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Poliomyelitis outbreaks in Angola genetically linked to India: Risk factors and implications for prevention of outbreaks due to wild poliovirus importations

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ABSTRACT

We conducted an investigation of two outbreaks of poliomyelitis in Angola during 2007–2008 due to wild poliovirus (WPV) genetically linked to India. A case-control study including 27 case-patients and 76 age- and neighborhood-matched control-subjects was conducted to assess risk factors associated with paralytic poliomyelitis, and epidemiologic links to India were explored through in-depth case-patient interviews. In multivariable analysis, case-patients were more likely than control-subjects to be undervaccinated with fewer than four routine doses of oral poliovirus vaccine (adjusted matched odds ratio [aMOR], 4.1; 95% confidence interval [CI], 1.2–13.6) and have an adult household member who traveled outside the province of residence in the 2 months preceding onset of paralysis (aMOR, 3.2; 95% CI, 1.2–8.6). No epidemiologic link with India was identified. These findings underscore the importance of routine immunization to prevent outbreaks following WPV importations and suggest a possible role of adults in sustaining WPV transmission.

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1. Introduction

When the World Health Assembly established the Global Polio Eradication Initiative in 1988, approximately 350,000 cases of paralytic poliomyelitis per year occurred in >125 endemic countries. By 2008, the number of poliomyelitis cases had declined to 1659 cases, and only four countries (Afghanistan, India, Nigeria, and Pakistan) had never interrupted indigenous wild poliovirus (WPV) transmission. However, progress towards poliomyelitis eradication has been complicated by the reintroduction of WPV from endemic countries to countries that were previously polio-free. During 2008–2009, 21 countries in Africa that had previously interrupted indigenous WPV transmission reported cases of poliomyelitis due to WPV originating from Nigeria or India [1,2].

Angola, located in south central Africa, detected its last indigenous WPV case in 2001 and was polio-free from 2002 to 2004. Key to the successful interruption of indigenous WPV transmission were the country's immunization strategies, including routine vaccination and supplemental immunization activities (SIAs) with oral polio vaccine (OPV). Established in 1979, Angola's routine immunization schedule includes four doses of trivalent OPV (tOPV) administered at birth, and at 2, 4, and 6 months of age. In addition, nationwide SIAs targeting all children <5 years of age for additional doses of OPV have been held at least twice per year since 1996. Despite these immunization activities, during 2005–2008 Angola received three genetically distinct WPV importations from India, which resulted in outbreaks of paralytic poliomyelitis, reestablished WPV transmission (transmission for >12 months after importation), and the subsequent reintroduction of WPV to other countries in central Africa [2,3].

To understand why Angola has been the site of entry for multiple WPV importations from India and why WPV transmission within Angola persisted, we conducted a field investigation in October–November 2008.

2. Methods

We reviewed routine immunization data from January 2005 to June 2008 and SIA data from January 2005 to November 2008 provided by the Expanded Program on Immunization (EPI) offices at Angola Ministry of Health and World Health Organization (WHO) Angola. Administrative vaccination coverage with OPV for routine immunization and SIAs were calculated by dividing the reported

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number of doses administered by health care providers by the estimated number of eligible children in the population. Official population estimates were provided by the Angola Ministry of Health.

Possible cases of paralytic poliomyelitis are detected through Angola's national acute flaccid paralysis (AFP) surveillance system, which was established in 1997. An AFP case is defined as the sudden onset of weakness and floppiness in any part of the body in a child <15 years of age or suspected poliomyelitis in a person of any age. Upon identification of a case, a surveillance officer conducts an investigation, including collection of stool samples for virologic testing for the presence of poliovirus and a follow-up examination approximately 60 days after onset to assess for residual paralysis. Poliovirus isolation, intratypic differentiation, and genetic analysis are performed using standard protocols at the WHO Regional Reference Laboratory for Poliomyelitis in Johannesburg, South Africa [4,5].

A matched case-control study to evaluate risk factors associated with poliomyelitis in Angola was conducted in October–November 2008. A case was defined as a laboratory-confirmed wild poliovirus infection genetically linked to the 2007 or 2008 importations in a patient identified in the national AFP surveillance database who had onset of AFP from April 2007 to September 2008. Case-patients were traced using contact information obtained from AFP surveillance case investigation forms, and from district surveillance officers and health workers. There was only one case-patient per household. Three age- and neighborhood-matched control-subjects were selected for each case from non-case households surrounding the case household using a random direction and random number list, and were matched within 6 months of the case-patient's age. No more than one control-subject was selected from each household.

