

INADEQUATE PROTECTION AGAINST YELLOW FEVER OF CHILDREN VISITING ENDEMIC AREAS

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Abstract. The guidelines of the World Health Organization call for immunization against yellow fever at least 10 days before travel to endemic areas. The goal of this study was to determine whether these guidelines have been applied in 2 travel clinic settings in teaching hospitals in Israel and the United Kingdom specifically for children traveling to endemic areas. Two groups of children aged 9 months to 15 years ($n = 98$), who were planning to travel to yellow fever–endemic areas, were evaluated regarding characteristics related to the administration of yellow fever vaccine before travel. Overall, 19 children in both clinics (19.4%; 95% confidence interval, 12.1–28.6) had received their yellow fever vaccination < 10 days before departure (no interclinic difference). Eleven of these children received the vaccine < 7 days before departure. We found that the World Health Organization guidelines for yellow fever vaccination are frequently not followed. An initiative to explain to the public the importance of vaccination well before travel to endemic areas should be undertaken.

INTRODUCTION

Yellow fever (YF) is a mosquito-borne viral hemorrhagic fever with a case fatality rate of up to 50%. The disease is endemic in tropical areas of Africa and South America,^{1,2} which have a combined population of 468 million in 34 African countries alone.³ The incidence of disease within the indigenous population between 1985 and 1996 has increased dramatically, reaching 23,543 cases and 6,421 deaths.^{3,4} Official reports, however, appear to underestimate the true magnitude of these epidemics, which are projected at 200,000 cases and 30,000 deaths each year.^{3,5} Data from YF epidemics in Africa over the past 30 years indicate that a large proportion of cases have occurred in children.⁴

Yellow fever has 2 types of transmission cycles: jungle and urban. In the jungle cycle, the virus is transmitted among nonhuman primates by different mosquito vectors, mainly *Haemogogus spegazzini* and *Aedes africanus*. The main vector within villages and urban settlements are *Aedes aegypti*. This mosquito breeds in all types of domestic collections of fresh water: vases, old tires, coconut shells, etc. After an extrinsic incubation period of 21 days, peridomestic *Ae. aegypti* mosquitoes bite a susceptible human. The natural history of YF infection in most cases (85%) is that of a short, acute febrile disease with full recovery. After an incubation period of 3–6 days, there is a sudden onset of fever, myalgia, and headache. The few physical signs that may present include a relative bradycardia (Faget's sign), conjunctival injection, and facial flushing. In a minority of cases, especially in epidemic situations, a severe, biphasic febrile disease with jaundice and hemorrhagic manifestations have been observed.⁶ The second phase of the disease is marked by fever, chills, nausea, vomiting, and somnolence. Jaundice becomes evident, with purpuric hemorrhages, melena, hepatic and renal failure, and meningoencephalitis. The case fatality ratio may be as high as 20–50%.

Although some members of the indigenous population in YF-endemic areas may have naturally acquired immunity against YF, nonimmune travelers are particularly vulnerable to infection.^{7–9}

An effective, live, attenuated YF vaccine based on the

17D strain has been used in humans since 1936.¹⁰ This is one of the most protective vaccines available, resulting in a protective antibody response in 95% of recipients. Immunity after vaccination is likely to be lifelong, but boosters are required every 10 years.¹¹ The guidelines of the World Health Organization (WHO), and the Advisory Committee of the Immunisation Practices (ACIP) call for administration of this vaccine to all people 9 months of age or older traveling to endemic areas.^{10,11} The vaccine should be administered at least 10 days before travel to allow for development of protective antibody; vaccination is accompanied by an international certificate of administration to ensure validity.^{12–14} Unvaccinated travelers may be stopped at a border and may be forced to receive vaccination, possibly via non-sterile needles. This kind of vaccination carries considerable risk of exposure to blood-borne viruses, particularly hepatitis B, hepatitis C, and human immunodeficiency virus.

International travel continues to grow at an ever-increasing rate.¹⁵ Global figures indicate that air travel grows by 50% every decade, mostly owing to increased tourism to Asia and South America. Data from our Israeli clinic, obtained over the past 4 years, indicate a 10% annual growth rate in the number of travelers attending the Israeli clinic, with a 75% increase in those needing a YF vaccination. These figures are mirrored at the travel health center in the United Kingdom, which has seen a 70% increase in the number of travelers attending the clinic since its establishment in 1999 and a corresponding 115% increase in those travelers requiring YF vaccination. Along with this trend, there is the increasing risk of infection and subsequent transmission of infectious diseases. Travelers to areas of high endemicity for YF have received little attention in relation to this specific vaccination and its administration before travel. This study explored whether the WHO guidelines have been adhered to by a group of Israeli and British children traveling with their families to YF-endemic countries with the potential risks of exposure with its incumbent public health sequelae.

