PanAfrican Medical Journal

For review

Submitted July 13, 2012

Emerging epidemic of iatrogenic Acute Flaccid Paralysis in children under 15 years in Uganda

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Abstract

Background

Poliomyelitis a differential diagnosis of Acute Flaccid Paralysis (AFP) is a major disability. The prevalence of AFP associated with an intramuscular gluteal injection (s) among children below 15 years of age with fever reported through the AFP surveillance system between 2002 and 2008 in Uganda was studied.

Methods

A cross sectional study using AFP surveillance data. Any child aged below 15 years, who developed sudden flaccid paralysis between 1st January 2002 and 31st December 2008 was enrolled. NPEC conducted a desk review of completed AFP investigation forms for final classification. A case of an Injection Related Paralysis was defined as sudden onset of flaccid paralysis setting in within 72 hours of receipt of a gluteal intramuscular injection.

Results

1,987 AFP cases were detected out of which 651 (33%) were related to injections. Monoplegias and Non Polio Enterovirus related paralysis

accounted for 24% and 9% respectively. Of the 651 cases, 488 (75%) were due to injectable quinine.

Conclusion

There is a high prevalence of AFP disability associated with gluteal intramuscular injections among children aged below 15 years reported through an AFP surveillance system in Uganda. Uganda may face a preventable epidemic of Injection Related Paralysis once polio is eradicated.

Key words: Acute Flaccid Paralysis, fever, emerging epidemic, Iatrogenic, Poliomyelitis, gluteal injections

Background

Poliomyelitis due to Wild Polio Virus (WPV) is among the various differential diagnosis of Acute Flaccid Paralysis (AFP) and a leading cause of long term disability which is sometimes associated with death [1]. The world will be declared polio free when all regions have documented the absence of wild poliovirus transmission for at least three consecutive years. An AFP surveillance system that identifies cases in children less than fifteen years of age is a core strategy of the Poliomyelitis Eradication Initiative (PEI). The AFP surveillance system in Uganda was established in 1996 to investigate all AFP cases initially in high risk districts and it was later scaled up to cover all districts in 1999. The National Polio Expert Committee (NPEC) is a technical committee responsible for classifying all AFP cases reported through the surveillance system. It comprises virologists, neurologists, epidemiologists,

paediatricians and an orthopaedic surgeon. During its course of reviewing AFP cases, NPEC was struck by an unusual number of cases of AFP that were iatrogenic in nature and in particular Injection Related Paralysis. This study is addressing this concern and highlights the potential danger of this emerging epidemic with a view to control and prevents it.

AFP is a clinical syndrome characterised by sudden onset of weakness of muscles, progressing to maximum impairment of nerve function within few days. The term “flaccid” indicates the end-stage manifestations of impaired nerve function of the locomotor system and is associated with absence of power, hyporeflexia and hypotonia in affected limbs. The AFP clinical syndrome is aetiologically associated with a variety of differential diagnose which may include poliomyelitis, injection neuritis, Guillain-Barre syndrome (GBS), transverse myelitis and traumatic neuritis [2, 3]. Although Acute flaccid paralysis due to injections is rarely reported in the African region, some members of NPEC and a few authors in Asia have documented this problem [4, 5, 6]. Accurate diagnosis of the cause of AFP has profound implication for therapy and prognosis [3].

In accordance with the virological classification criteria, NPEC in Uganda conducts desk reviews of all reported and investigated AFP cases for final classification. All AFP cases classified as non-polio must have a working alternate diagnosis. This study highlights the excessive prevalence of AFP disability associated with a history of intramuscular gluteal quinine injections among children with febrile conditions reported through the public health surveillance system.

In view of the study findings, clinical, training and practice policies are discussed and we suggest a way forward of controlling this iatrogenic disability in Uganda and probably in the East African region.

Methods

This study reviewed all AFP cases aged 15 years and below reported and investigated in Uganda from 2002 to 2008. All completed case investigation forms as collated and entered in the national AFP surveillance database were reviewed.