Verbal consent was obtained and a standard questionnaire was administered to subjects ≥15 years of age or to caregivers of subjects <15 years of age. The standard questionnaire included questions about demographic information, number of OPV doses received, and travel and other exposures, including exposure to travelers, markets, airports, and train stations, within 2 months prior to AFP onset. In addition, a supplemental household questionnaire, which asked more detailed questions about travel and international exposures, was administered for case-patients. Information gathered from the supplemental questionnaire and epidemiologic links to India among case-patients enrolled in the case-control study were explored in a descriptive analysis.

Routine vaccination history was obtained from the caregiver-held vaccination card or by caregiver recall when the card was not available. History of SIA doses was obtained by recall only. Because SIAs may use tOPV, monovalent OPV type 1 (mOPV1), or monovalent OPV type 3 (mOPV3), it was necessary to calculate the number of type-relevant SIA doses received. The number of type-relevant SIA doses received (mOPV1 or tOPV doses for WPV type 1 [WPV1] case-patients; mOPV3 or tOPV doses for WPV type 3 [WPV3] case-patients) was considered to be the number of SIA doses reported by the subject, but could not exceed the number of type-relevant SIA doses offered in Angola after the subject's birth, before the subject was 5 years of age, and before onset of AFP.

For the analysis, so that case- and control-subjects had comparable opportunity to receive all four routine OPV doses, control-subjects <6 months of age matched to case-patients ≥6 months of age at the time of AFP onset were excluded. Subjects with unknown routine vaccination history were classified as having fewer than four routine OPV doses. When total number of type-relevant OPV doses was calculated, subjects with unknown vaccination histories for birth dose, routine doses, or SIA doses were included, but the unknown histories contributed zero doses to the total number of doses.

Table 1
Estimated routine immunization coverage with the birth dose and three routine doses of trivalent oral polio vaccine (tOPV) among children by birth year, Angola, January 2005–June 2008.

Year	Birth dose of tOPV[a]	Three routine tOPV doses[b]
2005	58%	46%
2006	59%	44%
2007	76%	83%
January–June 2008	69%	75%[c]

[a] *Source*: Ministry of Health, Luanda, Angola, October 2008.
[b] *Source*: WHO/UNICEF estimate for coverage with three routine tOPV doses given at 2, 4, and 6 months of age [12].
[c] WHO/UNICEF estimate for January–December 2008 [12].

Risk factors for poliomyelitis were evaluated in matched analysis using conditional logistic regression. Two separate multivariable models were created: one model used routine OPV doses as the vaccination variable and one model used total type-relevant OPV doses as the vaccination variable. Risk factors with Wald chi-squared p-value <0.10 in the univariate analysis were tested in the multivariable model, and the final multivariable models were created using backward elimination of variables with a p-value >0.05 in the model and whose elimination resulted in <10% change in the point estimate of the odds ratios for the variables remaining in the model. Forward selection models using the same criteria were created for the purposes of comparison. Vaccine effectiveness (VE) was estimated using the formula $VE = (1 - aMOR) \times 100$, where aMOR is the adjusted matched odds ratio for ≥4 OPV doses vs. <4 OPV doses. Because of the low case-to-infection ratio for poliovirus, the rare disease assumption is satisfied, the odds ratio is good estimate of relative risk, and this formula provides an acceptable estimate of vaccine effectiveness.

3. Results

3.1. Vaccination coverage

Reported administrative coverage with the birth dose of tOPV increased from 58% in 2005 to 69% in January–June 2008 and estimated coverage with three routine tOPV doses increased from 46% in 2005 to 75% in 2008 (Table 1). In addition, 14 national and 5 sub-national SIAs were conducted in Angola during 2005–2008, with reported administrative coverage ranging from 75% to 107% (Table 2, Fig. 1).

3.2. Confirmed poliomyelitis cases

During 2005–2008, a total of 49 laboratory-confirmed cases of poliomyelitis were reported in Angola, all of which had WPV isolates genetically related to one of the three WPV strains imported from India (Fig. 1). Following the first importation, a total of 13 WPV1 cases were reported during 2005–2007; the second importation resulted in 12 WPV1 cases reported during 2007–2008; the third importation resulted in 24 WPV3 cases reported during 2008.

