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Factors associated with the administration of rabies PrEP and Japanese encephalitis vaccine to pediatric international travelers at a U.S. travel clinic: a retrospective analysis

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Abstract

Factors associated with the administration of rabies PrEP and Japanese encephalitis vaccine to pediatric international travelers at a U.S. travel clinic: a retrospective analysis

By

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Background: Pediatric travelers are an understudied population although an estimated 2.4 million United States children travel internationally yearly. Long-term pediatric travel can be associated with higher risk of infections, like Japanese encephalitis (JE) and rabies. This study aims to describe factors associated with the administration of JE vaccine and rabies pre-exposure prophylaxis (PrEP) in pediatric travelers and determine if cost and timing of the pre-travel visit are barriers for these vaccines.

Methods: A retrospective chart review was conducted on children (<18 years of age) who visited the Emory TravelWell Center in Atlanta, Georgia between June 1, 2011 to June 30, 2015 for pre-travel consultation. Abstracted data included demographics and travel itinerary details. Descriptive statistics, univariate, and multivariate analyses were conducted to examine associations between method of payment and administration of JE vaccine and rabies PrEP.

Results: 352 travelers were analyzed, and the majority of travelers (68%) self-paid for the pre-travel consultation. Africa was the most common destination region (35%), followed by Asia (32%). Almost 50% of travelers pre-travel visit was <21 days from departure date and 58% was <28 days. On subset analysis of Asia only travelers (n=108), JE vaccine was administered to 11.1% of children, with 17.6% not vaccinated due to insufficient time before departure. Sufficient time to complete JE vaccine series (aOR= 8.03; 95%CI 1.25, 51.75) was significantly associated with JE vaccine administration while cost covered by insurance showed no difference in JE vaccine administration (aOR=0.82; 95%CI 0.14, 4.67). Rabies PrEP was administered to 9.3% of children, with 9.6% not vaccinated due to insufficient time (n=332). However, for rabies PrEP, method of payment and sufficient time to complete rabies series were both significantly associated with rabies PrEP administration (aOR = 3.44; 95% CI 1.24, 9.58) and (aOR=17.36; 95%CI 3.65,82.55).

Conclusions: Cost was a barrier to travel prophylaxis administration for rabies PrEP but not for JE vaccine, though having sufficient time to complete rabies PrEP or JE vaccine both had significant association with vaccine administration. These results highlight the importance of a well-timed pre-travel consultation, so there is sufficient time to complete travel vaccination series for pediatric international travelers.

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Chapter 1: Literature Review

Introduction

In 2019, there were approximately 38 million United States (U.S.) citizens who traveled overseas, excluding visitors to Canada and Mexico [1]. In 2016, an estimated 2.81 million U.S. international travelers were children or adults traveling with children [2]. Pediatric travelers (ages 0-17 years) are an understudied population, although it is estimated that 2.4 million U.S. children travel internationally yearly [3].

The number of international travelers is increasing as is the growing numbers of exotic destinations. More travelers are going to low and middle income countries (LMIC) where they are more at risk for travel related illness and exposure to tropical infectious diseases[4, 5]. Long-term travelers going to these destinations are more likely to be a traveler who is 'visiting friends and relatives', often referred to as a VFR traveler, "which is an immigrant, ethnically and racially distinct from the majority of the population of the country of residence, who returns to his or her home country to visits friends or relatives" [6, 7]. VFR travelers can also include the spouse or children of the immigrant, who were born in the country of residence, which is often a higher-income country than the country of origin [7]. VFR travelers are at increased risk of travel-related illness due to higher risks of exposure and inadequate protection measures [4]. In addition, VFR travelers are more likely to adopt local-health related behaviors during the trip, and underestimate the perceived risk of travel and are less likely to seek pre-travel health advice or travel immunizations due to cost [4, 8, 9]. It has been reported that as few as 17% of VFR travelers seek pre-travel health advice in a review of ill returning VFR travelers [6].

Pediatric VFR travelers are especially vulnerable and should have a pre-travel consult with a provider that has the expertise of both travel medicine and pediatrics to be able to

provide recommendations on immunizations, travel and routine, and medications unique to this population. Pediatric VFR travelers are at increased risk of infection, the most severe and life-threatening being malaria infection [2]. Pediatric VFR travelers are four times more likely to acquire malaria while traveling compared to tourist travelers and are more likely to be infected if they are not on malaria chemoprophylaxis [2, 6]. Children are responsible for 11-23% of all imported cases of malaria and the majority of these infections after travel to sub-Saharan Africa [6]. In addition, the proportion of imported cases among pediatric VFR travelers is reported to be 50-84% of cases [6]. Also in a Spanish study of pediatric malaria cases 100% of the cases were in immigrant or VFR children and all of the VFR children with imported malaria were taking inappropriate malaria chemoprophylaxis [6]. Similarly, there are reports that pediatric VFR travelers are less likely to receive rabies pre-exposure prophylaxis (PrEP) vaccinations [6]. However, data is lacking on the quantifiable risk of death due to rabies in unimmunized pediatric travelers.

According to one study vaccine preventable diseases reported among all travelers was approximately 2% and of these less than 20% had a pre-travel health visit [9]. Specifically, in pediatric travelers, the reported rate of pre-travel consultation visits is even lower at approximately 10% [10]. In a multi-center, GeoSentinel 2010, study on illness post-travel for over 1500 pediatric travelers, it noted that they had higher morbidity, required hospitalization, lacked pre-travel health visits and were more often VFR travelers compared to adults seen at GeoSentinel clinics [11]. Also one-quarter of the children in this study were diagnosed with animal bites, and 50% of those were due to dog bites [11]. They noted that 97% of children with animal bites received rabies post-exposure prophylaxis but they had no data on if these

children received rabies PrEP [11]. The two most common preventable diagnoses for these pediatric travelers were animal bites and malaria [11]. And although malaria is the often the most common systemic febrile illness, up to 40% of the time the specific cause is not identified for the febrile syndrome, which could include causes like Japanese encephalitis [9, 11]. This study highlights the importance of a comprehensive pre-travel visit for pediatric travelers, to not miss key opportunities for prevention, like with administration of rabies PrEP and malaria chemoprophylaxis. It is clear that pediatric international travelers are a unique population and may be more susceptible to travel-related illness than adult travelers based on current evidence of their under-utilization of pre-travel health advice.

Statement of the problem

There is a need to understand the complex relationship between pediatric international travelers and the potential barriers to pre-travel consultation and administration of recommended travel vaccinations in the United States. Pediatric travelers are unprepared for international travel due to a variety of factors and this makes them vulnerable to obtaining a travel-related illness. Children are inherently a vulnerable population, due to their limitations in communication based on age and also their reliance on adults to protect them from harm and risks, that they are often unaware that exist. These risks are increased when children travel and are in unfamiliar surroundings. Despite millions of U.S. children traveling abroad yearly, the data on post-travel illnesses suggest that many of these children are unprepared for these international trips. Administration of travel vaccinations in pediatric international travelers prevents unnecessary infections and the morbidity and mortality related to that specific disease, whether that is typhoid, yellow fever, Japanese encephalitis, or rabies, for example;

and that is why pre-travel consultations are important to public health. The public health problem is the failure of pediatric international travelers to obtain necessary travel vaccinations or medications advised at the pre-travel consultation visit [12]. There seems to be a lack of data on pre-travel visits for pediatric international travelers, most of the studies available are on post-travel visits for travelers of all ages, not specifically pediatric travelers. And this has created a knowledge gap on the unique challenges of pediatric international travelers and their barriers to seeking and following pre-travel guidance and vaccine administration. The frequency that U.S. travelers (adult and pediatric) seek pre-travel consultations is highly variable (10-40%) based on previous studies and there continues to be a knowledge gap on the barriers for travelers to seek the pre-travel visit. The purpose of this study is to describe the characteristics of pediatric international travelers who are seen for a pre-travel visit and to identify the potential barriers to following recommendations for vaccine administration for children seen at the Emory TravelWell Center in Atlanta, Georgia. In addition, this study will focus on potential barriers to administration for two travel vaccinations, Japanese encephalitis vaccine and rabies pre-exposure prophylaxis (PrEP). These two vaccines were chosen because they both require a series of vaccinations that are expensive and require at least three to four weeks to complete, which may contribute to cost and timing barriers for pediatric travelers. Yet, both of these vaccines are specifically important to preventing infection in pediatric travelers, especially rabies which children are at higher risk for due to their behaviors around animals and Japanese encephalitis due to exposures playing outdoors and possibly not reporting small bites from mosquitoes.

Research Questions

What are the factors that influence the outcomes of pre-travel consultation and vaccine administration for pediatric patients preparing for international travel that presented to Emory TravelWell Center?

Question 1: Does having insurance coverage impact the outcome of the pre-travel consultation and administration of vaccines for pediatric international travelers who presented to the Emory TravelWell Center? Is cost a barrier to vaccine administration for Japanese encephalitis vaccine and rabies vaccine, specifically?

