Introduction

Among wildlife, nonhuman primates (NHPs) are known to harbor a large diversity of zoonotic pathogens and are among the primary mammals targeted for zoonotic disease surveillance [1]. They are the principal host and sometimes an important intermediate host of many zoonotic RNA viruses. Among these viruses, rabies virus, the agent of a lethal encephalitis, is responsible for around 55,000 human deaths every year [2]. Human rabies is a fatal disease once clinical signs develop. Rabies postexposure prophylaxis (PEP) consists of thorough wound care, in combination with rabies vaccine and administration of rabies immunoglobulin (RIG) if necessary. Despite evidence of rabies virus spillover in NHPs and of transmission of rabies from NHPs to humans, neither the World Health Organization (WHO) nor the United States Centers for Disease Control and Prevention (CDC) provide specific guidelines regarding rabies PEP following NHP-related injuries. Guidance emphasizes the role of most frequent reservoirs and vectors. The recommendation of WHO is to provide vaccine and RIG in severe, type III injuries (transdermal bites or scratches, lick on broken skin or mucous membrane, and contacts with bats) and vaccine only in minor, type II injuries (minor scratches or abrasions without bleeding) following exposure from any wild mammal (including implicitly NHPs) in a previously unvaccinated person [2]. At the international level, PEP
Methods

We searched for all accessible publications and reports containing relevant information on rabies in NHPs and human rabies and rabies exposure and PEP following NHP-related injuries. We also analyzed selected data concerning NHPs submitted for rabies diagnosis in France and rabies PEP following NHP-related injuries sustained by French international travelers.

Search strategy

To retrieve information, we conducted a literature search from 1960 to January 2013, using the MEDLINE and SCOPUS databases, and cross-referenced the following terms: “rabies,” “nonhuman primates,” and “monkey.” We also used these same search terms to conduct a Google search over the same period. We systematically scanned meeting reports from the Southern and Eastern African Rabies Group (SEARG). We also scanned the reference lists and bibliographies of all material identified from these searches for potentially relevant primary studies that could be included in the review.

Inclusion criteria

We considered all types of reports in English, French, Spanish, or Portuguese language, with the exception of NHP experimental laboratory studies. All reports of rabies in NHPs and rabies transmission to humans by infected NHPs were included, whether clinically diagnosed or biologically confirmed. Also included were studies of travelers seeking care for rabies PEP in various settings.

Analysis of data concerning NHPs submitted for rabies diagnosis in France and of French national rabies postexposure prophylaxis data

In France, veterinary and medical doctors collaborate closely to detect cases and organize the medical responses to rabies. On the one hand, dogs and cats responsible for human exposure are kept under veterinary surveillance, when possible. If the animal dies for any reason, laboratory diagnostics are performed to rule out rabies. On the other hand, primary health-care management of patients seeking rabies PEP is delivered through an official national network of Antirabies Medical Centers distributed throughout the country [8]. All data collected by veterinarians and medical doctors are collected and analyzed by the French National Reference Centre for Rabies (NRCR), at Institut Pasteur in Paris.

Data collected by the NRCR concerning NHPs submitted for rabies diagnosis in France and human rabies exposure to NHPs in travelers returning to France were analyzed for the periods 1999–2012 and 1994–2011, respectively.

Results

South America (Appendix S1, Tables 1 and 2)

Rabies in NHPs is well described in Northeast Brazil in Rio Grande do Norte, Ceará, Piauí and Pernambuco States, where rabies cases were documented in marmosets (Appendix S1). These monkeys are highly adaptable to different habitats and can be found on plantations and in urban parks. They are also commonly captured and kept as pets. A new antigenic variant of rabies virus was identified in marmosets and humans bitten by marmosets, which strongly suggests, in conjunction with surveillance data, that these viruses represent a unique, independent rabies endemic cycle [9]. According to the Brazilian Ministry of Health, over the last three decades 20 human rabies cases were reported following marmoset-related injuries in Ceará and Piauí States [9,10]. In recent years, antibodies against rabies have also been found in capuchin monkeys in southeastern Brazil in the state of São Paulo [10], and 2 rabies cases were recorded from the same state in monkeys for which the species was not documented, according to the Pan American Health Organization (PAHO) epidemiological
information system. Finally, 4 rabies cases were reported in monkeys (species not available) from Mato Grosso in 2010–2011 according to PAHO. In Peru, rabies cases were suspected in humans following pet monkey bites (species not available) from 1999 to 2006 in the region of Lima, although monkeys tested positive by serology, further laboratory investigations led to the conclusion of false positive [11]. Three rabies cases were documented in squirrel monkeys imported from Peru to the United States in the early 1960s [12], as well as one in a marmoset where infection was very likely vaccine-induced [13].