3.3. Characteristics of study subjects

For the case-control study, 33 eligible cases were identified in the AFP database with AFP onset April 2007–September 2008. Of these, 27 (82%) case-patients were able to be traced and were enrolled in the study, along with 76 age- and neighborhood-matched control-subjects (81 control-subjects were interviewed, but 5 were excluded because they were <6 months of age and were matched with case-patients who were ≥6 months of age).

Table 2
History of polio supplemental immunization activities (SIAs)[a] in Angola, 2005–2008.

Year	Month	Location	OPV formulation	Administrative coverage[b]
2005	July	Luanda province All other provinces	mOPV1[c] tOPV[d]	100%
2005	August	Nationwide	tOPV	90%
2005	September	Nationwide	mOPV1	105%
2005	December	Nationwide	mOPV1	106%
2006	March	Benguela, Huambo, Huila, Namibe provinces	mOPV1	97%
2006	July	Nationwide	mOPV1	75%
2006	September	Nationwide	mOPV1	102%
2006	December	Nationwide	mOPV1	102%
2007	June	Nationwide	mOPV1	104%
2007	July	Nationwide	mOPV1	107%
2007	August	Nationwide	mOPV1	105%
2008	March	Luanda province	mOPV1	104%
2008	April	Luanda province	mOPV1	100%
2008	May	Nationwide	mOPV3[e]	98%
2008	June	Nationwide	mOPV3	106%
2008	July	Nationwide	mOPV1	105%
2008	September	Benguela, Kwanza Sul, Luanda, Lunda Norte, Lunda Sul, Moxico provinces	mOPV3	102%
2008	October	Nationwide	mOPV1	101%
2008	November	Kwanza Sul province	mOPV1	Not available

[a] Mass campaigns conducted during a short period (days to weeks) during which a dose of oral polio vaccine (OPV) is administered to all children aged <5 years, regardless of previous vaccination history. Campaigns can be conducted nationally or in portions of the country.
[b] *Source*: Ministry of Health, Luanda, Angola, October 2008. Administrative coverage is the number of doses administered by health workers divided by the official government estimate of the target population (children aged <5 years).
[c] mOPV1, monovalent oral polio vaccine type 1.
[d] tOPV, trivalent oral polio vaccine.
[e] mOPV3, monovalent oral polio vaccine type 3.

Enrolled cases included 8 WPV1 cases genetically linked to the 2007 importation and 19 WPV3 cases genetically linked to the 2008 importation. Case-patients resided in 11 districts in 3 provinces; 18 (67%) were from Luanda province, 5 (19%) were from Benguela province, and 4 (15%) were from Kwanza Sul province. A total of 22 (82%) case-patients were alive with residual paralysis 60 days after AFP onset; 2 (7%) were alive with no residual paralysis and 3 (11%) had died. Demographic characteristics such as age, gender, and parental education were similar for case-patients and control-subjects (Table 3). Median age on the date of AFP onset of the case-patient was 20 months for case-patients (range, 7 months–15 years) and 21 months for control-subjects (range, 7 months–16 years); 18 (67%) of case-patients were <24 months of age at the time of AFP onset.