Null hypothesis 1: There is no difference in frequency of vaccine administration for pediatric international travelers for those who have insurance coverage for the cost and those who do not have insurance coverage.

Question 2: How does timing of pre-travel consultation visit affect the frequency of administration of JE and rabies PrEP vaccinations given to pediatric international travelers? Specifically, does having sufficient time (> 28 days) to complete JE vaccine series and having sufficient time (> 21 days) to complete rabies PrEP series prior to trip departure affect the frequency that these vaccines are given to pediatric international travelers.

Null hypothesis 2: There is no difference in frequency of vaccine administration for pediatric international travelers for those that have sufficient time to complete the JE or rabies PrEP series and those who do not have sufficient time to complete these series prior to trip departure.

Goals of this Study

This study will show the importance of having a pre-travel consultation prior to international trips for pediatric patients, who are vulnerable to disease and infections based on

their typical age-appropriate behavior and or developmental stage. It will be important to understand the barriers to pre-travel consultation and vaccine administration for pediatric international travelers, so that both travel medicine providers and primary care providers can be educated on how to approach these visits and promote parents to seek pre-travel consultation. By answering the research questions this study will inform public health practice of travel medicine for pediatric international travelers.

Literature Review

Pre-travel consultation

It is important that all travelers, especially families traveling with children, have a pre-travel consultation to assess the risk, communicate the risks and manage the risks of international travel. In an US airport based study, 404 questionnaires were completed and it noted that only 36% of international travelers had pre-travel counseling; of those, 60% sought advice from a primary care provider, 10% from a travel subspecialist, and 30% from family and friends [13]. A pre-travel consultation consists of a thorough review of the traveler's medical history, the itinerary, trip duration, travel purpose and activities, which all help to determine health risks to the traveler [14]. The medical history should include a review of the following: underlying medical conditions, medications, allergies, surgeries, hospitalizations, special conditions, immunizations, prior experience with malaria prophylaxis and illnesses related to travel [15]. In a pre-travel visit after an individualized risk assessment is completed, then the traveler should be educated about anticipated health risks, and provide risk management measures, such as immunizations, malaria prophylaxis and other medications as indicated [14].

In an individual's risk assessment during the pre-travel consultation, the provider should identify health risk that the traveler will encounter during the specific itinerary, which must account for the destination country or countries, rural or urban setting of travel, season of travel, time to departure, type of accommodations, duration of trip, and anticipated activities [14]. For pediatric travelers it is important to ensure they are up-to-date on routine childhood vaccinations and then also make recommendations for travel-related vaccinations. Routine childhood vaccinations that are relevant for travel that should be up-to-date are the following: hepatitis A vaccine; hepatitis B vaccine; diphtheria, tetanus, and pertussis vaccine; influenza

vaccine; measles-mumps-rubella (MMR) vaccine; meningococcal vaccine; and polio vaccine [16]. Travel vaccinations that are often advised based on the itinerary are the following: Japanese encephalitis (JE) vaccine, rabies pre-exposure prophylaxis (PrEP) vaccine, typhoid vaccine and yellow fever vaccine. Malaria prophylaxis should be prescribed at pediatric specific weight-based dosages [16]. Although malaria is outside of the scope of this project, it is one of the most serious infections that pediatric international travelers can acquire and parents traveling with children in malaria-endemic areas should be counseled on proper prevention strategies [2]. And finally, parents should be counseled to avoid mosquitoes, ticks and arthropods that carry various diseases by using protective measures like insect repellant and insecticide treated nets [2, 16].

Japanese encephalitis

Japanese encephalitis (JE) is a mosquito-borne viral infection that is endemic throughout most of Asia and parts of the western Pacific [16, 17]. JE virus is a single-stranded RNA virus that belongs to the genus *Flavivirus* and is closely related to both West Nile and Saint Louis encephalitis viruses [17, 18]. The virus is transmitted to humans through the bite of infected mosquito, predominantly the *Culex* species [17]. JE virus circulates in an enzootic cycle in pigs which serve as amplifying vertebrate hosts and wading water birds are virus reservoirs [17, 18]. Humans are incidental hosts or dead end hosts, because they usually do not develop a level or duration of viremia sufficient to infect mosquitoes [18, 19]. JE virus is the most common vaccine-preventable cause of encephalitis in Asia [18]. Transmission primarily occurs in rural agricultural areas, most often associated with rice cultivation and flood irrigation, where the *Culex* mosquito prefers to breed; although these ecologic conditions can occur near or sometimes within urban centers [17, 18]. The risk can be seasonal in temperate climates, where

human disease usually peaks in summer and fall [16, 18]. Seasonal rains cause increases in mosquito populations and therefore increased transmission of the JE virus [19]. And the risk can be year-round in more tropical climates that have some seasonality based on monsoon rains and irrigation practices [16, 18]. JE has become mainly a disease of children because in endemic countries adults have acquired immunity due to infections when they were children [18]. However travel-associated JE infection can occur in travelers of any age [18]. The risk to short-term (<1 month) travelers and those who limit their travel to urban centers is considered low because of they have a lower likelihood of acquiring JE in these settings [16].

JE vaccine has been available in the United States since 1993, and from 1993 to 2017 only 12 JE cases among US travelers have been reported to the Centers for Disease Control and Prevention (CDC) [18]. And from 1973 to 2017, 84 JE cases among travelers or expatriates from nonendemic countries were published or reported to the CDC [18]. And prior to 1973, there were more than 300 cases of JE infection reported among soldiers from the United States, the United Kingdom, Australia and Russia [18]. The current overall incidence of JE among people from nonendemic countries traveling to Asia is approximately <1 case per 1 million travelers [18]. However travelers who stay for >1 month in rural areas with active JE virus transmission might have similar risk to the susceptible pediatric resident population of 6 to 11 cases per 100,000 children per year [18]. And before the introduction of JE vaccine, summer outbreaks of JE occurred recurrently in Japan, Korea, China, Okinawa and Taiwan [19]. And from 1999 to 2009 there had been a pattern of enlarging recurrent seasonal outbreaks in Vietnam, Thailand, Nepal, and India, with smaller outbreaks in the Philippines, Indonesia and northern Australia [19]. In addition, with global warming, the territories of several mosquito-borne infections,

including that of JE, are expanding with recent JE epidemics reaching Pakistan, Papua New Guinea and southeastern Russia [17].

Most human infections with JE virus are asymptomatic and <1% of people infected with JE virus develop neurologic disease [18]. Acute encephalitis is the most commonly recognized clinical manifestation of JE virus infection , and according to World Health Organization (WHO) about 1 in 250 infections results in these type of severe clinical infections and approximately 68,000 global clinical cases yearly [18, 20]. The incubation period is 4-15 days [17, 18]. Clinical symptoms usually start with a sudden onset of high fever, chills, headache and vomiting. Mental status changes, focal neurologic deficits, generalized weakness, and movement disorders may develop over the next few days [17, 18]. The classic description of JE includes a parkinsonian syndrome with mask-like facies, tremor, cogwheel rigidity, and choreoathetoid movements [18]. Neurologic manifestations may include meningeal signs like nuchal rigidity or photophobia (meningitis), parenchymal (encephalitis) or spinal cord (myelitis) involvement [19]. Milder infections may present as aseptic meningitis, undifferentiated febrile illness or acute flaccid paralysis [18]. Seizures are more common in infected children with 50-85% developing focal or general seizures, compared to 10% of adult cases [18, 19]. Unfortunately, seizures are associated with a poor clinical outcome [19]. Among symptomatic patients, the fatality rate is 20-30% [17, 18]. And among survivors, 30-50% have serious neurologic, cognitive, or psychiatric sequelae [17, 18].

JE should be suspected in a patient with evidence of neurologic infection and who has recently traveled to or resided in an endemic country in Asia or the western Pacific [18]. A suspected case of JE virus infection should be confirmed with a laboratory diagnosis by

performing a JE virus-specific IgM-capture ELISA on CSF or serum [18]. There is no specific antiviral treatment for JE, so care consists of supportive care and management of complications, such as controlling seizures and reducing cerebral edema [19] [18]. Recovery of neurologic deficits caused by JE viral infection may take weeks to years [19]. And as mentioned previously, up to one-third of patients have permanent seizure disorders, motor and cranial nerve paresis, and movement disorders [19]. Persistent behavioral and/or psychological abnormalities occur in 45-75% of survivors and are more severe in children [19].

It is important to understand that since the majority of human JE infections are asymptomatic, the cases that are reported are a gross underestimate of the infectious burden of an area [19]. The ratio of infections to symptomatic JE cases has been estimated to vary between 1:25 and 1:300 in endemic countries, with lower rates observed in northern Asian indigenous persons and higher rates were measured in non-indigenous military personnel [19].