Rabies cases were reported sporadically in monkeys in Argentina, Bolivia, Colombia, Cuba, Ecuador, and Paraguay, according to PAHO. One case was documented in a ringtail monkey imported from Colombia to the United States in 1947 [12].

It must be pointed-out that no information is provided about the diagnostic criteria that were used for cases reported by PAHO.

**Africa (Appendix S1, Table 2)**

Data published in the medical literature about rabies in African NHPs are scant [14–18]. Meeting reports of the SARG (web site:

### Table 1. Human rabies cases following nonhuman primate-related injuries.

<table>
<thead>
<tr>
<th>Country of exposure</th>
<th>Year</th>
<th>Animal</th>
<th>number of human cases</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>America</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil (States of Ceará and Piauí)</td>
<td>1980–2008</td>
<td>Marmoset</td>
<td>20</td>
<td>9,10</td>
</tr>
<tr>
<td>Asia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India (Australian traveler)</td>
<td>1988</td>
<td>Monkey</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>India</td>
<td>1998</td>
<td>Monkey</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>India</td>
<td>1999</td>
<td>Monkey</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>India (German traveler)</td>
<td>2004</td>
<td>Monkey (NB/had also contacts with dogs)</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>1975</td>
<td>Monkey</td>
<td>1</td>
<td>22</td>
</tr>
</tbody>
</table>

1confirmed by molecular analysis.
2confirmed by histological observation of Negri bodies in the brain.
3rabies diagnosis was assessed on clinical criteria only.
4confirmed by fluorescent antibody testing of brain samples, molecular analysis and mouse inoculation with brain material.
5species not stated.

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### Table 2. Confirmed rabies in imported nonhuman primates.

<table>
<thead>
<tr>
<th>Country of importation</th>
<th>Year</th>
<th>Animal (number of cases)</th>
<th>Country of origin</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>1929</td>
<td>Monkey</td>
<td>Not stated</td>
<td>12</td>
</tr>
<tr>
<td>US</td>
<td>1936</td>
<td>Monkey</td>
<td>Not stated</td>
<td>12</td>
</tr>
<tr>
<td>US</td>
<td>1947</td>
<td>Ringtail (Cebus spp.)</td>
<td>Colombia</td>
<td>12</td>
</tr>
<tr>
<td>US</td>
<td>1955</td>
<td>Cynomolgus (Macaca fascicularis)</td>
<td>Philippines</td>
<td>12</td>
</tr>
<tr>
<td>US</td>
<td>1961</td>
<td>Squirrel monkey (Saimiri sciureus)</td>
<td>Peru</td>
<td>12</td>
</tr>
<tr>
<td>US</td>
<td>1963</td>
<td>Squirrel monkey (Saimiri sciureus)</td>
<td>Peru</td>
<td>12</td>
</tr>
<tr>
<td>US</td>
<td>1963</td>
<td>Squirrel monkey (Saimiri sciureus)</td>
<td>Peru</td>
<td>12</td>
</tr>
<tr>
<td>UK</td>
<td>1965</td>
<td>Rhesus (Macaca mulatta)</td>
<td>India</td>
<td>19</td>
</tr>
<tr>
<td>US</td>
<td>1972</td>
<td>Capuchin monkey</td>
<td>Not stated</td>
<td>Center for Disease Control, 1972 (internal report)</td>
</tr>
<tr>
<td>US</td>
<td>1972</td>
<td>Chimpanzee</td>
<td>Sierra Leone</td>
<td>19</td>
</tr>
<tr>
<td>US</td>
<td>1974</td>
<td>Marmoset (Saguinus nigricollis)</td>
<td>Peru</td>
<td>Center for Disease Control, 1976 (internal report), 13</td>
</tr>
</tbody>
</table>

1confirmed by histological observation of Negri bodies in the brain.
2confirmed by mouse inoculation with brain material.
3confirmed by fluorescent antibody testing of brain samples.
4This monkey had been vaccinated with a modified live-virus rabies vaccine of avian origin, 13 days before the onset of symptoms. The viral isolate from the rabid monkey had characteristics consistent with an egg-adapted vaccine strain suggesting that the monkey’s infection was vaccine-induced. These included a short incubation period in mice (4–5 days), absence of fluorescent rabies antibodies detectable virus in salivary glands and corneas of the mice, only rare inclusions typical of Negri bodies produced on mouse passage, and high titered growth in eggs on first passage.
5These monkeys had been vaccinated with a modified live-virus rabies vaccine (strain ERA) 43 and 28 days before the onset of the symptoms, suggesting that the monkey’s infection was vaccine induced, although sequencing or typing were not done.
6species not stated.

doi:10.1371/journal.pntd.0002863.t002
African NHP. Despite intensive searches, we were unable to find a pattern in which people were exposed to these monkeys and received rabies PEP. More than 50 people were exposed to these monkeys and received rabies PEP. Despite intensive searches, we were unable to find a documented human rabies case following exposure from an African NHP.