All Health Units in Uganda that function as routine surveillance reporting sites were involved. Within each site, trained clinical health workers and surveillance focal persons are involved in routine detection, reporting and investigation of AFP cases based on the surveillance case definition.

The study design was cross sectional which involved examination of retrospective secondary data of all cases below 15 years of age, who developed Acute Flaccid Paralysis between 1st January 2002 and 31st December 2008. They were reported and investigated through the Uganda National AFP Surveillance system for purposes of documenting progress towards polio eradication in Uganda [8].

The surveillance case definition for an acute flaccid paralysis, was any child aged 15 years or less who developed sudden flaccid paralysis affecting either one or more limbs. Any children aged 15 years and below were enrolled in this study through the surveillance system in Uganda. For each case, data on dates of onset of paralysis, presence of fever before onset of flaccid paralysis,

distribution of paralysis and affected limbs, age at onset, prior history of receipt of injections and type of drug/s given, dates of injection/s and the reporting district was documented using a standardized AFP case investigation form.

At the detecting sites informed consent from each caretaker of the child is requested, following which, two stool specimens are routinely collected at an interval of 24 to 48 hours and transported to Uganda Virus Research Institute(UVRI), EPI Laboratory at +2 to +8^{o}C within 72 hours of collection.

At the laboratory, the stool specimens were processed according to a standard protocol [9]. An aliquot from positive cultures (indicative of presence of poliovirus) were referred to the Regional Reference Laboratory in South Africa National Institute of Communicable Diseases (NICD), for further characterisation using intra-typic differentiation (ITD) to determine whether the poliovirus was a Wild or Sabin type.

NPEC examined all reported AFP cases in the study to determine both virological status and possible causes of paralysis. For some of the AFP cases investigated beyond 14 days of onset of paralysis or with incomplete epidemiological and clinical data, NPEC members did field investigations to carry out clinical and neurological examination in order to improve on reliability and validity of the final clinical diagnosis.

In this study, Injection Related Paralysis (IRP) was defined as a case of sudden onset of flaccid paralysis setting in within 72 hours of receipt of a gluteal intramuscular injection, paralysis occurring in the injected limb(s), a

case had adequate stool specimens (that is two stool specimens collected 24-48 hours apart and within 14 days of onset of paralysis), in whom no enterovirus was isolated and with or without residual paralysis after 60 days.

All AFP case records from all districts in Uganda reported between 1st January 2002 and 31st December 2008 were entered in a computer, cleaned and analysed using EPIINFO version 2002. The AFP-cause analysis was made for all IRP cases.

Since the study was part of the national public health surveillance system in the country, no Institutional Review Board approval was sought or obtained. When the decision was made to publish the results, approval was obtained from the Uganda Ministry of Health through the Uganda National Expanded Program on Immunization. Reported results have no direct linkage to individual cases for identification.

Results

One thousand nine hundred and eighty seven (1,987) cases with acute onset of flaccid paralysis were identified in the study period and of these 1,179 (59%) were males and 1,458 (74%) were below 5 years of age. The AFP rates per 100,000 population under 15 years were 2.48 in the central region, 2.18 for Eastern region, 2.07 Western region and 1.37 for the Northern region. One thousand nine hundred and eighty-four cases (99%) had 2 stool specimens collected for virus isolation, of these 1,656 (83%) had stool specimens collected within 14 days of onset of paralysis and 468 (24%) stool specimens had an isolate. Of the 468 isolates, 410 (88%) were non polio enteroviruses; 20 (4%) had mixed polio isolates (that is a mixture of two or

three of the polio viruses), 14 (3%), 10 (2%) and 14 (3%) had Sabin 1, Sabin 2 and Sabin 3 isolates respectively.

Out of the 1,987 cases, IRP and Non Polio Entero Virus related paralysis accounted for 651 (33%) and 178 (9%) respectively during the review period (figure 1). Of the 651 cases with IRP, 488 (75%) cases met the case definition used for this study giving an overall prevalence rate of 24%. One hundred and sixty three (163) cases, which constituted the difference between 651 and 488 either had an isolate or were investigated beyond 14 days of paralysis onset.