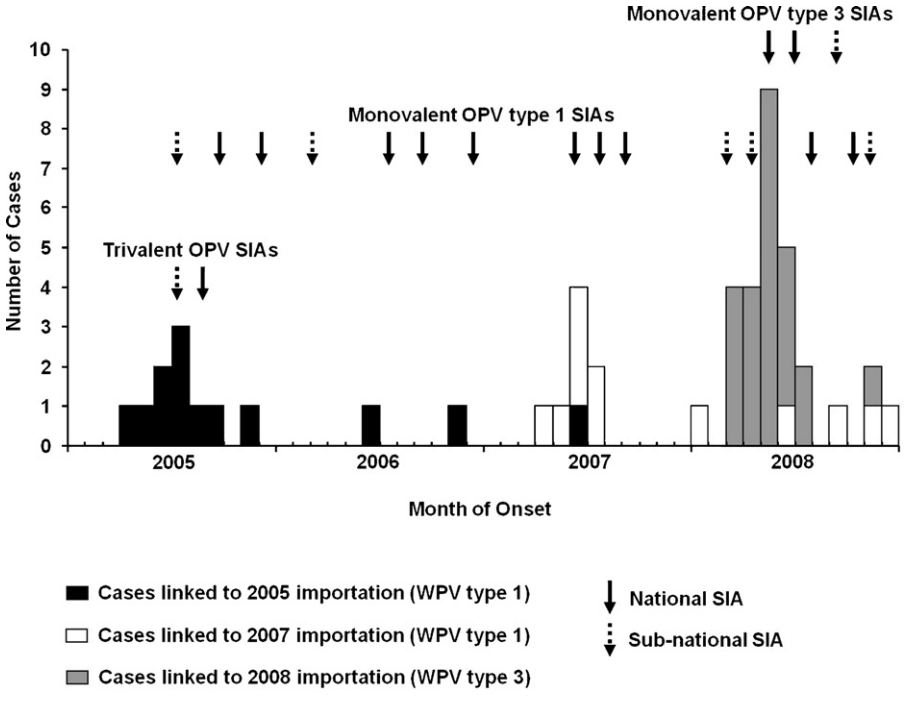

Fig. 1. Confirmed wild poliovirus (WPV) cases by month of paralysis onset and supplemental immunization activities (SIAs) with oral polio vaccine (OPV), Angola, 2005–2008.

Table 3
Demographic characteristics, travel exposures, and oral polio vaccine (OPV) doses of the poliomyelitis case-patients related to the 2007 and 2008 wild poliovirus (WPV) importations from India and age- and neighborhood-matched control-subjects, Angola, April 2007–September 2008.

	Case-patients (n = 27) No. (%)	Control-subjects (n = 76) No. (%)	MOR (95% CI)[a]	p-value
Age at AFP[b] onset				
7–11 months	4 (15%)	15 (20%)	Reference	Reference
12–23 months	14 (52%)	31 (41%)	2.2 (0.4–11.2)	0.33
24 months–4 years	8 (30%)	27 (36%)	1.5 (0.2–10.5)	0.69
≥5 years	1 (4%)	3 (4%)	–	–
Gender				
Male	16 (59%)	46 (61%)	1.0 (0.4–2.4)	0.97
Female	11 (41%)	30 (39%)	Reference	Reference
Highest level of schooling (parent or caregiver)				
None or primary school	13 (50%)	30 (40%)	1.4 (0.6–3.5)	0.41
More than primary school	13 (50%)	45 (60%)	Reference	Reference
Travel out of province in 2 months before AFP onset				
Yes	3 (11%)	9 (12%)	0.8 (0.2–3.5)	0.76
No	24 (89%)	67 (88%)	Reference	Reference
Travel out of Angola in 2 months before AFP onset				
Yes	0 (0%)	0 (0%)	–	–
No	27 (100%)	76 (100%)	Reference	Reference
Household member traveled out of province in 2 months before AFP onset				
Yes	15 (56%)	24 (32%)	2.7 (1.1–6.7)	0.03
No	12 (44%)	52 (68%)	Reference	Reference
Household member traveled out of Angola in 2 months before AFP onset				
Yes	0 (0%)	2 (3%)	<0.1 (<0.1–>999.9)	0.99
No	27 (100%)	74 (97%)	Reference	Reference
Community member traveled out of province in 2 months before AFP onset				
Yes	14 (52%)	27 (36%)	2.1 (0.8–5.3)	0.11
No	13 (48%)	49 (64%)	Reference	Reference
Community member traveled out of Angola in 2 months before AFP onset				
Yes	5 (19%)	5 (7%)	4.7 (0.9–25.8)	0.07
No	22 (81%)	71 (93%)	Reference	Reference
Birth dose of tOPV[c]				
No	1 (5%)	2 (3%)	1.0 (0.1–11.9)	1.00
Yes	19 (95%)	56 (97%)	Reference	Reference
Routine tOPV doses, excluding birth dose[d]				
0 doses	1 (5%)	1 (2%)	1.7 (0.1–30.8)	0.71
1 dose	6 (32%)	5 (9%)	8.5 (1.6–46.3)	0.01
2 doses	4 (21%)	9 (16%)	2.5 (0.6–10.4)	0.22
3 doses	8 (42%)	42 (74%)	Reference	Reference
Total routine tOPV doses, including birth dose[e]				
<4 doses	19 (70%)	36 (47%)	3.7 (1.2–11.1)	0.02
4 doses	8 (30%)	40 (53%)	Reference	Reference
Type-relevant SIA OPV doses[f]				
WPV1 case-patients (n = 8) and control-subjects (n = 20)[g]				
0 doses	0 (0%)	4 (27%)	<0.1 (<0.1–>999.9)	1.00
1 dose	0 (0%)	0 (0%)	–	–
2 doses	1 (25%)	4 (27%)	<0.1 (<0.1–>999.9)	1.00
≥3 doses	3 (75%)	7 (47%)	Reference	Reference
WPV3 case-patients (n = 19) and control-subjects (n = 56)[h]				
0 doses	13 (81%)	35 (67%)	>999.9 (<0.1–>999.9)	1.00
1 dose	1 (6%)	6 (12%)	1.2 (<0.1–>999.9)	1.00
2 doses	1 (6%)	6 (12%)	–	–
3 doses	1 (6%)	5 (10%)	Reference	Reference
Total type-relevant OPV doses (total routine + type-relevant SIA doses)[i]				
<4 doses	14 (52%)	28 (37%)	3.3 (0.9–11.4)	0.06
≥4 doses	13 (48%)	48 (63%)	Reference	Reference

