

Standard Review

The role of vaccine derived polioviruses in the global eradication of polio-the Nigeria experience as a case study

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This review reports the role of vaccine derived poliovirus (VDPV) in the global eradication of poliomyelitis. A vaccine derived poliovirus (VDPV) is a rare strain of poliovirus, genetically mutated from the strain contained in OPV. The OPV contains a weakened or attenuated version of poliovirus, activating an immune response in the body. A vaccinated person transmits the weakened virus to others, who also develop antibodies to polio, ultimately stopping transmission of poliovirus in a community. The World Health Assembly in 1988, resolved to eradicate poliomyelitis from the world by the year 2000 and since then, the Global Polio Eradication Initiative (PEI) of the World Health Organization (WHO) has led to a decline in global polio incidence, from an estimated 350,000 cases in 1988 to under 3,500 in the year 2000, with the last remaining global poliovirus reservoirs confined to parts of Southeast Asia and Sub-Saharan Africa. In the African Region (AFRO) of the WHO, eradication strategies were accelerated following supporting resolutions by WHO's Regional Committee for African in 1995 and the organization for African Unity in 1996. Despite the reported success in National Immunization days (NIDs), establishment of acute flaccid paralysis (AFP) surveillance and accelerated efforts to meet the year 2000 targets including "mopping-up" executed in 1999 and subsequent years, Nigeria, the most populous country in Africa, remains one of the major reservoirs for wild poliovirus transmission. Conversely, American region (AMRO) of the WHO was certified as polio-free in 1994 as was the Western Pacific Region (WPRO) in 2000. Recommendations have therefore being presented on ways of evaluating vaccine administration to boost its output in checkmating the increasing waves of paralytic poliomyelitis (including vaccine associated paralytic poliomyelitis-VPP) and prevalence of wild poliovirus in the country. However, there are obstacles to the global eradication which involve among others, vaccine derived polioviruses (VDPVs) in areas with low oral poliovirus vaccine (OPV) coverage. In addition, long term excretion of neurovirulent immunodeficiency-associated vaccine derived polioviruses (iVDPVs) can lead to poliovirus spread to contacts. Overcoming these obstacles is challenging.

Key words: Global eradication, Poliovirus, poliomyelitis, vaccine administration, vaccine derived poliovirus (VDPV).

BACKGROUND OF THE STUDY

Poliomyelitis is an acute infectious systematic viral disease affecting human and is of widely varying severity from a non specific illness to almost irreversible paralysis or death due to polioviruses of serotypes 1, 2 and 3 infections. In rarely severe cases, death is often due to

asphyxiation especially children below the age of five years, it has remained endemic in some parts of the world including Nigeria. Poliomyelitis has been ravaging many developing countries especially those in sub-Saharan Africa. The cumulated number of children with

wild poliovirus recorded has been increasing astronomically especially in Africa continent and particularly in Nigeria (White and Fenner, 1994; WHO, 1997, 2000; Abdulraheem and Saka, 2004).

In 1988, the World Health Assembly launched the Global Polio Eradication Initiative, which aimed to use large-scale vaccination with the oral vaccine to eradicate polio worldwide by the year 2000. Although important progress has been made, polio remains endemic in several countries. Also, the current control measures will likely be inadequate to deal with problems that may arise in the post-polio era. A panel convoked by the National Research Council concluded that the use of antiviral drugs may be essential in the polio eradication strategy (WHO, 1997, 2000; Abdulraheem and Saka, 2004; GPEI, 2007; Agbeyegbe, 2007).