Of the 488 IRP cases, males accounted for 313 (64%) and children aged between 1 and 5 years accounted for 285 (58%) of cases (figure 2). Regional distribution of IRP cases followed a similar pattern as earlier presented for all AFP cases. The right lower limb was the most affected accounting for 51%. This is usually the convenient limb for administering injections.

Injectable anti-malarial specifically quinine and chloroquine were administered to 367 (75%) cases of which quinine accounted for 346 (94%) of all anti-malarials.

Two hundred and eighty nine (289) cases had information on the health facility that administered the injection, out of which 184 (64%) were given by private clinics. Other health facilities included health centres, hospitals and drug shops that accounted for 66 (23%), 21 (7%) and 18 (6%) respectively.

The occurrence of IRP was most observed during the months of March to June and then September through November (figure 3) which coincide with rainy seasons and periods of high malaria transmission.

Over the years the age specific incidence rate gradually increased from 0.82 in 2002 to 2.07 per 100,000 population in children aged between 1 and 4 years (table 2). 16.2% of the total population are children aged between 1 and 5 years [7].

Discussion

Injection related paralysis following intramuscular injections in the gluteal region was found as a major cause of Acute Flaccid Paralysis of lower limbs, particularly in children below five years of age in Uganda during 2002 -2008. This is a result of treating febrile conditions in children with intramuscular injections at first contact with a health worker. Our findings are similar to studies done in other developing countries [10, 12, 14, 15, 16].

Gluteal injection related paralysis follows an injury to the sciatic nerve by an injection near or into the nerve. Quinine injection in gluteal muscle has been reported as the most cause of AFP among children [4]. Administration of intramuscular injections in the gluteal region is still a common practice in Uganda despite the potential risk of direct trauma to the sciatic nerve resulting into post injection neuritis. A history of recent injections in paralysed limbs for treatment of febrile illness provides a characteristic lead for diagnosing iatrogenic injection neuritis. Fever may be present for other causes of AFP. Given the high burden of malaria in Uganda, usually the first line of treatment is an injection for clinical malaria. This study observed that most cases with

injection related paralysis were seen during rainy season, also peak months for the vector of malaria transmission (figure 4).

Injection related paralysis needs to be differentiated from acute poliomyelitis fixed by an injection [3,6]. This is because in case of wild poliovirus paralytic poliomyelitis during the viraemic phase, the virus can be fixed to the nerve if the child is injected with an irritant and the infection results in permanent paralysis. In our study we excluded all cases that could have been poliomyelitis by focusing on cases that were investigated within 14 days of onset of paralysis, therefore making it unlikely to be poliomyelitis. The findings in this study show excessive burden of paralysis following gluteal intramuscular injections hence the need to address this problem. A high prevalence of IRP was observed in private clinics with the most probable cause being unqualified personnel administering injections and a possibility of inadequate support supervision on injection safety by higher levels in private clinics. Quinine intramuscular injections should be avoided. Other routes of administration to provide a comparable level of absorption and effect in any given individual's situation and condition should be used.

Globally, the aetiology of AFP is broad and there is substantial variation by aetiology and across age, ethnicity and geographic areas. In absence of WPV, GBS accounts for at least 50 percent of AFP cases followed by non polio enterovirus infection, traumatic neuritis, and acute transverse myelitis in descending order [13]. The trend of IRP in Uganda may be due to inappropriate administration of injections by the health workers following the

Integrated Management of Childhood Illnesses (IMCI) policy. The policy for management of febrile illnesses recommends the use of injectable quinine as the pre-referral management of a child with severe febrile illnesses [11]. This study has noted that in Uganda traumatic neuritis is the most common cause of AFP and this is good ground for review of the IMCI policy by Ministry of Health. Quinine dihydrochloride should be given by rate-controlled infusion in dextrose solutions at a rate not exceeding 5 mg salt/kg bw per hour to avoid complications such as injection neuritis and muscular fibrosis.