[a] MOR, matched odds ratio, and CI, confidence interval, from conditional logistic regression.
[b] AFP, acute flaccid paralysis.
[c] tOPV, trivalent OPV. Seven case-patients and 18 control-subjects had unknown birth dose of tOPV histories.
[d] Eight case-patients and 19 control-subjects had unknown routine tOPV histories.
[e] Unknown total routine OPV histories classified as <4 total routine doses.
[f] SIA, supplemental immunization activity. Type-relevant OPV doses = tOPV or monovalent OPV type 1 for WPV type 1 subjects, tOPV or monovalent OPV type 3 for WPV type 3 subjects.
[g] WPV1, wild poliovirus type 1. Five WPV1 case-patients and five WPV1 control-subjects had unknown type-relevant SIA dose histories.
[h] WPV3, wild poliovirus type 3. Three WPV3 case-patients and four WPV3 control-subjects had unknown type-relevant SIA dose histories.
[i] Unknown total routine OPV dose and SIA OPV dose histories contributed zero to total OPV doses.

3.4. Travel and international exposures

No case-patients traveled outside of Angola in the 2 months prior to AFP onset, and case-patient travel out of the district or province of residence was not associated with poliomyelitis (Table 3). In addition, although a higher proportion of case-patients (5 [19%]) than control-subjects (5 [7%]) knew a community member who traveled outside of Angola within the 2 months prior to onset of AFP, this difference was not statistically significant (matched odds ratio [MOR], 4.6; 95% confidence interval [CI], 0.9–25.8; p = 0.07). However, case-patients were almost three times more likely than control-subjects to have a household member who traveled out-

Table 4
Risk factors for poliomyelitis related to the 2007 and 2008 wild poliovirus (WPV) importations from India in Angola, April 2007–September 2008[a].

	Type of OPV doses considered in model			
	Total routine tOPV doses[b]		Total type-relevant OPV doses[d]	
	aMOR (95% CI)[c]	*p*-value	aMOR (95% CI)	*p*-value
Vaccination				
<4 doses	4.1 (1.2–13.6)	0.02	2.9 (0.8–11.2)	0.11
≥4 doses	Reference	Reference	Reference	Reference
Household member traveled out of province in 2 months before AFP onset				
Yes	3.2 (1.2–8.6)	0.02	2.6 (1.0–6.6)	0.05
No	Reference	Reference	Reference	Reference
Community member traveled out of Angola in 2 months before AFP onset				
Yes	2.7 (0.4–20.6)	0.33	3.7 (0.5–25.3)	0.18
No	Reference	Reference	Reference	Reference