The World Health Assembly in 1988, resolved to eradicate poliomyelitis from the world by the year 2000 and since then, the Global Polio Eradication Initiative (PEI) of the World Health Organization (WHO) has led to a decline in global polio incidence, from an estimated 350,000 cases in 1988 to under 3,500 in the year 2000, with the last remaining global poliovirus reservoirs confined to parts of Southeast Asia and Sub-Saharan Africa. The American region (AMRO) of the WHO was certified as polio-free in 1994 as was the Western Pacific Region (WPRO) in 2000. However, there are obstacles to the global eradication which involve among others, vaccine derived polioviruses (VDPVs) in areas with low oral poliovirus vaccine (OPV) coverage. In addition, long term excretion of neurovirulent immunodeficiency-associated vaccine derived polioviruses (iVDPVs) can lead to poliovirus spread by contacts (WHO, 1997, 2000; Abdulraheem and Saka, 2004; Adu et al., 2007; GPEI, 2007; Agbeyegbe, 2007). Overcoming these obstacles is challenging.

In developing countries like Nigeria, poliomyelitis is a public health problem and it was first brought to focus in 1961. In 1984, the annual coverage on immunization in Nigeria was 21% with Nigeria reporting the highest cases of poliomyelitis in Africa region (EPA, 1989). In 1992 alone, about 957 cases of poliomyelitis were reported to the World Health Organization (Adu et al., 1996).

The effort is how to eradicate poliomyelitis through the efficient and purposeful national immunizations programme. The vaccine, invented by Albert Sabin, is easier to give, offers much stronger protection and can beneficially "infect" other family members or neighbors, protecting them too. But in rare cases, it can mutate into something resembling wild polio virus, which can paralyze or kill. Ten billion doses of oral vaccine had been given in the last 10 years, so such mutations are presumably extremely unusual (McNeil, 2007). The rationale for providing several doses of OPV is to ensure initial seroconversion

against all the types of poliovirus and not to boost waning immunity. Oral polio vaccine is ineffective if given before the age of six months. This is because of the vaccine neutralization by maternal polio antibodies in the baby and also in the breast milk. Nevertheless, several studies show that among breastfed infants, who are fed OPV in the first three days of life, 20 to 40% develop serum antibodies and 30 - 60% excrete vaccine virus (Halsey and Galazka, 1985; Abdulraheem and Saka, 2004).

Polio often circulates undetected; in only one of 200 infections will it cause paralysis, which signals health officials to look for the virus in the area (McNeil, 2007). Outbreaks of vaccine-derived polio are unusual but not unheard of. Individual cases have been known for years. For example, a former lieutenant governor of Virginia was partly paralyzed in 1973, apparently after changing the diapers of his son, who had received oral vaccine (McNeil, 2007). The first spreading outbreak of a vaccine-derived strain, in which 22 children were paralyzed, was detected in 2001 in the Dominican Republic and Haiti (McNeil, 2007). Experts now believe another took place in Egypt in the late 1980s but went unnoticed amid the much larger numbers of wild-type infections. There have been in the Philippines, Madagascar, China and Indonesia (McNeil, 2007). All were eventually eliminated by immunizing more children, and experts argue that the latest outbreaks were able to spread because, until recently, only 30 to 40% of the children in northern Nigeria were vaccinated. About 70% of the children in Nigeria have been vaccinated now (McNeil, 2007). In 2000, the United States switched to inject vaccine made from killed virus, which cannot mutate. But oral drops with the live, weakened version of the virus are still used in most poor countries, including those where the disease has never been eliminated: Nigeria, India, Pakistan and Afghanistan (McNeil, 2007).

Nigeria indeed is fighting an unusual outbreak of polio caused by mutating polio vaccine; the only remedy is to keep vaccinating children there. The ongoing outbreak in 18 northern states of Nigeria's 36 states started in 2006 and was reported in September 2007 issue of *Morbidity and Mortality Weekly Review* of CDC (Adejaja, 2007). This polio outbreak is only appearing in areas where people are refusing to be vaccinated or where there is not enough oral polio vaccine. Heightened immunization campaign for children was a necessity to stop the endemic from spreading (Adejaja, 2007). The best way to overcome the outbreak of vaccine-related polio virus is to increase immunization coverage, making sure that all children get the vaccine (Adu, 2007). This review therefore reports the role of vaccine derived poliovirus (VDPV) in the global eradication of poliomyelitis.