Given there is no treatment for JE infection it is best to prevent the infection. Prevention of JE, like any mosquito borne disease is to avoid mosquito bites by using mosquito repellant, wearing long-sleeved shirts and pants, avoiding outdoor activities in the evening and by sleeping under permethrin-treated mosquito nets or in screened or air-conditioned accommodations [18, 19]. In addition to personal protective measures there is one JE vaccine licensed and available in the United States, an inactivated Vero cell culture-derived vaccine, Ixiaro® (JE-VC) [18]. Ixiaro® is manufactured by Valneva Austria GmbH. It was approved by the U.S. Food and Drug Administration (FDA) in March 2009 for use in people ≥ 17 years old and in May 2013 for use in children 2 months through 16 years old in both the U.S. and the European Union [18, 21, 22]. There are other inactivated and live attenuated JE vaccines are

manufactured and used in other countries but are not approved for use in the U.S. [18]. For children 2 months through 17 years old, the Ixiaro® vaccine is administered as 2 intramuscular doses given 28 days apart [18, 22]. For travelers who received their first JE vaccine series ≥ 1 year prior to potential JE virus exposure, Advisory Committee on Immunization Practices (ACIP) recommends providing a booster dose prior to departure [18].

The safety and efficacy of Ixiaro® has been well established and is much different than the previous JE vaccine, JE-VAX. JE-VAX (JE-MB), the mouse brain derived vaccine against JE virus was licensed in the U.S. in 1992, production of JE-MB was stopped in 2006 and it was discontinued in 2011 after remaining doses expired [23, 24]. JE-VAX had a history of rare but serious adverse reactions to include severe allergic reactions and neurologic side effects, with severe local reaction reported in 20% and systemic adverse effects in 10% of people [24]. And as mentioned previously the current JE vaccine, Ixiaro®, was not licensed for use in pediatric patients until 2013 but it was used either off-label or by enrolling children in ongoing clinical trials between 2011 when JE-VAX was no longer available and 2013 when Ixiaro® was approved for children [23, 24]. Ixiaro® was used off-label for at risk children in a U.S. Travel Clinic from 2011 to 2014 and assessed for its tolerability. Of the 92 patients, less than 18 years of age who received at least one dose of Ixiaro®, during that time, only 7 adverse events were documented and only one was determined to be possibly related to the vaccine. And no serious adverse events were found on chart review. This study reinforced the decision to expand Ixiaro® vaccination to the pediatric population [24]

In a 2018, uncontrolled, open-label Phase 3 study of 100 children aged 2 months to less than 18 years of age, planning to travel to countries where JE is endemic, the safety and

immunogenicity of Ixiaro® was evaluated [25]. The primary endpoint was the rate subjects had severe adverse events (SAEs) or medically attended adverse events (MAEs) up to Day 56 after first Ixiaro® injection, and none were reported, which was not surprising given the small sample size of 100 healthy children, and the rates were similar to adults studies (1% SAEs) and children from endemic countries (0.5% SAEs) [25]. All subjects available to be tested on day 56 (62/62; 100%) developed protective levels of JE neutralizing antibodies by Day 56 and 31/34 (91.2%) retained protective titers at seven months post vaccination [25]. Overall, this study confirmed the safety profile and immunogenicity of Ixiaro®, seen in larger studies done in endemic countries [25]. An Ixiaro® pediatric phase 3 study was conducted in the Philippines, an endemic country for JE. In this 2017 age-stratified study of 1,869 children, 2 months to 17 years of age were randomized to either Ixiaro® or one of the control vaccines, Prevnar or Havrix® 720, were monitored for adverse events and assessed up to day 56 and 7 months after the first dose of vaccine given [26]. Subjects receiving JE vaccine had comparable rates of unsolicited AEs within all age groups compared to control vaccines, Prevnar or Havrix® 720 [26]. In this same study, they also evaluated immunogenicity, and found that at both the 0.25mL (<3 years old) and the 0.5mL (≥ 3 years old, the adult dose) doses, that >99% of the subjects had protective antibody titers at day 56 and that at month 7, seroconversion was maintained in 85.5-100% of subjects [27].

Unlike previously published data on children vaccinated with Ixiaro®, the 2020 study, provided support for the recommendation for a booster dose in children who remain at risk of JE from 1 year after the primary series, which was consistent with the recommendation for adults [28]. This was due to the considerable decline in geometric mean titers for JE virus

neutralizing antibody titers, compared to the initial titer determined 4 weeks after the first immunization with Ixiaro® compared to that measured at day 56-60.8 [28].

Indications for recommending JE vaccine for travelers

The indications for recommending JE vaccine for travelers is multifactorial and should be considered for the following short-term, long-term and frequent travelers to JE endemic areas. JE vaccine is indicated for short-term travelers whose itinerary or activities might increase their risk for exposure to JE virus, for example extensive outdoor activities or those staying in accommodations without air conditioning, window screens or bed nets [18, 29]. JE vaccine is also indicated for long-term (>1mo) travelers who plan to be in endemic areas during JE virus transmission season [18, 29]. And finally JE vaccine is indicated for frequent travelers to JE endemic areas, regardless of the duration of each individual trip [18, 29]. JE vaccine is not recommended for travelers with trips limited to urban areas and outside of JE virus transmission season, these factors are considered very low-risk itineraries [18].

Rabies

Rabies is a fatal, acute, progressive encephalomyelitis caused by neurotropic viruses in the family Rhabdoviridae, genus *Lyssavirus* [30, 31]. Rabies is a zoonotic disease, transmitted from animals to humans, typically by the infected saliva from a bite by a rabid animal [31, 32]. Rabies virus is neurotropic and gains access to the peripheral nervous system at a nerve synapse at the site of the bite, and then travels through peripheral nerves to the central nervous system, where most viral replication occurs [30]. Once viral replication occurs, this results in clinical signs in the infected patient [30, 33]. Dogs are the most common reservoir of the virus, in developing countries, with more than 99% of human deaths caused by dog-mediated rabies [31, 33]. However, since all mammals are assumed to be susceptible to

infection, in addition to dogs the major rabies reservoirs include monkeys, raccoons, skunks, foxes and bats [30, 31, 34]. Animal reservoirs can vary based on the country, but bat bites anywhere in the world, should be evaluated and considered for prophylaxis [30, 31]. The virus cannot infiltrate intact skin, however because bats have tiny teeth, their bites can be overlooked, it is out of abundance of caution that a person sleeping in a room with a bat is evaluated for rabies infection [30].

Rabies is estimated to cause 59,000 human deaths yearly in over 150 countries, with 95% of cases occurring in Africa and Asia [33]. The burden of rabies infections has disproportionally affected rural populations and children under 15 year of age [33]. Different variants of *Lyssaviruses* exists and vary by region and have adapted to various mammalian hosts, such as dogs, bats, foxes, jackals, mongooses, raccoons and skunks [30]. Although dog-mediated rabies has been eliminated by animal vaccination programs in Western Europe, Canada, the United States, Japan and some Latin American countries [30, 33], canine rabies still exists in Africa, Asia and parts of Central and South America [30, 33]. Rabies has caused an estimated 35,000 human deaths per year in Asia, with 59.9% of those deaths in India [33]. The cost of postexposure prophylaxis (PEP) is highest in Asia, estimated at 1.5 billion USD per year [33]. In Africa, canine derived rabies causes an estimated 21,000 human deaths per year [33]. Africa, according to WHO, is estimated to spend the least on PEP and have the highest cost of human mortality [33]. The rate of rabies exposures in travelers is estimated to range from 16 to 200 per 100,000 travelers, the wide range is due to inconsistent surveillance and reporting procedures [30]. The true burden of disease and therefore risk to travelers, is likely

underestimated due to chronic underreporting and political neglect in many developing countries [33].

Clinical signs and symptoms of rabies begins once the virus invades the peripheral nervous system and then reaches the central nervous system and terminates in acute fatal encephalitis[30]. Once clinical signs are evident, most patients die quickly without intensive supportive care, to date less than 20 cases of human survival have been documented, and only a few survivors had no history of pre-exposure prophylaxis (PrEP) or PEP [30, 34]. The asymptomatic incubation period is typically 1 to 3 months, but it can range from 7 days to 1 year [32, 33]. The incubation period has such a wide range because it depends on several factors; the location of bite - closer proximity to the brain will result in faster onset of symptoms; severity of the bite wound; the amount of virus inoculated within the wound; and the degree of innervation at the site of the bite wound [33]. Initial symptoms can be non-specific and often include fever, pain, unusual or unexplained tingling, pricking or a burning sensation (paresthesia) at the wound site [30, 33].

Rabies infection manifests in two forms: furious (classical or encephalitic) form in 80% of human cases and the paralytic form in 20% of cases [32, 33]. Encephalitic rabies is characterized by hyperexcitability, hypersalivation, autonomic dysfunction, periods of agitation alternating with lucidity, spasms of swallowing muscles can be stimulated by the sight, sound, or perception of water (hydrophobia) and sometimes aerophobia [30, 32, 33]. After a few days of these symptoms, the infection consistently leads to coma and death by cardio-respiratory arrest [33]. In paralytic rabies there is flaccid paralysis in the bitten limb that ascends symmetrically or asymmetrically, followed by gradual paralysis then death by respiratory failure

[32, 33]. Paralytic rabies has a less intense but longer course than encephalitic rabies and is often misdiagnosed and underreported [32, 33].