Asia and the Middle East (Appendix S1, Tables 1 and 2)

Few published results about rabies in NHPs in Asia are available. Unfortunately, country reports about animal rabies in Asia that can be found in reports of symposium on rabies control in Asia co-organized by the Merieux Foundation and the WHO do not address NHPs specifically. Rabies cases were reported in monkeys, langurs, and baboons in India [20], including one case in a macaque imported to London in 1965 for laboratory experiments [21]. One case was reported in a macaque imported from the Philippines to the United States in 1955 [12]. Rare human rabies cases following monkey bites have been reported in local populations in India and Sri Lanka, based on clinical diagnosis [20,22,23] and in two travelers returning from India to Australia and Germany, based on histopathology in the first case and direct immunofluorescence and virus isolation in the second case [24,25]. One case was documented in a pet monkey in Jordan [26]. In France, only one NHP imported from Indonesia was submitted for rabies diagnosis to the NRCR from 1999 to December 2012, and it was found negative.

NHP-related injuries requiring rabies PEP in travelers (Table 3)

A number of studies were conducted in travelers seeking care for rabies PEP in various settings [27–40]. Data are available from more than 2000 people, and the proportion of injuries related to NHP exposures is about 31%, with the smallest proportion observed in US military personnel stationed in Afghanistan (8%) and the largest reported from travelers returning from Bali, Indonesia, at various GeoSentinel clinics (69%). Overall, dogs are usually the most frequently reported species responsible for injuries requiring rabies PEP in travelers. However, NHPs rank second in most studies and first in studies conducted in travelers returning from Southeast Asia (34,35,37,40). In France, data are available from 1606 travelers exposed to NHPs from 1994 to 2011, representing 1.7% of the total number of people and 15.6% of travelers seeking PEP in France for exposure to any animal, during the same period. The number of travelers exposed to NHPs and receiving PEP in France has increased since 2002, especially in 2004 and 2005 (Figure 1) because of a strong demand for antirabies prophylaxis following a well-publicized rabies case in a dog imported to France in 2004 [8]. This proportion increased to 3.1% by 2008–2011 (Figure 1), further indicating that the NHP-related injuries in rabies-enzootic countries is a public health problem of increasing importance. The largest proportion of travelers exposed to NHPs and receiving PEP in France during the period 1994–2012 had returned from Asia and the Middle East (53.3%), followed by Africa (36.9%) and the Americas (5%). In Asia and the Middle East, the most frequent country of exposure was Thailand (22.4% of the treated patients).

Discussion

We retrieved a total of 134 confirmed cases of rabies in NHPs which have been reported from various sources in South America, Africa, and Asia, including 13 cases in animals imported to Europe and the US. We retrieved 25 cases of rabies transmission to humans following NHP-related injuries, 20 of which occurred in Brazil. Rabies cases in NHP from Brazil were confirmed by genetic analysis [9]. Additionally 4 capuchin monkeys were found with positive serology in southeastern Brazil [10]. By contrast, 21 NHPs from other regions in Latin America were reported rabid by the PAHO with no information about the methods used for the assessment of rabies. It is therefore possible that these so-called “cases” were actually healthy animals with a positive-serology. Such so-called “cases” reported in Peru, finally turned out not to be rabies [11]. We cannot exclude that rabies cases reported in NHPs from São Paulo and Mato Grosso in Brazil and from other countries in South America by the PAHO could be actually healthy animals with positive serology. There are issues with the PAHO data that may contain inaccuracies and should not be considered the gold standard. Imported cases from Peru and Colombia, however, were confirmed by fluorescent rabies antibody examination of brain tissue, demonstration of negri bodies on microscopic examination or rabies induced in mice inoculated with brain tissue [12,13]. Cases reported in wild NHPs in various countries in Africa by the SEARG (Appendix S1) and other authors [14–18], in India [20] and Jordan [26], as well as in the imported cases from Sierra Leone [19] India [21] and the Philippines [12] were all confirmed by brain tissue histology, fluorescent antibody testing of brain tissue and mouse inoculation.