Trends in global eradication of polio infection

The goal of global eradication of poliomyelitis by the year 2000 was approved by the World Health Assembly in

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1988 and was adopted by the World Health Organization (WHO). The program has two main objectives: no more cases of poliomyelitis caused by wild polioviruses and the absence of wild poliovirus circulation, as evidenced by examining specimens from humans and the environment (Wright et al., 2000). The effort is how to eradicate poliomyelitis through the efficient and purposeful national immunizations programme. The rationale for providing several doses of OPV is to ensure initial seroconversion against all the types of poliovirus and not to boost waning immunity. Oral polio vaccine is ineffective if given before the age of six months. This is because of the vaccine neutralization by maternal polio antibodies in the baby and also in the breast milk. Nevertheless, several studies show that among breastfed infants, who are fed OPV in the first three days of life, 20 to 40% develop serum antibodies and 30 - 60% excrete vaccine virus (Halsey and Galazka, 1985; Abdulraheem and Saka, 2004).

In line with World Health Organization (WHO) global polio eradication initiative (GPEI), Nigeria and other polio endemic countries have designated National Immunization Days (NIDs) for mass vaccination campaigns (GPEI, 2007; Agbeyegbe, 2007). The deadline of the global polio eradication initiative coordinated by the WHO is approaching rapidly. Eradication may not be accomplished in the year 2000 itself, but it is imminent (Agbeyegbe, 2007).

The success of this eradication programme could not be achieved without the highly effective, live, attenuated oral poliovaccine (OPV), as formulated by Albert Sabin (Sabin and Boulger, 1973). The advantages of this vaccine are numerous, e.g. it confers lifelong humoral and mucosal immunity, it is cheap to produce and easy to administer and it is fairly stable (Melnick, 1996). There are, however, a few disadvantages, the most prominent being the frequent reversion to neurovirulence upon replication in humans (Macadam et al., 1989; Dunn et al., 1990; Georgescu et al., 1994) and the capacity to cause vaccine-associated paralytic poliomyelitis (VAPP), which occurs in approximately one case per 750,000 first doses of OPV (CDC, 1997).

Extensive use of the two available vaccines, the live attenuated oral poliovirus vaccine (OPV), or the Sabin vaccine, and the inactivated poliovirus vaccine, or the Salk vaccine, has dramatically reduced the numbers of poliomyelitis cases caused by wild poliovirus infection (Ward et al., 1993). The use of OPV still remains unresolved and this is perhaps because of the different neutralizing antibody level in different geographical areas. In temperate climates immunity rates to all the three polio serotypes after the three doses is about 95% whereas a developing country like India, has 50 - 60% (John and Jayabal, 1972). Five doses of OPV are required to get to 90 - 95% seroconversion rates (John, 1967). The prevention of further cases of poliomyelitis is essential if this disease is to be eradicated. This is best achieved by an oral polio vaccine (Sabin) manufactured with all three types of attenuated live virus. At least two; and preferably

three (and sometimes more) doses should be given to all children and to all babies from birth onwards.

The prevention of further cases of poliomyelitis is essential if this disease is to be eradicated. This is best achieved by an oral polio vaccine (Sabin) manufactured with all three types of attenuated live virus. At least two; and preferably three (and sometimes more) doses should be given to all children and to all babies from the age of three months onwards. Intensive immunization campaigns are necessary in the developing countries of the world. Epidemics of paralytic poliomyelitis in the developing countries of the tropics and subtropics have, in fact, shown a threefold increase in the past 10 years and are continuing to increase. Nationwide immunization campaigns are therefore an urgent necessity for all developing countries and, once started, must continue if future epidemics are to be prevented.