The main limitations of this study was lack of a comprehensive and timely 60 day follow up of all AFP cases to determine the presence of residual paralysis. Secondly, the earlier years 2002 -2005 of the surveillance system lacked information on history of injection, implicated drug and number of injections given due to the design of the surveillance at that time. Thirdly, the study team relied on secondary data which was provided by surveillance focal persons who had different training backgrounds on neurological examination.

Conclusion

This study has revealed that while poliomyelitis related disability will become history once eradication is achieved, we may end up with an epidemic of AFP cases due to IRP if gluteal injections are not stopped. We recommend that if necessary as matter of policy, quinine should be given intravenously. Thirdly, there should be enforcement of private clinic regulations. We also identified a relatively high prevalence rate of NPEV paralysis which also calls for further studies. Finally, nerve conduction studies as part of sentinel surveillance may be considered as part of the surveillance system.

Acknowledgments

To the health workers who collect and transport specimens for AFP laboratory investigations at UVRI and who carried out the 60 day follow up of the children. The EPI laboratory staff at Uganda Virus Research institute and Polio lab staff at the National Institute of Communicable Diseases, South Africa who carried out the virological investigations of the stool specimens. The data clerks: Justine Waibi (RIP), Ms Molly Birungi and Ms Prossy Kakooza who entered the data. The Ministry of Health and World Health Organisation who funded the collection of the data.

Competing interests

The authors declare that they have no conflicts of interest.

Authors' contributions

All authors have contributed to this study in ways consistent with the authorship criteria.

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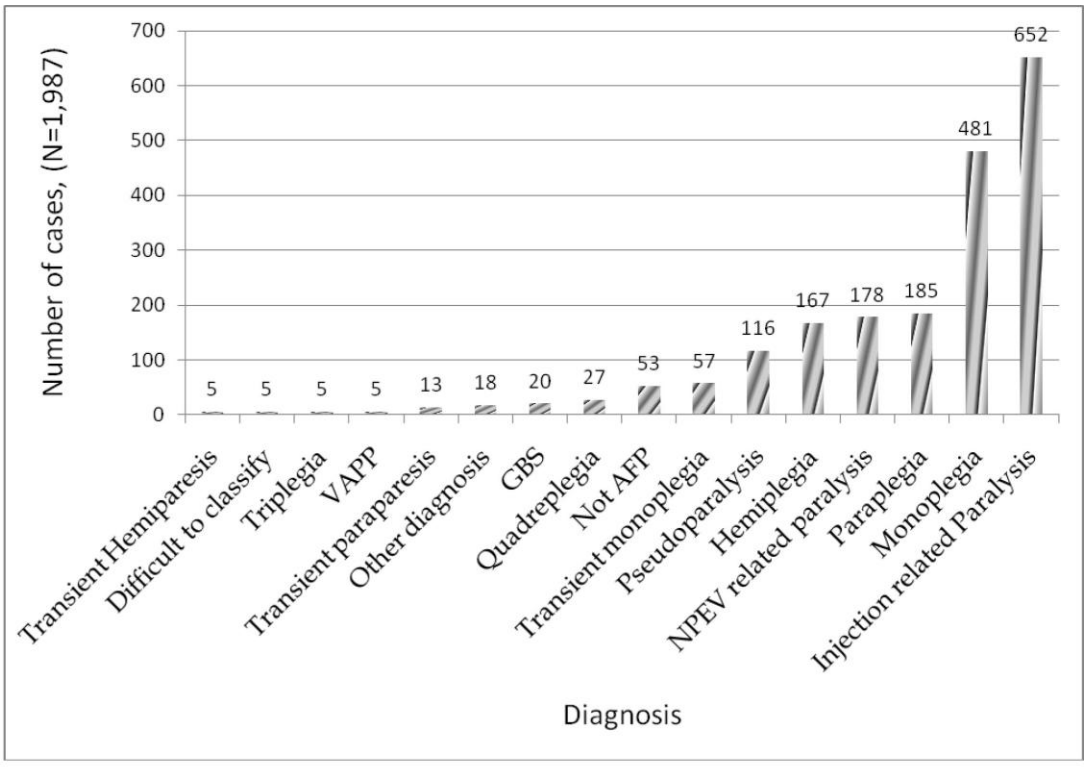
Figures