Diagnosis can be difficult because there are not widely available tests to diagnose human rabies infection antemortem or before the onset of clinical disease [30, 33]. Rabies should be included in the differential diagnosis of all patients who present with unexplained, acute progressive viral encephalitis, regardless of exposure history or if not living in areas endemic for rabies [33]. Given the long incubation period it may be difficult to identify a specific exposure for rabies virus [30]. Definitive antemortem diagnosis requires high-complexity experimental test methods on multiple samples [30]. Rising levels of rabies virus-neutralizing antibodies, especially in the cerebrospinal fluid, is diagnostic in an unvaccinated, encephalitic patient [30]. Rabies is a nationally notifiable disease in the U.S. and the CDC is designated at the national rabies reference laboratory [30]. For postmortem diagnosis, the gold-standard technique is to detect rabies virus antigen in infected tissues, preferably brain smears or touch impressions collected by a biopsy by fluorescent antibody test [33]. WHO recommends fluorescent antibody test because it gives reliable results in 95-99% of cases on fresh specimens [33].

There is no curative evidence-based treatment for rabies once clinical signs have appeared [30]. Most patients are managed with symptomatic and palliative supportive care [30]. All cases of suspected rabies exposure should be treated immediately to prevent the onset of clinical symptoms and death [33]. Rabies is considered universally fatal for practical purposes and preventive measures of proper wound care, PrEP and PEP are the only way to optimize survival if bitten by a rabid animal [30, 35].

Prevention of rabies in travelers must include education about risks, how to avoid bites or scratches from mammals, consideration of PrEP, how to clean a wound if bitten and how to obtain PEP [30, 35]. Travelers should avoid free-roaming mammals, avoid behaviors and actions that may provoke an animal bite, avoid contact with bats, monkeys and other wildlife. Although, most domesticated dogs are vaccinated against rabies in the U.S., travelers should not assume that dogs in foreign countries are vaccinated, and should avoid all dogs while traveling. Any suspected or documented bite or wound from a bat should be grounds for seeking PEP [30]. Children are at higher risk for rabies exposure and infection because of their curious nature, inability to sense danger from dogs and other animals; and potential lack of reporting an exposure [30]. Children have an increased risk of severe disease since they are more often bitten on the face, head or neck, due to their small stature [30].

Pre-exposure vaccination

Pre-exposure vaccination for rabies or rabies PrEP is recommended for certain international travelers based on frequency of rabies infection in the destination country; the availability of rabies PEP, rabies immune globulin (RIG); the risk profile of the traveler based on planned activities; if they will be in remote areas and finally the traveler's length of stay [30, 32, 35-37].

In the U.S., rabies PrEP consists of a series of 3 intramuscular injections given on days 0, 7, and 21 or 28 in the deltoid with human diploid cell rabies vaccine (HDCV) or purified chick embryo cell (PCEC) vaccine [30]. If all 3 doses of rabies vaccine cannot be completed prior to travel, then the traveler should not start the series since little data exist to guide PEP after partial immunization series is given [30]. Preexposure vaccination does not eliminate the need

for urgent medical attention after a rabies exposure, but it does simplify PEP [30, 36]. In addition PrEP may also provide some protection when an exposure to rabies virus is not recognized or if PEP is unintentionally delayed [30]. Travelers who have completed the 3 dose PrEP vaccination series or have received full PEP are considered previously vaccinated and do not require routine boosters [30, 31].

Indications for recommendations for rabies pre-exposure prophylaxis

The CDC has criteria for pre-exposure immunization for rabies based on the risk category of the individual [30]. The highest risk category is those at continuous risk, then in descending order the other categories are frequent, infrequent and rare [30]. The infrequent risk category, that has a greater risk than the general population, includes travelers visiting areas where rabies is enzootic and immediate access to medical care, including RIG, is limited; should receive a primary course of PrEP but do not require serologic testing or booster vaccination [30, 31].

Wound management

Any animal bite or scratch should be thoroughly cleaned with generous amounts of soap and water, povidone iodine, or other disinfectants with virucidal activity [30]. It is essential that all travelers are informed that immediately cleaning bite wounds substantially reduces the risk of rabies virus infection, especially when followed by well-timed administration of PEP [30, 33]. For patients that did not receive, PrEP vaccination, if suturing is required it should be delayed for a few days unless RIG can be injected into the wound tissues prior to closure [30].

Postexposure prophylaxis

According to WHO, postexposure prophylaxis for rabies infection should be administered based on the category of exposure to suspect rabid animal [33]. Category 1 exposures include touching or feeding animals, licks on intact skin and are not considered true exposures, so no PEP or wound care is indicated [33]. Category 2 exposures include nibbling of uncovered skin, minor scratches or abrasions without bleeding and require immediate vaccination and wound care management [33]. Category 3 exposures include single or multiple transdermal bites or scratches, licks on broken skin; contamination of mucous membrane with saliva from licks, exposures to bats; require immediate PEP vaccination and administration of RIG and wound care management [33, 38].

PEP for someone previously vaccinated with PrEP consists of 2 does of modern cell-culture vaccine given 3 days apart, days 0 and 3 and RIG is not required [30, 38]. These doses should be given as soon as possible after exposure and they do not have to be the same brand as the PrEP vaccinations [30, 31]. PEP for an unvaccinated patient, someone who did not receive PrEP, consists of administration of RIG, 20 International Units/kilogram for human RIG or 40 IU/kg for equine RIG and a series of 4 injections of rabies vaccine over 14 days, or 5 doses over a 1 month period in immunosuppressed patients [30, 31]. After wound cleansing, as much of the dose-appropriate volume of RIG that is anatomically feasible should be injected at the wound site. The goal is to put the RIG in the areas where the infected saliva may have contaminated wounded tissue [30]. Any remaining RIG dose must be injected intramuscularly at a site distant from the site of rabies vaccine administration. If volume of RIG is insufficient to inject all the wounds, it should be diluted with normal saline, this can be an issue with children

whose body weight may be small in relation to the size and number of wounds [30]. It is important to educate travelers that RIG is difficult to access in many countries and this should be considered when doing the risk assessment and determination if PrEP should be administered [33, 35, 38]. Recent studies show that only 5-20% of travelers received RIG in the country of exposure when indicated [38].

Rabies vaccine has the common adverse reactions of a local reaction after vaccination, which includes pain, erythema, swelling and itching at the injection site; or mild systemic reactions like headache, nausea, abdominal pain, myalgias and dizziness [30]. Approximately 6% of people receiving booster vaccinations with human diploid cell vaccine (HDCV) may have systemic hypersensitivity reactions but the likelihood of these reactions are reduced by using PCEC vaccine [30]. PrEP with PCEC vaccine administered to over 1,200 children in clinical trials and has been proven safe, well tolerated and immunogenic [39].

Pre-travel consultations in pediatric international travelers

There is limited information about pre-travel consultations and vaccine administration for pediatric international travelers, especially long-term or VFR travelers. Specifically U.S. pediatric international travelers are an understudied population and that is why the review of the literature includes information on Canadian and European pediatric travelers. In a descriptive analysis conducted on pre-travel consultations completed from January 2013 to August 2014 at a large tertiary care center in Toronto, Canada, they noted that of the 370 pre-travel visits that 48% were for children <18 years of age and that children <5 years of age were more likely to have VFR travel ($p< 0.0001$) and children VFRs (cVFRs) were more likely to travel for >28 days than children traveling for vacation (43% vs 1%, $p <0.0001$)[40]. And the majority (85%) of the VFR travelers, accommodations were staying with locals, friends and or relatives

and 98% traveled to urban destinations [40]. Among cVFRs, about half traveled to destinations in Asia and 27% to Africa, specifically cVFRs were more likely to travel to Asia than children traveling for vacation (51% vs 16%, p <0.0001) [40]. Rabies vaccine and Japanese encephalitis vaccine were the least prescribed interventions at 0%, compared to the most frequently prescribed vaccines of hepatitis A (60%) and typhoid vaccines (58%) [40].

In a smaller Greek airport based study, conducted from 2011 to 2015, 68 adolescents (12 to 18 years) participated, all with destinations to either Africa or Asia [41]. Most (69%) adolescents planned to stay for less than 1 month and 60% main purpose for travel was VFR; VFRs, compared to non-VFR adolescents, more frequently traveled to sub-Saharan Africa and Southeast Asia, stayed in local residences, and stayed for longer durations [41]. However only 31% of all adolescent travelers had pre-travel consultations, compared to 19% of children and 29% of adults (p-value = 0.009) and of the 31% of adolescent pre-travel consultations, 57% of these visits were completed 8-14 days before departure, which is not enough time to complete certain travel vaccinations, like rabies or JE vaccine [41]. However more adults (28%) received pre-travel consultations > 28 days before trip departure compared with adolescents (5%) and children (5%); p-value < 0.001 [41]. And it was noted that vaccination against rabies, typhoid fever, JE and meningococcus was highly inadequate for adolescents traveling to endemic areas [41].