[a] Multivariable models created using risk factors with Wald chi-squared *p*-value <0.10 in univariate analysis and using backward elimination of variables with a *p*-value >0.05 in the model and whose elimination resulted in <10% change in point estimate of the odds ratios for the other variables in the model.
[b] Total routine trivalent oral poliovirus vaccine (tOPV) doses, including birth dose; unknown routine vaccination histories classified as <4 doses.
[c] aMOR, adjusted matched odds ratio, and CI, confidence interval, from conditional logistic regression, adjusting for vaccination, household travel out of province, and community travel out of Angola.
[d] Total type-relevant oral poliovirus vaccine (OPV) doses (trivalent OPV or monovalent OPV type 1 for WPV type 1 subjects, trivalent OPV or monovalent OPV type 3 for WPV type 3 subjects); unknown total routine vaccination histories and unknown SIA dose histories contributed zero to total doses.

side the province of residence in the 2 months prior to AFP onset. Of 15 case-patients with a household member who traveled outside the province of residence, 5 (33%) were from Benguela or Kwanza Sul and traveled to Luanda, where the case-patient's WPV genotype was known to be circulating prior to the AFP onset; the other 10 (67%) case-patients were from Luanda and household members traveled to 9 different provinces. Detailed information about which household members traveled was available from the supplemental questionnaire for 10 (67%) of the 15 case households with travel out of the province, and all 10 reported that those who traveled were adults (age range 20–52 years for the nine households with known ages of the travelers; in the tenth household, traveler was listed as "father").

In the 2 months prior to AFP onset, two (8%) case-patients had contact with an international traveler or foreigner (from India and Mali) and household members of nine (33%) case-patients had contact with an international traveler or foreigner (from Cuba, Germany, Guinea, India, Lebanon, Mali, Senegal, and Switzerland). However, compared with control-subjects, exposure of the case-patient (MOR, 0.6; 95% CI, 0.1–3.2; $p = 0.58$) or household member of case-patient (MOR, 1.0; 95% CI, 0.4–2.6; $p = 0.97$) to an international traveler or foreigner was not associated with poliomyelitis. Only one case-patient and her mother had contact with a person from India. This contact took place in an open air market in Luanda, but the extent and type of contact is not known. No other case-patient or case household had contact with someone who lived in or traveled to India. No case-patients or control-subjects knew of community members who traveled to India, community members who had contact with someone from India, or community members who had contact with someone who traveled to India. There was no significant association between poliomyelitis and any of the other travel exposures assessed, including child or household exposure to an airport, train station, market, or other large public gathering (data not shown).

3.5. Vaccination status

In matched univariate analysis, 8 (30%) case-patients compared with 40 (53%) control-subjects, reported having received all four OPV doses offered through routine immunization (MOR, 3.7; 95% CI, 1.2–11.1; $p = 0.02$) (Table 3). In contrast, the number of type-relevant SIA doses received prior to onset of AFP did not differ significantly between case-patients and control-subjects. The majority of case-patients (65%) and control-subjects (58%) with known SIA dose history did not have any type-relevant SIA doses prior to AFP onset. For the 16 (84%) WPV3 case-patients and 52 (93%) WPV3 control-subjects with known SIA dose history, the median number of type-relevant SIA doses received was zero (case-patient range, 0–3 doses; control-subject range, 0–3 doses). The median number of type-relevant SIA doses received among WPV1 case-patients was 3.5 (range, 2–4 doses) compared with 2 (range, 0–5 doses) for WPV1 control-subjects; however, SIA dose history was reported for only 4 (50%) WPV1 case-patients and 15 (75%) WPV1 control-subjects. When total number of type-relevant OPV doses were considered, 14 (52%) of case-patients compared with 28 (37%) control-subjects were undervaccinated with fewer than four total type-relevant OPV doses, but this difference was not statistically significant (MOR, 3.3; 95% CI, 0.9–11.4; $p = 0.06$).

3.6. Multivariable analysis and vaccine effectiveness

Backward elimination and forward selection resulted in identical multivariable models, and the final models using different vaccination variables are displayed in Table 4. In the first multivariable analysis, where number of routine vaccination doses was used as the vaccination variable, poliomyelitis was associated with having fewer than four OPV doses through routine vaccination and having a household member who traveled outside the province of residence in the 2 months prior to AFP. Estimated vaccine effectiveness for four routine tOPV doses versus fewer than four routine tOPV doses was 76% (95% CI, 19–93%; $p = 0.02$). In a sensitivity analysis, if subjects with unknown routine vaccination histories were classified as having received four doses, case-patients were more likely than control-subjects to be vaccinated, but this difference was of borderline statistical significance (aMOR, 3.0; 95% CI, 1.0–9.3; $p = 0.06$); however, if case-patients with unknown histories were classified as having received four doses but control-subjects with unknown histories were classified has having received fewer than four routine doses, the difference disappeared (aMOR, 0.8; 95% CI, 0.3–2.2; $p = 0.68$). If subjects with unknown histories were excluded, case-patients were more likely than control-subjects to be vaccinated (aMOR, 4.1; 95% CI, 1.1–14.7; $p = 0.03$), but having a household member who traveled out of the province was no longer associated with paralytic polio (aMOR, 2.5; 95% CI, 0.8–7.8; $p = 0.11$).