Figure 1: Final diagnosis made by NPECfor AFP cases detected in Uganda, 2002-2008



Others include: tumours or infections of the spinal cord (e.g. TB), transient monoparesis

Figure 2: Age distribution of Injection Related Paralysis cases, 2002-2008

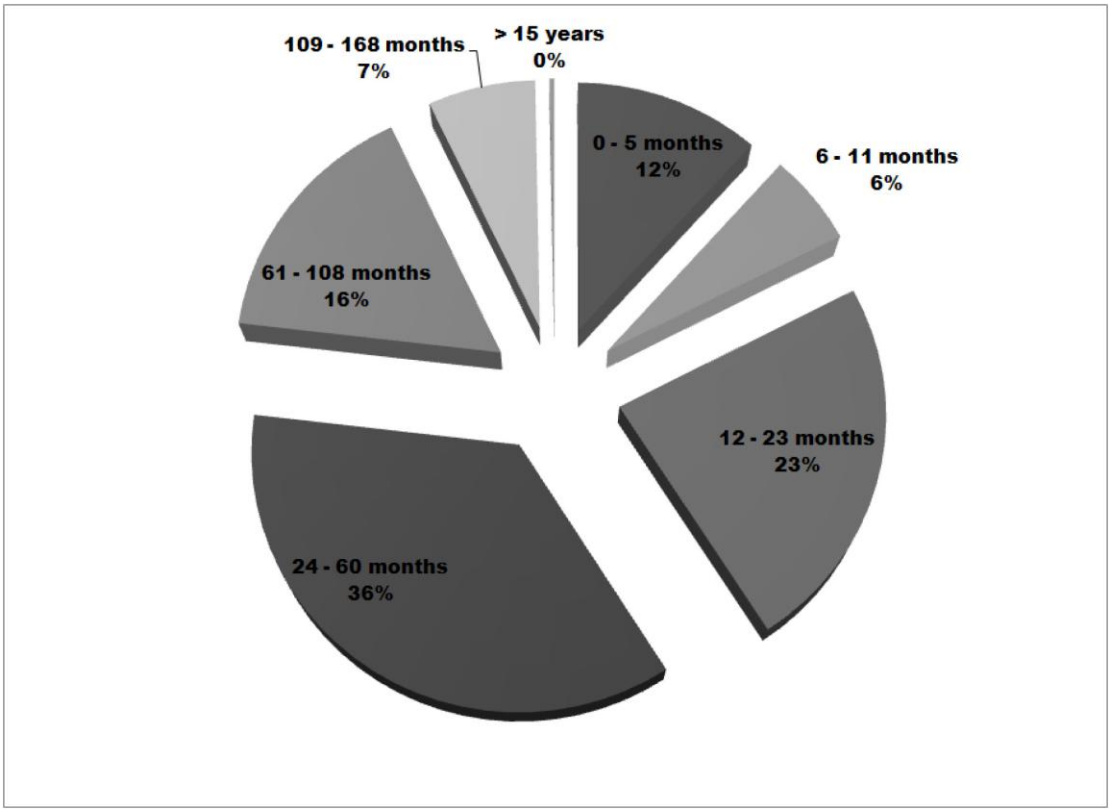


Figure 3: Seasonal occurrence of injection neuritis cases in Uganda, 2002-2008

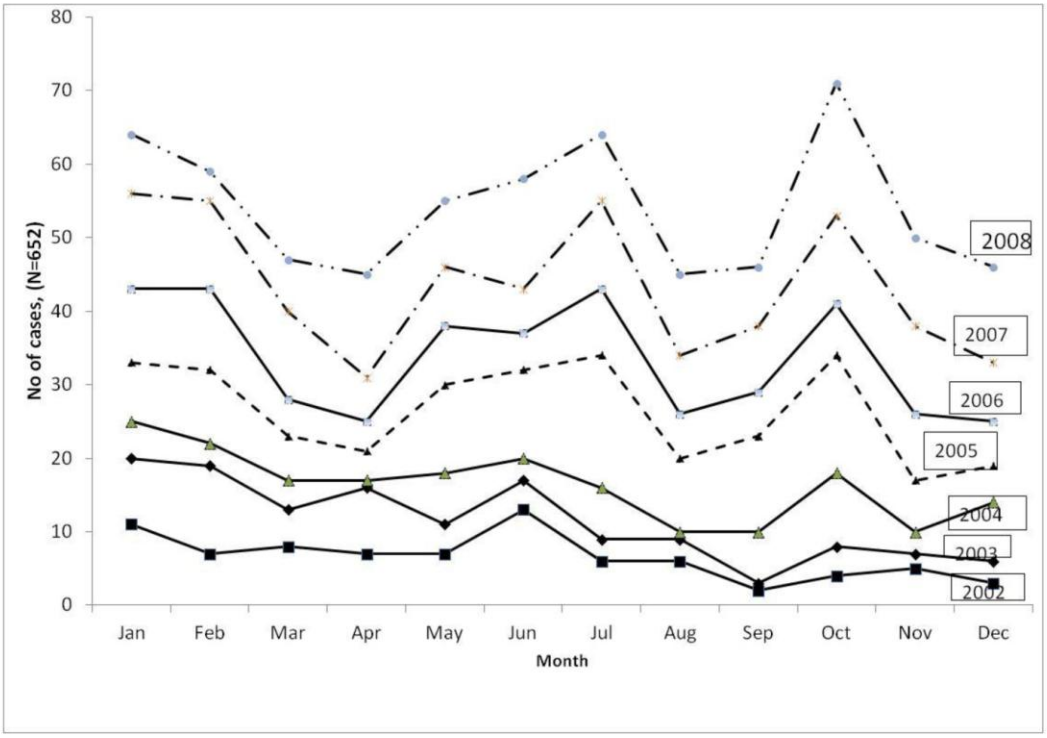


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Table 1: Demographic features of Injection Related Paralysis cases in Uganda, 2002-2008		
Variable	**No. of cases (n=652)**	**%**
Sex		
Male	410	63
Female	242	37
Age		
0 – 5 months	76	12
6 – 11 months	38	6
12 -23 months	153	24
2 – 5 years	234	36
6 – 10 years	105	16
11 – 15 years	44	7
> 15 years	2	0
Affected Limb		
Right lower limb only	298	46
Left lower limb only	265	41
Bilateral lower limbs	86	13
Hemiplegia	3	0
Regional distribution		
Central	249	38
Eastern	202	31
Western	158	24
Northern	43	7
Medication given		
Quinine only	512	79
Chloroquine only	45	7
Antibiotics	6	1
Unknown drug	87	13
Age specific Incidence rate/100,000	< 1yr	1-4 yrs
2002	2.88	0.82
2003	4.17	0.12
2004	0.44	1.00
2005	0.60	1.54
2006	0.25	1.51
2007	0.91	1.57
2008	0.94	2.07

Table 2: Age specific incidence rate of Injection Related Paralysis cases in Uganda, 2002-2008			
Age specific Incidence rate/100,000	***< 1yr***	***1-4 yrs***	***< 5yrs***
2002	2.88	0.82	1.25
2003	4.17	0.12	0.97
2004	0.44	1.00	0.88
2005	0.60	1.54	1.34
2006	0.25	1.51	1.25
2007	0.91	1.57	1.43
2008	0.94	2.07	1.83