In a 2013 GeoSentinel Network study of illness in over 40,000 returned travelers between 2007 and 2011, it was noted that only 40.5% of all ill travelers reported having a pre-travel consultation visit [9]. VFR travelers were noted to have a higher burden of disease than other travelers and very low rates of pre-travel advice (18.3%) [9]. In a 2006 study it was noted

that only 16% of immigrant VFRs sought pre-travel consultation advice and they also more often presented with potentially preventable travel-related illnesses than did tourist travelers [4].

Identifying reasons for lack of pre-travel consultations for pediatric travelers

It is established that pre-travel consultations for all travelers are underutilized and even more so for pediatric travelers. Global TravEpiNet (GTEN), which is a consortium of travel medicine clinics in the US, conducted a study from 2009 to 2012, where over 32,000 travelers that presented for a pre-travel visit at 19 travel clinics, it was noted that only 10% of those travelers were children (<18 years of age) [42]. Since the amount of children that travel is lower than adults, there is less information known about the specific risks to pediatric travelers [5]. Preparing a child to travel is more complicated than for adults because the provider must ensure that the child's routine immunizations are up-to-date, and that they meet the age or weight requirements for travel-related vaccines or malaria prophylaxis [5]. And if parents do not schedule the pre-travel visit far in advance of the scheduled trip, there might be insufficient time to catch-up on routine immunizations or complete travel vaccines series, like rabies PrEP or JE vaccine [5]. In the GTEN study above, children traveled equally for leisure (36%) and for VFR (36%) but VFR children were more likely to present <14 days before departure for pre-travel consultation (44% vs 28%) and trip duration was 28 days or longer (70% vs 22%) [42]. VFR travelers are more likely to travel last minute due to unexpected emergencies with family or friends, such as visiting a sick relative or attend a funeral service [6].

At five Boston-area travel clinics, data was collected from 2008 to 2010, on over 15,000 adult travelers, Asia was the most common destination, with 20% traveling for greater than one

month. Of those traveling to JE-endemic countries in Asia, over one-third with trips greater than 1 month had insufficient time to complete a series of either JE or rabies vaccine [43]. And in Greek adolescents traveling to Asia and Africa over half (57%) sought pre-travel counseling only 8-14 days prior to departure, which is insufficient time to complete rabies PrEP or JE vaccination [41].

Strategies must be developed to engage pediatric travelers in timely, pre-travel care and improve acceptance of pre-travel healthcare interventions. Based on previous research the top reasons for refusal of a recommended travel vaccine are concerns about cost, safety, or lack of concern about the illness [44]. Parents or guardians of one-third of the children refused at least 1 recommended travel-related vaccine, including refusal of rabies (44%) and JE (41%) [42, 44]. Specifically parents or guardians of pediatric VFR travelers were more likely to refuse rabies vaccine [42]. Pediatric VFR travelers are more at risk in general due to adopting local-health related behaviors during the trip, underestimating the perceived risk of travel and aversion to pre-travel consultation and intervention costs [9]. And all of these factors contribute to barriers to seeking travel vaccination and create a health disparity for the vulnerable population of pediatric VFR travelers. For all travelers (adult and pediatric) in this study, the most common reason for refusal of travel-related vaccines was lack of the concern about the illness [44]. In a multivariable analysis to evaluate predictors of accepting all vaccines recommended at the pre-travel encounter, the parents' of youngest patients (0-5 years) were more likely to accept recommended vaccines. Also, travelers with trip durations of < 4 weeks were more likely to accept all vaccine than travelers with trips > 4 weeks (OR 1.41, 95%CI [1.03-1.92]) [44]. But despite JE vaccine having a low incidence of serious adverse events, the cost of up to $500 U.S.

dollars for the series is cost prohibitive when parents have to pay for them out of pocket since travel vaccines are not covered by the Vaccines for Children program or most insurance plans [45].

Although the literature has evaluated some of the unique challenges to pediatric travelers and the barriers to their care, further investigations need to be done. Pediatric travelers (ages 0-17 years) are an understudied population, although it is estimated that 2.4 million U.S. children travel internationally yearly [3]. In particular, long-term pediatric travel may be associated with higher risk of exposure to infectious diseases such as Japanese encephalitis (JE) and rabies. While recommended for long-term travelers, vaccines for these diseases can be prohibitively expensive. This retrospective study aims to describe factors associated with the administration of rabies pre-exposure prophylaxis (PrEP) and JE vaccine in pediatric travelers, who presented to Emory TravelWell Center, to identify barriers to uptake.

Chapter 2: Manuscript

Title: Factors associated with the administration of rabies PrEP and Japanese encephalitis vaccine to pediatric international travelers at a U.S. travel clinic: a retrospective analysis

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Abstract:

Background: Pediatric travelers are an understudied population although an estimated 2.4 million United States children travel internationally yearly. Long-term pediatric travel can be associated with higher risk of infections, like Japanese encephalitis (JE) and rabies. This study aims to describe factors associated with the administration of JE vaccine and rabies pre-exposure prophylaxis (PrEP) in pediatric travelers and determine if cost and timing of the pre-travel visit are barriers for these vaccines. **Methods:** A retrospective chart review was conducted on children (<18 years of age) who visited the Emory TravelWell Center in Atlanta, Georgia between June 1, 2011 to June 30, 2015 for pre-travel consultation. Abstracted data included demographics and travel itinerary details. Descriptive statistics, univariate, and multivariate analyses were conducted to examine associations between method of payment and administration of JE vaccine and rabies PrEP. **Results:** 352 travelers were analyzed, and the majority of travelers (68%) self-paid for the pre-travel consultation. Africa was the most common destination region (35%), followed by Asia (32%). Almost 50% of travelers pre-travel visit was <21 days from departure date and 58% was <28 days. On subset analysis of Asia only travelers (n=108), JE vaccine was administered to 11.1% of children, with 17.6% not vaccinated due to insufficient time before departure. Sufficient time to complete JE vaccine series (aOR= 8.03; 95%CI 1.25, 51.75) was significantly associated with JE vaccine administration while cost covered by insurance showed no difference in JE vaccine administration (aOR=0.82; 95%CI 0.14, 4.67). Rabies PrEP was administered to 9.3% of children, with 9.6% not vaccinated due to insufficient time (n=332). However, for rabies PrEP, method of payment and sufficient time to complete rabies series were both significantly associated with rabies PrEP administration (aOR = 3.44; 95% CI 1.24, 9.58) and (aOR=17.36; 95%CI 3.65,82.55). **Conclusions:** Cost was a barrier to travel prophylaxis administration for rabies PrEP but not for JE vaccine, though having sufficient time to complete rabies PrEP or JE vaccine both had significant association with vaccine administration. These results highlight the importance of a well-timed pre-travel consultation, so there is sufficient time to complete travel vaccination series for pediatric international travelers.

Background:

In 2019, there were approximately 38 million United States (U.S.) citizens who traveled overseas, excluding visitors to Canada and Mexico [1]. Pediatric travelers (ages 0-17 years) are an understudied population, although it is estimated by the Centers for Disease Control and Prevention (CDC) that 2.4 million U.S. children travel internationally yearly [3].

More travelers are going to low and middle income countries (LMIC) where they are more at risk for travel related illness and exposure to tropical infectious diseases[4, 5]. Long-term travelers going to these destinations are more likely to be a traveler who is 'visiting friends and relatives', often referred to as a VFR traveler, "which is an immigrant, ethnically and racially

distinct from the majority of the population of the country of residence, who returns to his or her home country to visits friends or relatives" [6, 7]. VFR travelers are at increased risk of travel-related health problems and are less likely to seek pre-travel health advice or travel immunizations [4, 8]. Pediatric VFR travelers are especially vulnerable and should have a pre-travel consult with a provider that has the expertise of both travel medicine and pediatrics to be able to provide recommendations on immunizations, travel and routine, and medications unique to this population.

There is a need to understand the relationship between pediatric international travelers and the potential barriers to pre-travel consultation and administration of vaccinations in the United States. Administration of travel vaccinations in pediatric international travelers prevents unnecessary infections and the morbidity and mortality related to that specific disease, whether that is, Japanese encephalitis or rabies, for example; and that is why pre-travel consultations are important to public health.

There seems to be a lack of data on pre-travel visits for pediatric international travelers, most of the studies available are on post-travel visits for travelers of all ages, not specifically pediatric travelers. And this has created a knowledge gap on the unique challenges of pediatric international travelers and their barriers to seeking and following pre-travel guidance and vaccine administration.