In the second multivariable analysis using total type-relevant OPV doses as the vaccination variable, poliomyelitis was associated only with having a household member who traveled outside the province in the 2 months prior to AFP. In this model, estimated

vaccine effectiveness for at least four OPV doses versus fewer than four OPV doses was 66% (95% CI, −28–91%; $p = 0.11$).

4. Discussion

From 2005 through 2008, Angola experienced three overlapping polio outbreaks due to three separate WPV importations from India, one of which has continued into 2010. In addition, spread of WPV from Angola to neighboring countries has resulted in polio outbreaks in Nambia, the Democratic Republic of the Congo (DRC), and the Republic of the Congo, as well as outbreaks in the Central African Republic and Burundi following spread from DRC, and continues to pose a risk to these and other polio-free countries [2,3,6,7]. This study demonstrated that incomplete routine immunization, defined as receipt of fewer than four tOPV doses according to the national routine immunization schedule, contributed to the outbreaks in Angola, and that polio case-patients had a greater odds of having an adult household member who traveled out of the province of residence in the 2 months prior to AFP onset.

No epidemiologic link to India was identified in the case-control study. In a further effort to identify possible routes of importation from India to Angola, we attempted to assess patterns of travel and trade between the two countries. Data from commercial airlines showed that there were no direct flights between India and Angola. However, attempts to obtain additional data on travel visas, migration patterns, and trade were unsuccessful. To follow up anecdotal reports of Indian settlements and traders in Angola, we interviewed 42 health workers and community leaders in the communities with poliomyelitis cases included in the case-control study. While the presence of foreign travelers, immigrants, and traders was reported in all communities, only two interviewees reported Indian immigrants living in their communities (one reported a group of three adults, one reported one family), and only two reported an Indian trader or product in a community market. No settlements of Indian immigrants or traders were identified. Therefore, the explanation for the repeated WPV importations from India to Angola remains unknown.

In the case-control study, the estimate of vaccine effectiveness for four routine tOPV doses (76%) compared to less than four doses is consistent with a previous estimate for at least four tOPV doses compared to zero doses during a 1999 polio outbreak in Angola (75%) [8] and with point estimates of vaccine effectiveness for at least three tOPV doses in other developing countries (70–81%) [9–11]. These findings indicate that achieving high OPV coverage through routine immunization is an effective method of decreasing the risk of poliomyelitis outbreaks following WPV importations. However, in this study, four dose OPV coverage among both case-patients and control-subjects was low (30–53%), corroborating the historically low reported routine immunization coverage in Angola. WHO/UNICEF estimates of Angola's routine immunization coverage with three doses of OPV (excluding birth dose), have been entirely based on population estimates and reported number of doses administered without corroborating surveys. These estimates have increased from 16% in 1987 to 75% in 2008, but were <50% until 2007 [12]. Our findings indicate that a sizeable proportion of the Angolan population remains susceptible to WPV infection and cast doubt on the recently reported routine coverage levels.

SIAs are intended to increase population immunity against WPV by providing all children <5 years with additional OPV doses, regardless of routine immunization status. However, in this study, there was no significant difference in number of type-relevant SIA doses received when case-patients were compared with control-subjects; most case-patients (65%) and control-subjects (58%) with known SIA dose histories had not received any type-relevant SIA doses prior to AFP onset. This result was partly a consequence of the fact that most case-patients (70%) in the study were infected with WPV3, and Angola only used mOPV1 during SIAs between September 2005 and April 2008. The 12 WPV3 case-patients (63% of WPV3 case-patients, 44% of all case-patients) that were born after the last tOPV SIA in August 2005 and had onset of AFP prior to the first mOPV3 SIA in May 2008 did not have any opportunity to receive a type-relevant OPV dose after routine immunization. The 2.5 years without an opportunity to receive a type 3-relevant dose during an SIA, together with sub-optimal routine immunization coverage, led to a larger population of children who were susceptible to infection with WPV3 and likely contributed to the magnitude of the WPV3 outbreak. In addition, this result is incompatible with reported administrative coverage of ≥100% during numerous SIAs since 2005. In our study, when asked about each of the four most recent national SIAs, the proportion of eligible control-subjects who reported receiving an SIA dose ranged from 84% to 93%, suggesting that SIA coverage in the country has been significantly overestimated.