The reports collated in this study support the view that confirmed rabies cases in NHPs are rarely reported compared with human rabies cases. In light of numerous biological reports establishing the susceptibility of NHPs to rabies, we might have expected the number of NHPs with rabies to have been greater than observed. Several explanations for this finding are possible.

First, with the possible exception of the cluster of marmosets in Ceará State, Brazil [9], NHPs are not known to be a reservoir for maintaining a rabies virus variant in the wild. Second, given that dogs are a domesticated species, sharing a closer bond and degree of interaction with humans than do NHPs, the difference in the contact rates with dogs may account, in part, for the difference in reported rates of rabies between humans and NHPs. However, NHPs are frequently kept as pets and can be close to humans in some regions. Finally, underreporting of rabies in NHPs is likely to be significant. The passive nature of rabies surveillance likely accounts for underreporting of rabid NHPs. Rules pertaining to the submission of animal specimens for rabies diagnosis and reporting to national authorities are sometimes weak and may only cover the few species considered to be economically important or those most important in terms of public health. Last, rabies cases in NHPs are not notifiable in many countries and as such are not recorded in official statistics.
Underreporting of rabies in NHPs is a major impediment to understanding the epidemiology of this disease and may hinder the development of control strategies. We show that a review of published reports can be an important way to overcome the problem of underreporting and can contribute to the advancement of the understanding of the importance of rabies in NHPs as a potential hazard to humans. Moreover, valuable information exists in internal reports, which is not easily available since it is not indexed in MEDLINE and SCOPUS databases.

More complete and precise information pertaining to rabies in NHPs is needed. This information could be obtained through field surveys. We believe a greater effort should be directed toward coordinating and frequently reviewing the need for rabies PEP after exposure to animal species such as NHPs that are not primary reservoirs of rabies. Information obtained in this way should be regularly collected, updated, and made available to the medical community. To this end, efforts towards greater openness and accessibility of information regarding the incidence of rabies in NHPs and its geographic distribution would provide a much-needed basis for improving and sustaining the public health debate around the risk evaluation of rabies after human exposure to these species.

To address the possibility of reintroduction of rabies through NHPs, countries that are designated as rabies-free should strongly

### Table 3. Proportion of injuries caused by nonhuman primates among international travelers injured by potentially rabid animals.