In particular, long-term pediatric travel may be associated with higher risk of exposure to infectious diseases such as Japanese encephalitis (JE) and rabies. While recommended for long-term travelers, vaccines for these diseases can be prohibitively expensive since they often require out-of-pocket payment. Yet, both of these vaccines are specifically important to

preventing infection in pediatric travelers, especially rabies which children are at higher risk for due to their behaviors around animals and Japanese encephalitis due to not reporting small bites from mosquitoes. This study aims to describe factors associated with the administration of rabies pre-exposure prophylaxis (PrEP) and JE vaccine in pediatric travelers to identify barriers to uptake. Primarily, this study will analyze how cost of the pre-travel visit and vaccine administration can be a potential barrier for receiving rabies PrEP and JE vaccine. Secondly, it will look at how insufficient time to complete these vaccination series based on timing of the pre-travel visit can be a barrier to vaccine administration.

Methods:

Study site and population

A retrospective chart review for an observational cross-sectional study was conducted on patients aged 0 to 17 years of age who presented to the Emory TravelWell Center in Atlanta, Georgia between June 1, 2011 and June 30, 2015 for pre-travel consultation. Eligible participants included any patient aged 0 to 17 years of age who presented to the U.S. travel medicine clinic detailed above for a pre-travel consultation visit. Abstracted data included demographics, pre-travel healthcare, and travel itinerary details for all pediatric travelers during the study period. After data cleaning, all analyses were performed in SAS version 9.4 [46]. Descriptive statistics were performed on the main study variables and p-values describing the differences between travelers who self-paid and those who had cost covered by insurance for the pre-travel visit and the recommended travel vaccinations were calculated for each variable using chi-square, Fisher's exact test or t-test where appropriate. In univariate analyses, calculation of unadjusted odds ratios provided insight into an association between exposures of interest, such as length of stay (LOS), VFR traveler, and sufficient time to complete JE or Rabies

series prior to travel and the outcome of interest, JE or Rabies vaccine administration. For the JE analysis a subset of study participants whose destination was an Asian country was used for both the univariate and multivariate analyses. A p-value of < 0.05 was considered significant.

Multivariate analysis:

The goal of the analysis was to determine the adjusted odds ratio of method of payment- insurance coverage (exposure) in those who did or did not have JE or rabies PrEP vaccine administered (outcome). For the multivariate analyses, two different models were undertaken, with JE and rabies PrEP vaccine administration analyzed separately. Model diagnostics included testing for interaction and confounding assessment. For the JE model, after univariate analysis, the variables significantly associated with JE vaccine administration were included in a multivariate stepwise logistic regression. The same steps were taken for the rabies PrEP model analysis. Adjusted odds ratios (aOR) for the exposure variable (method of payment) as well as the other variables were calculated through logistic regression. Multivariate logistic regression was used to assess the association between cost of vaccine and vaccine administration while controlling for potential confounding factors such as age, sex, or purpose of travel. A p-value of < 0.05 was determined to be significant. All analyses were done using SAS version 9.4 [46].

Human Subject & Ethical Approval Considerations:

This study was approved by the Emory Institutional Review Board (IRB). Participant privacy was assured by the use of de-identified study identification numbers in the dataset created from the retrospective chart review.

Results:

Overall characteristics:

Chart review was completed on 352 pediatric patients, who were seen from 2011 to 2015, at Emory TravelWell Center, and who were included in this analysis. Demographic data and details of travel characteristics of the pediatric international travelers are described in Table 1. The mean age of travelers was 9.9 years and a wide range of ages seen, from 1 week old to 17 years old. 25% were young children, between 0 to 5 years old. There were slightly more females than males (54% vs 46%).

Of all travelers, 33% traveled to visit friends and or relatives (VFRs). Other travel purposes included leisure (37%), missionary work and/ or volunteer (18%), education or research (6.6%), accompanying parents on business (4.5%) and adoption (<1%). Africa was the most common destination region (35%), followed by Asia (32%), North and Central America (28%), South America (4%), Europe and Australia and Oceania combined (1%). The top 5 destination countries were India (15.3%), Kenya (5.3%), and China, Ethiopia and Nigeria tied for third place (4.7% each). The majority of travelers were visiting both urban and rural locations (52.7%), followed by urban only (34.6%) and rural only (12.7%).

The trip duration included a wide range from 4 days to 1300 days, with the longer trips due to parents with extended business trips or temporary relocation for business, research or missionary work. The median and mode for trip length was 14 days and the interquartile range was 18 days. When travelers presented to clinic for their pre-travel consultation and or travel vaccinations varied from last-minute visits within 24 hours of departure (3%) to those who planned in advance with clinic visits more than 4 months from departure (3%). But 95% of all visits were less than 90 days prior to departure date. Almost 50% of travelers presented to

clinic at 21 days or less from departure date. And 58% of travelers presented to clinic at 28 days or less from departure. This is important to note since it requires 21 days to complete the rabies PrEP series and 28 days to complete the JE vaccine series.

The majority of travelers self-paid for the pre-travel consultation and vaccinations (68%), compared to those who had cost covered by corporations or insurance (32%). The demographic details of the travelers that had costs of the pre-travel consultation visit and vaccines covered by insurance compared to those who had to self-pay were similar and no statistical significance identified on univariate analyses (Table 2).

Given JE vaccine is only indicated for specific destinations to Asian countries and itineraries with more rural than urban travel, a subset analysis of travelers only visiting Asia was used (n=108). JE vaccine was given to 11.1%, refused by parents/guardians in 4.6% and not given due to insufficient time in 17.6% of indicated pediatric travelers. There were 51 (48%) VFR travelers who traveled to Asian countries and 21 VFR travelers with LOS >28 days and none of these travelers received JE vaccine. Rabies PrEP vaccine is indicated more often based on risk of activities planned during the trip, it was given to 9.3%, refused by parents/guardians in 4.5% and not given due to insufficient time in 9.6% for the 332 travelers reviewed.

Results of the univariate analyses:

On univariate analysis of the outcome, JE vaccine administration was significantly associated with sufficient time (> 28 days) to complete JE vaccine series (OR = 6.67; 95% CI 1.34, 33.14), length of stay > 28 days (OR = 17.72; 95% CI 2.15, 146.05) and age (OR = 1.25; 95% CI 1.05, 1.49) (Table 3). However, there was not a significant association between JE vaccine

administration and method of payment, but since this was the primary exposure it was retained in the model for multivariate analysis.

On univariate analysis of the outcome, Rabies PrEP vaccine administration was significantly associated with method of payment (OR = 2.82; 95% CI 1.33, 5.97), sufficient time (21 days) to complete Rabies PrEP series (OR =13.7; 95% CI 3.19, 58.98), and length of stay > 28 days (OR = 22.43; 95% CI 7.48, 67.26) (Table 4). Age was also significantly associated with Rabies PrEP vaccine administration, see Table 4 for details.

Results of the multivariate analyses:

First model: JE vaccine administered was the outcome with the primary exposure method of payment (n= 105). Tests of interaction showed no interaction of the covariates with the exposure variable. After confounding assessment, the best model that retained precision was chosen. The variables retained in the model are detailed in Table 3 with the adjusted odds ratios. All variables retained in the model except method of payment were statistically significant (see Table 3). Those with cost covered by insurance showed no difference in JE vaccine administration (aOR = 0.82; 95% CI 0.14, 4.67). Of note travelers with sufficient time to complete JE vaccine series had an adjusted odds ratio of 8.03 (95% CI 1.25, 51.75), this was significant.

Second model: Rabies PrEP vaccine administered was the outcome with the primary exposure method of payment. Tests of interaction showed no interaction of the covariates with the exposure variable. After confounding assessment, the best model that retained precision was chosen. The variables retained in the model are listed in Table 4, along with the adjusted odds ratios. In this model, those with cost covered by insurance was associated with Rabies

PrEP vaccine administration (aOR = 3.44; 95% CI 1.24, 9.58), and it was significant. In addition, having sufficient time (>21 days) (aOR = 17.36; 95% CI 3.65, 82.55) and LOS >28 days (aOR = 24.67; 95% CI 7.00, 87.02) were both associated with rabies PrEP administration.