PATIENTS AND METHODS

The study was carried out at the travel health clinics of the B'nai Zion Medical Centre, Haifa, Israel, and the Royal

Free Travel Health Centre, Royal Free and University College Medical School, London. The enrollment period was undertaken from March 1, 1999, and continued for 1 year. Children aged 9 months to 15 years who appeared to be in good health were eligible for this survey if they were planning to travel to a YF-endemic zone. Those families whose travel itinerary included a stopover in a zone not endemic for YF were excluded from this analysis. The definition of a YF-endemic zone was based on the current WHO guidelines.¹⁴ The live YF vaccine type administered during the study period was that of the 17D strain (Pasteur-Merieux, Lyon, France, in Israel, and Medeva Pharma, Surrey, UK). Each traveler received a single 0.5-mL dose subcutaneously in the deltoid region.

The following travel health-related items were obtained prospectively for every eligible child from their parents. These included age, sex, primary destination, reason for travel, duration of stay, how long before travel YF vaccine was administered, and whether other vaccines and malaria chemoprophylaxis were given concurrently (not collected at the Haifa Centre). In order to validate the findings further in relation to the reasons given for presenting for YF vaccination at short notice—that is, < 10 days before departure—a second aspect of the study survey was undertaken. This included 30 adult travelers (15 at each participating center) who were asked prospectively to give a detailed explanation for their late presentation in the travel clinic.

Statistical analysis was carried out by GraphPad Instat software, version 3.01 (GraphPad, San Diego, CA).

RESULTS

During the 1-year study period, 98 children had received YF vaccine at the 2 centers; of these, 50 children had been enrolled at the Haifa Centre and 48 at the Royal Free Centre. There was clustering of travelers visiting the endemic areas during the holiday seasons. Although more than half of the British children traveled during July–August and in December, most Israeli children traveled during September–October. The median age of the children in both groups fell between the ranges of 6–15 years, but there were significantly more children in the younger age group (9 months–2 years) among the group of travelers from the United Kingdom (Table 1). Approximately half of those enrolled in each group were boys.

Although most children in both groups traveled to Africa, the specific destinations differed significantly. Twelve children in the Royal Free Centre group, as opposed to none in the Haifa Centre group, had visited Nigeria ($P < 0.0001$). Kenya was the most common destination for the Haifa Centre group ($n = 40$) and the second most common at the Royal Free Centre. Typically, those traveling from the United Kingdom visited countries within sub-Saharan Africa, whereas travelers from Israel visited Central and South America.

The reason for travel was cited by 48 and 29 of the parents at the Haifa and Royal Free Centres, respectively. The purpose of travel for all but 3 of the children at the Haifa Centre was a holiday, as compared with 9 at the Royal Free Centre ($P < 0.0001$). Seventeen children at the Royal Free Centre undertook travel for purposes of a family visit, and 2 con-

TABLE 1
Demographic and travel-related characteristics

Variable	Israeli children (<i>n</i> = 50)	UK children (<i>n</i> = 48)	<i>P</i> value*
Age			
9 months–2 years	1	8	0.0146
3–5 years	2	13	0.0071
6–15 years	47	27	<0.0001
Male sex	22	24	Not significant
Reason for travel			
Family visit	1	17	<0.0001†
Holiday	46	9	<0.0001†
Considered residence	1	2	–
Unknown	2	20	–
Presumed duration of stay			
1 week	14	2	0.0051
8 days–2 weeks	29	14	0.0080
15 days–3 weeks	2	6	–
>3 weeks	5	24	<0.0001
Unknown	0	2	–

* *P* value calculated by Fisher's exact test.

† Comparison based only on known destinations.

sidered living in the indicated countries for a prolonged period of time.

There were significant differences in the length of stay between the 2 groups, with the children attending the Royal Free Centre departing for longer journeys (Table 1).

The time interval between the administration of YF vaccine and presumed departure varied considerably. Overall, 19 children in both groups (19.4%; 95% confidence interval, 12.1–28.6) had received their YF vaccine < 10 days before departure. There were no differences between the 2 centers in regard to this short interval (found in 10 children at the Haifa Centre versus 9 children at the Royal Free Centre). A total of 11 children, 3 at the Haifa Centre and 8 at the Royal Free Centre, received YF vaccine < 7 days before departure ($P = 0.12$). In total, 79 children (80.6%; 95% confidence interval, 0.71–0.88) did receive YF vaccine at least 10 days before departure, as is advised by international recommendations.

Yellow fever vaccine was administered as the sole vaccine at the visit to the travel clinic for 2 children at the Haifa Centre and 30 at the Royal Free Centre. Other injections, which were given concomitantly at the same session for the other traveling children, included typhoid, hepatitis A, and meningococcal meningitis vaccines. Malaria chemoprophylaxis was prescribed for only 15 children at the Royal Free Centre. The remainder chose to receive a prescription from their general practitioners. Eight of the adult travelers at the Royal Free Centre, as compared with none at the Haifa Centre ($P = 0.0022$; Fisher's exact) gave valid reasons for requiring YF vaccination < 10 days before departure (Table 2).