<table>
<thead>
<tr>
<th>Study period</th>
<th>Place of exposure</th>
<th>Population</th>
<th>Design of the study</th>
<th>Total number of injured travelers (all animal species)</th>
<th>Proportion of nonhuman primate related injuries in travelers</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb 1987–Jan 1989</td>
<td>Nepal</td>
<td>Non-Indian expatriates and tourists presenting at the Katmandu CIWEC Clinic (main clinic for foreigners in Nepal)</td>
<td>Observational survey</td>
<td>51</td>
<td>19.2%</td>
<td>27</td>
</tr>
<tr>
<td>Jan 1996–Dec 1998</td>
<td>Nepal</td>
<td>Non-Indian tourist presenting at the Katmandu CIWEC Clinic (main clinic for foreigners in Nepal).</td>
<td>Observational survey</td>
<td>56</td>
<td>43.0%</td>
<td>28</td>
</tr>
<tr>
<td>Jul 1998–Mar 2005</td>
<td>Nepal</td>
<td>Expatriates and travelers presenting at the Katmandu CIWEC Clinic (main clinic for foreigners in Nepal)</td>
<td>Retrospective survey</td>
<td>544</td>
<td>27.9%</td>
<td>29</td>
</tr>
<tr>
<td>Aug–Dec 2004</td>
<td>Mainly Asia</td>
<td>Israeli travelers traveling one month and over)</td>
<td>Cohort survey (815 individuals)</td>
<td>13</td>
<td>30.8%</td>
<td>30</td>
</tr>
<tr>
<td>June 1998–May 2005</td>
<td>Mainly Asia, Latin America and Africa</td>
<td>Travelers seen after travel at GeoSentinel sites</td>
<td>Multicentric international retrospective survey</td>
<td>321</td>
<td>21.2%</td>
<td>31</td>
</tr>
<tr>
<td>May 1997–May 2005</td>
<td>Mainly Africa and South-East Asia</td>
<td>Injured travelers returning to Marseille (France), Melbourne (Australia) and Auckland (New-Zealand)</td>
<td>Retrospective survey</td>
<td>261</td>
<td>17.3%</td>
<td>32</td>
</tr>
<tr>
<td>Oct 1998–Feb 2006</td>
<td>Mainly South-East Asia</td>
<td>Injured travelers returning to Auckland and Hamilton (New-Zealand)</td>
<td>Retrospective survey</td>
<td>54</td>
<td>18.5%</td>
<td>33</td>
</tr>
<tr>
<td>Jan 1994–Dec 2007</td>
<td>Mainly North Africa and Asia</td>
<td>Injured travelers returning to Marseille (France)</td>
<td>Retrospective study</td>
<td>424</td>
<td>19.6%</td>
<td>34</td>
</tr>
<tr>
<td>Nov 2008–Mar 2010</td>
<td>Bali, Indonesia</td>
<td>Injured travelers returning to Marseille (France), Melbourne (Australia), Singapore and Auckland (New-Zealand)</td>
<td>Retrospective survey</td>
<td>45</td>
<td>68.9%</td>
<td>35</td>
</tr>
<tr>
<td>Jan 2000–Jul 2009</td>
<td>Mainly Asia and Turkey</td>
<td>Injured travelers returning to Liverpool (United Kingdom)</td>
<td>Retrospective survey</td>
<td>139</td>
<td>16.5%</td>
<td>36</td>
</tr>
<tr>
<td>Apr 2009–Jul 2010</td>
<td>Mainly Indonesia and Thailand</td>
<td>Injured travelers returning to 3 clinics in Queensland and 1 in Perth (Australia)</td>
<td>Prospective study</td>
<td>65</td>
<td>44.6%</td>
<td>37</td>
</tr>
<tr>
<td>Jun 2010–Feb 2011</td>
<td>Mainly Thailand and other South-east Asian countries</td>
<td>International travelers leaving Bangkok (Thailand)</td>
<td>Cross sectional survey</td>
<td>36 with animal species documented (out of 219)</td>
<td>38.9%</td>
<td>38</td>
</tr>
<tr>
<td>Sep–Dec 2011</td>
<td>Afghanistan</td>
<td>US military</td>
<td>Retrospective survey</td>
<td>126</td>
<td>7.9%</td>
<td>39</td>
</tr>
<tr>
<td>Jan 2008–April 2012</td>
<td>Mainly Indonesia, Thailand, India and China</td>
<td>Potential rabies exposure incidents reported to Public Health Units in the south Brisbane region of Queensland, (Australia)</td>
<td>Prospective study</td>
<td>136</td>
<td>55.8%</td>
<td>40</td>
</tr>
</tbody>
</table>

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consider permitting their entry only under license. Live animal importations to such countries would benefit from quarantine guideline under conditions approved by governmental veterinary services.

We show that, although rarely reported, documented cases of rabies infections in NHPs and subsequent transmission to humans do occur. Little is currently known about the pathobiology of rabies virus shedding in primates. The occurrence of documented transmission of rabies from NHPs to humans suggests that rabies PEP is indicated in patients injured by NHPs in rabies-enzootic countries. We were unable to find any report suggesting failure or death in previously unvaccinated persons who received vaccine without RIG after exposure to NHP, however, rabies status of NHP was not documented in these reports. From a clinical perspective, distinct recommendations are found depending on national guidelines. United Kingdom guideline state that the risk of rabies following NHP-related injury is extremely low and that rabies PEP with vaccine only should be applied in previously unvaccinated people [6,7]. A contrario, WHO, the US CDC, Canadian and French guideline state that the catastrophic nature of the disease with a nearly 100% mortality rate is what will drive treatment, not the low probability of the disease and that rabies vaccine and RIG should be applied in previously unvaccinated people [2–5]. As long as wild life studies addressing the role NHPs play in the disease transmission to humans are not available from various area where human exposure occur and as recommended by WHO, we consider that a precautionary principle should be applied and that RIG should be administered, as with any other animal exposures, despite the large number of doses that would be necessary, even in the setting of a RIG shortage.

Based on our review of published reports, a large number of international travelers sustain NHP-related injuries during their trips. Information about the risks posed by exposure to NHPs in enzootic countries, especially in India and Southeast Asia, should be disseminated to the traveling public to help minimize these injuries and the subsequent need for rabies PEP. Travelers should be encouraged to seek a pretravel medical consultation from their health-care provider 4–6 weeks before travel to discuss if rabies pre-exposure vaccination may be recommended in situations where travel activities may involve a higher potential for contact with animals such as NHPs. Travelers should also be encouraged to seek immediate medical care if injured by an NHP species.

Supporting Information

Appendix S1 Rabies in nonhuman primates from the Americas, Africa, Asia and the Middle East. (DOCX)

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Author Contributions

Wrote the paper: PG JB LD FRD PB PP DHE HB.
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