two-visit and one-visit intramuscular and off-label intradermal PrEP regimens. It will be helpful for US travel medicine providers if the CDC's Advisory Committee on Immunization Practices (ACIP) reviews and provides guidelines for use of the two-dose PrEP regimen in the future.

The World Health Organization recommends that all travellers who have not received rabies PrEP but are exposed to a potentially rabid animal seek rabies PEP including rabies vaccine, RIG, basic first aid, wound cleaning and disinfection.¹⁰ It is likely that most exposed individuals do not seek PEP and that a delay in treatment may render it ineffective. In Thailand, the risk of being bitten or licked by a potentially rabid animal was approximated to be 1.11 and 3.12 per 100 travellers per month, respectively ($n = 7600$), and only 37.1% exposed to an animal sought PEP.¹⁸ Travellers to Indonesia exposed to animals were more likely than travellers in Thailand to wait until returning home to receive RIG as opposed to receiving treatment in the country of exposure.⁷

Macacine alphaherpesvirus 1 (*Cercopithecine herpesvirus 1* or *herpesvirus B*). Herpesvirus B is endemic in Asian macaques and can result in fatal meningoencephalitis in humans.¹⁹ To date, all recorded human fatalities from this virus have been associated with occupational exposure in biomedical research facilities,²⁰ and the risk to travellers is unknown. Treatment involves immediate first aid and wound cleaning and antiviral therapy (e.g. acyclovir, valacyclovir or famciclovir) for high-risk exposures.¹⁹ There were 19 travellers who received herpes B virus PEP reported in the GeoSentinel database, and there were no reported cases of herpesvirus B infection.

Long-tailed macaques (*Macaca fascicularis*) in Bali, Indonesia, have been reported to be infected with the virus,²¹ and the exposure rate of tourists from bites and scratches from these animals is high in this area, particularly in the monkey forest in Ubud.²² Despite warnings to not feed the animals, as well as possible fines, visitors in Bali and other places frequently have physical contact with the animals, often when local photographers encourage them to do so.²³ Monkeys are culturally and religiously significant in some areas, particularly parts of Asia like Thailand, Indonesia, India and Nepal. International tourists

visiting these sites often hand-feed macaques, a practice that must be discouraged. Signage at animal parks, temples and other high-risk areas should be increased.

These animals are not found only in Asia; rhesus macaques at a popular public park in South Florida shed herpesvirus B, a potential public health threat to visitors.²⁴ It would be valuable to assess whether people are more or less likely to receive PEP in response to a monkey bite than a dog bite, and what they know about the risk of pathogen transmission from monkeys or other species. Transmission of herpesvirus B, as well as other retroviruses like simian foamy virus and simian T-lymphotrophic virus, to travellers with direct contact with nonhuman primates remains possible.^{4,25,26}

Pretravel consultations

Only 30% of travellers for whom information was available reported a pretravel consultation with a healthcare provider. However, many who have pretravel consultations still get injured by animals while abroad.²⁷ Pretravel consultations must be promoted, and their content should include the risk of all exposures (bite, scratch, lick, etc.) to animals (both domesticated and non-domesticated) and the importance of timely (in-country) post-exposure prophylaxis for rabies and herpesvirus B when warranted. Despite pretravel consultation, some travellers may risk dangerous exposures in the absence of effective physical and behavioral barriers.²⁵ Information about such risks is not currently available on travel websites although it is clearly warranted.²⁸

It is unclear how receiving a pretravel consultation affects the likelihood of seeking immediate treatment (PEP for rabies or herpesvirus B) after an animal exposure while abroad. For example, some travellers who received information about rabies in their pretravel consultations and who were rabies PrEP-naïve still may not to seek rabies PEP after an exposure while travelling. In the current data set, although over two-thirds of exposed travellers reported seeking health care after travel, it is unknown if any received health care at a site not part of the GeoSentinel network while travelling. It is important to systematically evaluate the effects of receiving a pretravel consultation on the probability of seeking health care abroad after an animal exposure (bite or non-bite), and how this varies by perceived risk of morbidity and mortality as well as other factors like age and gender.

Age and gender

Travellers of all ages had animal exposures and experienced both bites and non-bites. Children are at increased risk of bites, scratches and other exposures because they are smaller, less able to fend off attacks and generally have more contact with animals; they may also be less likely to report potential exposures.^{29–31} Younger travellers may also be more likely to take physical risks.³² Older travellers with comorbidities should take particular care, since comorbid immunocompromising conditions may increase their risk of a secondary infection at the site of a bite or injury and possibly decrease the immune response to rabies PEP.

Some reports suggest that fatalities resulting from animal exposures are male-biased.³³ Within the present data set, males reported more dog and bat bites while females reported more

monkey and cat bites, although the implication is unclear. What is clear is that pretravel counselling is needed, and that the counselling should take into account the influence of age, gender, immune competency and culture, among other factors, on risk of animal exposure.

Behavioral factors

Although many human exposures to animals are caused by aggressive or defensive animals, many also result from humans initiating contact with animals. For example, in a sample of 65 returned travellers to clinics seeking rabies PEP in Australian clinics, 60% initiated contact with the animals, usually monkeys and dogs.³⁴ Human desire for physical contact with other species is partly the combined result of our biophilia (what some consider to be innate tendencies to affiliate emotionally with other living organisms)^{35–36} and our urge to explore the world through touch (the haptic somatosensory system of identifying and communicating tactile information).^{37–38} Such motivations may perpetuate contact with unfamiliar animals, producing opportunities for injury and disease transmission.⁴

Limitations and Conclusions

While strengths of the GeoSentinel system include physician-confirmed diagnoses and wide geographic coverage (although limited in Africa and South America), the data collected are event-based and not population-based. The data are therefore not generalizable, nor are they representative of all travellers. Analyses are limited to only descriptive results because of lack of appropriate denominator; rates and risk estimates cannot be calculated, and comparative analyses assessing statistical significance between different types of travellers, time periods, regions, age groups or gender cannot be completed using the GeoSentinel database. The data set lacks information on the specifics of pretravel consultations, on pretravel vaccinations (including rabies PrEP) and on traveller activities during exposures. The data set does not systematically record trauma or the difference between a lick or a scratch (only bite versus non-bite). Non-infectious and symptom-based diagnoses are not routinely or systematically collected.

As international travel continues to increase, the interface between humans and other animals will continue to be a topic the field of travel medicine must address. An organized campaign by travel health specialists to address this issue of travel awareness around animals, in addition to necessary discussions on rabies, is overdue.

Author Contributions

M.P.M. conceived the project; K.M.A. conducted statistical analyses; M.P.M., K.M.A. and D.H.H. wrote the manuscript. P.S., L.C., M.P.G., P.G., A.D., F.C., K.C.K., E.B., L.E., M.S. and N.H. provided editorial comments.

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