To our knowledge, this is the first study to identify an association between poliomyelitis in children and within-country travel of adult household members, although adult travel has previously been implicated in WPV introduction into previously polio-free countries through case investigation and genetic sequencing data [13,14]. Together, this evidence suggests that older children and adults could play a role in sustaining WPV transmission. Two groups of older individuals could potentially play a role in WPV transmission. The first group is comprised of unvaccinated, undervaccinated, or fully vaccinated individuals who never acquired serologic or mucosal immunity and who are susceptible to infection and potential disease. A polio outbreak among adults 15–26 years of age in Namibia in 2006 [15] and the 15 year old case-patient included in this study indicate that this group exists among older individuals in the region due to low exposure to either vaccination or natural infection in childhood. The second group is previously vaccinated individuals with waning or incomplete mucosal immunity after immunization; this group might have sufficient immunity to protect them from clinical disease, but would be capable of asymptomatically shedding WPV when exposed. While there is evidence that older children and adults, even in populations that are highly vaccinated or have evidence of previous immunity, are capable of excreting WPV following exposure [16–18], the significance of this population as a possible reservoir of WPV or in sustaining WPV transmission is not known.

This study has some limitations. The findings of the investigation were dependent on caregiver recall, which introduced the potential for recall bias and resulted in partial or unknown vaccination histories for some subjects. For the purposes of this study, subjects with unknown routine vaccination histories were classified as having received fewer than four routine tOPV doses. Sensitivity analysis showed that the relationship between incomplete routine vaccination and paralytic poliomyelitis was similar if those with unknown histories were classified as having received four doses, but the relationship disappeared if case-patients with unknown histories were considered to have received four routine doses while control-subjects with unknown histories were considered to have fewer than four doses. Although the latter scenario is extremely unlikely, incomplete vaccination data, combined with the relatively small study size, might have limited the study's ability to accurately assess the effect of vaccination status. In addition, the effect of SIAs could not be evaluated in this study because 70% of cases were WPV3 while most of the SIAs in the time period of study were mOPV1. A further, inherent limitation is the reliance on confirmed paralytic cases, in that <1% of WPV infections result in paralytic poliomyelitis [19]. As well as likely dampening the magnitude of a household-associated risk factor such as travel, it is also unlikely

that the study included the index infection for either WPV outbreak in Angola, limiting this study's ability to identify an epidemiologic link between cases and India through case-patient interviews.

This investigation demonstrates that polio-free countries are vulnerable to outbreaks following importations when there is a susceptible population due to undervaccination. Experience in other countries that have detected WPV importations indicates that high vaccination coverage can limit WPV transmission and the number of polio cases that occur following an importation event; the decreased size of outbreaks in multiple African countries following WPV importations in 2008–2009 compared with outbreaks following WPV importations during 2002–2005 is at least partly attributable to improved vaccination coverage [2]. Reinforced by the findings from this study, one of the key strategies for preventing or limiting future outbreaks due to importations in Angola is to strengthen routine vaccination services and achieve higher coverage with four routine doses of tOPV. High-quality SIAs, more effectively reaching the target population and potentially using a newly available bivalent type 1 and 3 OPV [20], as well as intermittent tOPV instead of monovalent OPV [21], will also be necessary to address the existing lack of immunity in the population to both WPV1 and WPV3. Further research is needed to determine the extent of transmission in older children and adults during outbreaks and its role in perpetuating WPV circulation overall, and whether the addition of SIAs targeting older age groups could have an impact on WPV transmission. Although the precise mode by which WPV traveled from India to Angola is unlikely to be identified, additional data on the travel and trade patterns between the two countries might be helpful in understanding possible routes of transmission and in formulating evidence-based vaccination policy for international travelers.

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