DISCUSSION

This study demonstrated that nearly one in 5 children traveling to YF-endemic zones received YF vaccination less than the recommended 10 days before departure. This finding is especially remarkable in light of the nature of travel:

TABLE 2

Reasons travelers cite for receiving yellow fever vaccine just before departure

Reason	Israeli adults (n = 15)	UK adults (n = 15)
Funeral	0	4
Vaccine shortage	0	4
Last-minute booking	5	3
Late referral by doctor	0	2
Inadequate information provided by travel agent	5	0
Other	5	2

none of the participants at the Haifa Centre, where a reason for travel was indicated, required an urgent YF vaccination. This profile was different in the United Kingdom, where urgent travel was undertaken more often. This is perhaps explained by demographic differences between the United Kingdom and Israel, as well as the problems associated with the availability of YF vaccine in the United Kingdom as a result of manufacturing difficulties at the time of the survey. The latter also accounted for the significant increase in demand for YF vaccine at the Royal Free Travel Health Centre.

The importance of vaccination of travelers to YF-endemic areas cannot be overemphasized because YF is often fatal and the vaccine is extremely safe and effective. This study specifically pertains to 2 cohorts of traveling children residing in metropolitan cities within the United Kingdom and Israel and who are therefore representative of young travelers from both these countries. These young travelers visited almost exclusively countries within sub-Saharan Africa. Furthermore, the largest group of the travelers from the United Kingdom visited Nigeria, a country that has reported > 20,000 cases and 4,000 deaths associated with YF between 1984 and 1993.³ Kenya, which was the most popular destination for Israeli travelers, as well as Ghana, which was the third most popular destination for travelers from the United Kingdom, have also reported epidemics during the last decade.^{1,3}

Yellow fever continues to be a threat to those traveling to endemic zones.^{9,15} Furthermore, in some areas of South America, an urbanization of sylvatic YF has recently been reported.⁸ Yellow fever is one of 3 diseases, the others being cholera and plague, which are subject to international quarantine regulations. In most countries, the mere suspicion of YF requires immediate notification to the public and state health authorities.^{16,17}

Over recent years, there have been serious problems in providing YF vaccine to populations in endemic zones and to travelers visiting these areas.¹⁸ Previously, the prime concern underlying the restricted distribution and manufacture of YF vaccine was the thermolability of the vaccine. Current difficulties in terms of travelers' health include poor accessibility to specialized travel health clinics,¹⁸ lax enforcement of the international health regulations,¹⁹ and temporary vaccine shortages. In fact, the latter was stated as the reason for delay in receiving vaccine by 4 of the adult travelers at the Royal Free Centre. Yellow fever is a safe and highly effective vaccine, providing 95% immunogenicity.

Clear guidelines exist regarding administration of YF vaccination, on both international and national levels, which are

apparently well recognized among travel health practitioners. These guidelines call for YF vaccination to be administered to travelers at least 10 days before entering an endemic zone.¹⁴ Yet this study demonstrated that 19 of the children in this cohort attended the travel clinic in order to receive their vaccine < 10 days before leaving for their destination. The apparent "common knowledge" regarding administration and efficacy of YF vaccine a minimum of 10 days before departure to an endemic area appears to be unknown to the traveling public. This has been substantiated recently by a survey carried out in Germany that reported the alarming rate of protection of only 30% among those who traveled to endemic areas.²⁰ Our findings suggest that there may be a lack of accurate travel health information available for the traveling public. It is also surprising that although the practice of administering YF vaccinations with an insufficient time interval and subsequent lack of protection is well known, we were unable to find evidence of any previous studies documenting and investigating this phenomenon.

The reasons for the practice of receiving YF vaccination < 10 days before departure are yet to be fully understood. This small, prospective study among children and adult travelers revealed considerable differences between travelers from the United Kingdom and Israel. These dissimilarities may partly stem from the different demographic features of the 2 countries. Understandably, urgent travel at short notice may not allow adequate time to receive YF vaccine. In other cases, incorrect guidance by travel agents, other health care professionals not trained in travel medicine, family members, friends, and other unqualified personnel may well play an important role in inadvertently providing inaccurate travel health information. In fact, advertisements in both printed and electronic media constantly promote last-minute attractive deals to safaris in sub-Saharan Africa and other holiday resorts without any mention of the recommendation of travel related vaccines, including that of YF. There is European legislation that states that travel agents should provide information concerning health matters required for the journey and stay abroad.²¹

The findings of this study suggest that a comprehensive and international campaign should be initiated in an attempt to explain the importance of early vaccination against YF to travelers visiting endemic areas, which are becoming ever more popular destinations for travelers to explore. Cooperation between international health organizations, including travel agents and the media, may assist in ensuring the health of the traveling public through the provision of accurate travel health information.

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