Discussion:

This retrospective cross-sectional study provided valuable details on the demographics and travel patterns of 352 pediatric international travelers at a U.S. based travel clinic. While previous studies have focused on post-travel visits as a result of illness acquired during international travel, this is one of few studies to focus on the pre-travel visit for this specific population. The main study question on whether cost was a barrier to administration of travel vaccinations resulted in a significant association for rabies PrEP but a not significant association for JE vaccine using multivariate analyses. This was somewhat surprising given the cost for both of these vaccine series at Emory TravelWell Center are similar, with rabies PrEP cost approximately $330/dose and JE vaccine cost approximately $350/dose. Although other studies have hypothesized that cost might be an important barrier to travel vaccine administration, the results seem to be more inconsistent for JE vaccine, but this could be due to the lower frequency that it is indicated and prescribed for travelers [44]. However, it was interesting that the frequency of JE vaccine indicated and received (11.1%) was much less than those that were not given it due to insufficient time (17.6%) in pediatric international travelers in this study. Almost half of the travelers in this study presented for the pre-travel consultation visit less than 21 days prior to trip departure date, which is insufficient time to complete the rabies PrEP or JE vaccine series. In bivariate analysis there was a significant relationship between sufficient time to complete the vaccination series for both rabies PrEP and JE vaccine. These results highlight

the importance of a well-timed pre-travel consultation visit, so that there is sufficient time to complete travel vaccination series of rabies PrEP and JE vaccine for pediatric international travelers. Ideally the pre-travel visit should be scheduled at least 28 days prior to departure to remove the potential barrier of time so necessary travel vaccines can be given. In addition, on the separate multivariate analyses, for JE and rabies PrEP, there were significant associations between sufficient time to complete the respective series and vaccine administration. This suggest that the odds of vaccination were higher among those with sufficient time than those with insufficient time for both JE vaccine (subset of Asia only travelers) and rabies PrEP vaccine recipients. And these findings are consistent with prior studies that noted specifically that lack of time prior to departure to complete the series was a barrier for and contributed to the failure to vaccinate travelers for rabies and JE [44].

Although one-third of the travelers were VFR travelers in this study, unfortunately none of them received the JE vaccine, and therefore this potential association could not be fully evaluated. It is known that VFR travelers and long-term travelers (≥ 28 days) are more likely to refuse vaccines, despite being at potential higher risk of illness due to travel [11, 44]. And our study supported this finding with no JE vaccine administered to the 21 VFR travelers who had length of stay longer than 28 days and who visited Asian countries. It is possible that these VFR travelers did not perceive their risk for JE infection and therefore opted out of the preventative vaccine that was recommended at the pre-travel visit. Fortunately we were able to evaluate the relationship between long-term travel and JE vaccine administration that showed a significant association on both univariate and multivariate analyses. These findings contradict a previous travel vaccine refusal study conducted by GTEN, from 2012-2014, which noted that adult and

pediatric travelers with trip durations less than 4 weeks were more likely to accept all vaccines than those with trips longer than 4 weeks (OR 1.41, 95%CI [1.03-1.92] [44].

A limitation of this study is small sample size, 352 travelers, compared to the much larger multi-site studies conducted by GTEN or GeoSentinel, that include over 20,000 travelers (adult and pediatric). However, in studies that only include pediatric travelers, our study is of similar size. A strength of our study is that we were able to analyze the impact of insurance coverage status for all participants, unlike GTEN studies that typically only report if a participant refused care or vaccination due to cost, since they do not collect insurance coverage data directly. Given the small size of our study, on the subset analysis of Asia only travelers (n=108), none of the 12 travelers that received JE vaccine were VFR travelers, so that relationship could not be evaluated and it was removed from the JE multivariate analysis. As previously discussed it seems the VFR travelers self-selected out of JE vaccine administration possibly due to misconceptions about risk of the disease that is common amongst VFR travelers [4, 6, 40]. Lastly, there were limitations based on the retrospective study design, which was based on data abstraction from chart reviews, some of the data was missing for variables due to incomplete or inconsistent documentation.

The travelers that presented to Emory TravelWell Center might not be representative of all U.S. pediatric travelers, especially since travelers seen at this clinic that did not have to self-pay, were often covered by Emory's employee insurance provider or paid for by corporate accounts as children of business travelers. These travelers may represent children of higher socioeconomic status and may not be inclusive of VFR-immigrant travelers seen in other studies. Access to care can be a barrier to pre-travel consultations, regardless of insurance

status, since most health insurance providers do not consider travel vaccinations essential and require most travelers to self-pay [6]. And this was confirmed in our study with the majority (68%) of travelers required to self-pay for their pre-travel visit and vaccinations.

Overall, this study did show the importance of having a pre-travel consultation prior to international trips for pediatric patients, who are vulnerable to disease and infections based on their typical age-appropriate behavior and or developmental stage. Although this study did not find an association between method of payment and JE vaccine administration, which may have been due to unmeasured confounding in the subjective recommendation of JE for some travelers and not others with the same itinerary by travel medicine providers during the pre-travel consultations. It did note the significant association between insurance coverage and rabies PrEP administration, which supports our hypothesis that when cost is eliminated as a barrier, that uptake of this important vaccine increased. A notable strength of this study is that it highlighted the importance of scheduling the pre-travel consultation visit at least 4 weeks prior to trip departure date. Having adequate time to complete the vaccination series for both rabies PrEP and JE vaccine was a significant factor in obtaining these two vaccines. It would be important to increase awareness about the importance of a well-timed pre-travel consultation, so that both travel medicine providers and primary care providers can encourage parents to seek appropriate pre-travel consultation visits for children.

Further studies should be done to better understand barriers to care for the pediatric international traveler. Also these additional studies may provide specific evidence on why insurance companies should cover the costs of the pre-travel visit and travel vaccinations for pediatric travelers that are more vulnerable than adult travelers. Similarly, this additional

evidence may convince pharmaceutical companies to lower the costs of travel vaccines for vulnerable pediatric travelers. It would be important to determine the specific reasons for refusal of travel vaccinations, when timing is not the major factor. Parents may refuse travel vaccines, due to lack of concern about an illness they are unfamiliar with, like Japanese encephalitis, and this could be solved by providing more education on vaccine-preventable travel related diseases. Increasing the rate of travel-related vaccinations, is not only important for the individual pediatric traveler but also to decrease the spread of vaccine-preventable diseases once they return home.

Tables:

Table 1. Demographic characteristics of all pediatric international travelers visiting Emory TravelWell Center in Atlanta, Georgia for pre-travel consultation, from June 2011 to June 2015

CHARACTERISTIC	SUMMARY STATISTIC
Age	**(n = 343)**
Mean ± SD (Years)	9.9 ± 5.3
Range (Min – Max)	(0.02 – 17.0)
Sex	**(n = 352)**
Female	190 (54)
Male	162 (46)
Destination by Region	**(n = 339)**
Africa	117 (34.5)
Asia	108 (31.9)
Australia & Oceania	1 (0.3)
Europe	3 (0.9)
North & Central America	95 (28.0)
South America	15 (4.4)
Days prior to travel	**(n=330)**
Median	22
Range (Min – Max)	(0 - 328)
< 21 days	51 (47.2)
< 28 days	65 (59.3)
Length of Stay	**(n=333)**
Mean ± SD (Days)	62.5 ±177.9
Median	14
Range (Min – Max)	(4 -1300)
Destination Type	**(n =330)**
Rural	42 (12.7)
Urban	114 (34.6)
Both	174 (52.7)
Purpose for Travel	**(n =335)**
VFR (Visiting Friends & Relatives)	111 (33.1)
Leisure	125 (37.3)
Missionary Work / Volunteer	61 (18.2)
Education / Research	22 (6.6)
Business	15 (4.5)
Adoption	1 (0.3)
Method of Payment	**(n =350)**
Out-of-pocket	238 (68.0)
Corporate / Insurance coverage	112 (32.0)
All values are n (%) unless otherwise indicated. SD = standard deviation.	

Table 2. Characteristics of pediatric travelers by method of payment for pre-travel consultation and vaccines administered at the Emory TravelWell Center. P-values describing differences were determined from t-test, chi-square, or Fisher's exact test where appropriate, and considered significant if <0.05.

CHARACTERISTIC	Payment by Insurance (N =112)	Payment by Traveler (N =238)	p-value
Age	(n = 112)	(n = 229)	
Mean ± SD (Years)	9.85 ± 5.2	9.88 ± 5.5	0.9550
Range (Min – Max)	(0.02 – 17.0)	(0.16 – 17.0)	
Missing (9)		9	
Sex n (%)	(n = 112)	(n=238)	
Female	69 (61.6)	121 (50.8)	
Male	43 (38.4)	117(49.2)	0.0661
Missing (2)			
Length of Stay	(n=108)	(n=223)	0.8635
Mean ± SD (Days)	65.22 ± 155.4	61.62 ± 188.8	
Median	20.0	14	
Range (Min – Max)	(5 – 730)	(4 -1300)	
Destination Type n (%)	(n =106)	(n =222)	0.5939
Urban	39 (36.8)	75 (33.8)	
Any Rural	67 (63.2)	147 (66.2)	
Missing (22)	6	16	
Purpose for Travel n (%)	(n =108)	(n =225)	0.3237
VFR	40 (37.0)	71 (31.6)	
Non- VFR	68 (63.0)	154 (68.4)	
Missing (17)	4	13	
Days prior to travel	(n =108)	(n =220)	0.9756
Median	23.5	20.5	
Mean ± SD (Days)	32.6 ± 38.8	32.5 ± 36.5	
Range (Min – Max)	(0 – 328)	(0 -295)	
Missing (22)	4	18	
All values are *n* (%) unless indicated. SD = Standard deviation.			

Table 3. Univariate and multivariate analysis of study outcome, JE vaccine administered for subset of Asia only travelers, and study variables: method of payment, sufficient time to complete JE series, rural destination, length of stay, VFR traveler, age and sex.
(Bolded results are significant with a p-value <0.05)

Variable	Subset of Asia only travelers N (%)	JE vaccine recipients N (%)	Crude OR (95% CI)[a]	aOR[b] (95% CI)
Overall	**(N = 108)**			
JE vaccine received	12 (11.1)	12 (100)	---	---
JE vaccine not received	96 (88.9)	---	---	---
Method of Payment				
cost covered by insurance	35 (32.4)	4 (33.3)	1.05 (0.29, 3.75)	0.82 (0.14, 4.67)
cost self-paid	73 (67.6)	8 (66.7)	Referent	Referent
Sufficient time for JE series (>28 days)				
Yes	44 (41.5)	8 (80.0)	6.67 (1.34, 33.14)	8.03 (1.25, 51.75)
No	62 (58.5)	2 (20.0)	Referent	Referent
Missing	2	2		
Rural destination				
Yes	48 (45.3)	7 (70.0)	3.13 (0.76, 12.84)	n/a[d]
No	58 (54.7)	3 (30.0)	Referent	
Missing	2	2		
Length of Stay (>28 days)				
Yes	41 (39.0)	9 (90.0)	17.72 (2.15, 146.05)	32.96 (2.91, 373.73)
No	64 (61.0)	1 (10.0)	Referent	Referent
Missing	3	2		
VFR traveler[c]			---	---
Yes	51 (48.1)	0		
No	55 (51.9)	10 (100.0)		
Missing	2	2		
Age (continuous)			1.25 (1.05, 1.49)	1.34 (1.03, 1.73)
Sex				
Male	44 (40.7)	2 (16.7)	3.89 (0.81, 18.71)	n/a[d]
Female	64 (59.3)	10 (83.3)	Referent	

[a]95% CI = confidence interval [b]aOR= adjusted odds ratio. [c]There were no VFR travelers that received JE vaccine, this variable was not analyzed. [d]Those with n/a for the multivariate analysis were variables that were removed from the final model and not analyzed.

Table 4. Univariate and multivariate analysis of study outcome, Rabies PrEP vaccine administered, and study variables: method of payment, sufficient time to complete Rabies series, rural destination, length of stay, VFR traveler, age and sex.
(Bolded results are significant with a p-value <0.05)

Variable	Overall N (%)	Rabies PrEP recipients N (%)	Crude OR (95% CI)[a]	aOR[b] (95% CI)
	(N = 330)			
Rabies PrEP vaccine received	31 (9.4)	31 (100)	---	---
Rabies PrEP vaccine not received	299 (90.6)	---	---	---
Method of Payment				
cost covered by insurance	107 (32.4)	17 (54.8)	**2.82 (1.33, 5.97)**	**3.44 (1.24, 9.58)**
cost self-paid	223 (67.6)	14 (45.16)	Referent	Referent
Time for rabies series (>21 days)				
Yes	168 (51.4)	25 (92.6)	**13.72 (3.19, 58.98)**	**17.36 (3.65, 82.55)**
No	159 (48.6)	2 (7.4)	Referent	Referent
Missing	25	4		
Rural destination				
Yes	216 (66.1)	16 (59.3)	0.73 (0.33, 1.63)	n/a[c]
No	111 (33.9)	11 (40.7)	Referent	
Missing	25	4		
Length of Stay (>28 days)				
Yes	84 (25.8)	23 (85.2)	**22.43 (7.48, 67.26**)	**24.67 (7.00, 87.02)**
No	242 (74.2)	4 (14.8)	Referent	Referent
Missing	26	4		
VFR traveler				
Yes	106 (32.4)	10 (37.0)	1.25 (0.55, 2.83)	0.35 (0.11, 1.09)
No	221 (67.6)	17 (63.0)	Referent	Referent
Missing	25	4		
Age (continuous)			**0.88 (0.82, 0.95)**	0.91 (0.82, 1.01)
Sex				
Male	152 (45.8)	14 (45.2)	1.03 (0.49, 2.16)	n/a[c]
Female	180 (54.2)	17 (54.8)	Referent	
Missing	20			

[a]95% CI = confidence interval [b]aOR= adjusted odds ratio. [c]Those with n/a for the multivariate analysis were variables that were removed from the final model and not analyzed.

Chapter 3: Conclusions

Summary:

The goal of this study was to describe factors associated with the administration of rabies PrEP and JE vaccine in pediatric international travelers to identify barriers to uptake. This study noted that cost of the pre-travel consultation visit and vaccine administration can be a barrier to care, as with rabies PrEP, but that this is not the most important factor. In addition, this study determined that insufficient time to complete vaccination series prior to travel was a significant barrier to care. To promote timely pre-travel consultations, increased awareness is needed among primary care providers who most often see children, to ensure these clinicians understand the importance of pre-travel visits and can encourage parents to schedule them. In addition at the policy level, increased collaboration between the American Academy of Pediatrics (AAP) and the International Society of Travel Medicine (ISTM) could facilitate dissemination of information about the pre-travel visit for pediatric international travelers. Ultimately, it is clear that there are multiple barriers to care for pediatric international travelers and that they must be considered collectively and not individually to provide the best care for these patients.

Children are inherently a vulnerable population, due to their limitations in communication based on age and also their reliance on adults to protect them from harm and risks, that they are often unaware that exist. These risks are increased when children travel and are in unfamiliar surroundings. That is why a pre-travel consultation visit is important, so that the parents and children can receive a comprehensive risk-assessment based on the itinerary, destinations, and activities planned during the trip. Ideally this visit would be scheduled with a

travel medicine provider, who is trained in this field and can educate the family to keep the children safe and healthy during the trip. Preparing a child to travel is more complicated than for adults because the provider must ensure that the child's routine immunizations are up-to-date, and that they meet the age or weight requirements for travel-related vaccines or malaria prophylaxis [5]. If the visit cannot be scheduled with a travel medicine provider then the parents should seek guidance from their primary care provider and the visit should be scheduled at least one month prior to the international trip to have enough time to obtain vaccinations and medications.

Public Health Implications:

It is established that pre-travel consultations for all travelers are underutilized and even more so for pediatric travelers. In a GTEN study from 2009 to 2012, there were over 32,000 travelers that presented for a pre-travel visit at 19 travel clinics, only 10% of those travelers were children (<18 years of age) [42]. Since the number of children that travel is lower than adults, there is less information known about the specific risks to pediatric travelers [5]. This study demonstrated the importance of having a pre-travel consultation prior to international trips for pediatric patients, who are vulnerable to disease and infections based on their typical age-appropriate behavior and or developmental stage. It will be important to understand the barriers identified in this study to pre-travel consultation and vaccine administration for pediatric international travelers, so that both travel medicine providers and primary care providers can be educated on how to better approach these visits and promote parents to seek pre-travel consultation. This study helps to close the gap in knowledge of what the barriers to care are for pediatric travelers, and by using this information it can hopefully increase uptake of

travel vaccinations for this vulnerable population. It is established in the literature that by increasing vaccination rates, we have reduced the burden of infectious disease globally. Vaccination for infectious diseases helps with disease control and when it is successful, it can eliminate a disease from an entire country. This was done with measles, by maintaining more than 95% herd immunity with use of MMR vaccine, the U.S. declared the disease eliminated in 2000, due to absence of continuous disease transmission for more than 12 months [47]. However with an increase in anti-vaccinators and importation from abroad, the U.S. continues to see isolated outbreaks, with over 1200 cases of measles reported in 2019, which is the highest number of cases reported in the U.S. since 1992 [47]. And this is just one example of how important vaccinations are to controlling infectious diseases, the U.S. has eliminated dog-mediated rabies infection since 2004, through aggressive vaccination programs of domestic animals [48].

Given there were approximately 38 million U.S. international travelers in 2019, and with the current COVID-19 global pandemic, it is clear how easily an infectious disease can spread when no vaccine exists to mitigate its effect [1]. This study has reinforced the importance of educating pediatric international travelers and the key role that travel medicine plays in public health practice.

Future Directions:

This study focused on just two of the many travel vaccinations that are advised and indicated for pediatric international travelers. This type of analysis could be expanded to compare vaccine uptake for more common travel vaccinations like yellow fever or typhoid vaccine with rabies PrEP or JE vaccine, to determine if the barriers to administration differ. As

mentioned earlier, travel medicine providers see a limited amount of pediatric international travelers, so it would be important to consider how educating pediatricians or family medicine providers could improve care to pediatric international travelers. Also it would be important for travel medicine and primary care providers to collaborate, on how to improve vaccination uptake, not only for travel vaccines but even routine childhood vaccinations, like Hepatitis A or MMR, that are also important for travel. A limitation of this study was the smaller sample size, this issue could be solved by recruiting other travel medicine clinics in the U.S. to collect standardized information on pediatric international travelers and do either a prospective study or after several years do another retrospective study.

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