Current trends in global polio eradication

In 1981 a WHO-initiated collaborative study on various markers for the intratypic differentiation of polioviruses was conducted (WHO, 1981). The serum neutralization test with cross-absorbed antisera was shown to be superior to all other tests in the study. Since then, new developments in microbiological diagnostics and molecular virology have added new possibilities for the rapid and reliable intratypic differentiation of poliovirus isolates. Cross-absorbed intratype-specific polyclonal rabbit antisera (PABs) are currently used in an enzyme-linked immunosorbent assay (ELISA) format (Osterhaus et al., 1983; Glikmann et al., 1984). Differences in the antigenic structure between vaccine-related and wild-type poliovirus strains reflect differences in the viral RNA.

It is evident that towards the end of the eradication campaign, the role of the virus diagnostic laboratories is increasing, as all poliovirus isolations from paralytic cases require virological follow-up to elucidate the source of the agent (WHO, 2004b). That is, whether the paralysis is due to a wild-type infection or to VAPP, or to infection with a non-polio enterovirus causing polio-like symptoms (Melnick, 1984; Hayward et al., 1989). Since beginning of 2001, all polio isolates from WHO laboratory network are tested by two intratypic differentiation (ITD) methods; one antigenic and one genomic. All isolates that are Sabin-like in one test but not Sabin-like in the other are sequenced in VP1.

Recently, fears arose about the successful eradication of polio despite a reduction in polio endemic countries from 125 in 1988 to 7 in 2002, and a decline in reported cases of 1919 annually from about 350,000 (WHO, 2004f) globally during the same period. In 2003, polio cases in the world were on the increase and Nigeria went from being one of the seven countries with endemic polio to reporting the highest number of polio cases in the world (WHO, 2003). New cases of polio in nine hitherto polio-free countries resulted from wild poliovirus geneti-

cally linked to the poliovirus endemic in Nigeria (WHO, 2004d), while 7 of the countries-Benin, Burkina Faso, Cameroon, Chad, Cote d'Ivoire, Ghana and Togo were in West African, the other 2 were the Central African Republic and Botswana in the Southern region of Africa (Agbeyegbe, 2007).

The outbreak in Botswana reinforced fears of a global outbreak of polio. The present state of global travel presents a favorable environmental condition for the spread of infectious disease (CDC, 2000c). A remaining challenge to World Health Organization (WHO) Global Polio Eradication Initiative is the continued circulation of wild poliovirus in Nigeria (CDC, 2005b, 2006a, b, 2007). Wild poliovirus type 1 has spread from reservoirs in northern Nigeria (and southern Niger) to 18 previously polio-free countries in 2002 - 2005, from Guinea in the west to Indonesia at the southeastern rim of Asia, resulting in over 1200 cases associated with imported virus since 2002 (CDC, 2006b; Adu et al., 2007; Agbeyegbe, 2007).

Moreover, northern Nigeria remains by far the world's largest reservoir for wild poliovirus type 3, with 244 polio wild poliovirus type 3 cases reported in 2005 and 278 wild type 3 cases reported in 2006 (CDC, 2007). Coverage by supplementary immunization with NIDs has also been low and insufficient to block widespread wild poliovirus transmission in northern Nigeria (CDC, 2005b, 2007).

In 2003, some states in Nigeria opted out of the program, disrupting the campaign. Thereafter, Nigeria surpassed India reporting the highest polio cases globally (WHO, 2003; Agbeyegbe, 2007). The 2003 - 2004 polio vaccination boycotts in Nigeria threatened the global polio eradication initiative of having a polio-free world by 2005. Encouraged by the global eradication of small pox from the world in 1980, WHO launched the global polio eradication initiative in 1988 seeking to eradicate polio from the world by the year 2000 (Agbeyegbe, 2007).

By the end of 2003, Nigeria accounted for 45% of all global cases of polio and 70% of all cases in 2004. Within ten months, twelve polio free countries confirmed polio cases resulting from a poliovirus genetically linked to that endemic in northern Nigeria (WHO, 2004). The situation appeared to have been fully resolved when Kano the last state holding out resumed polio vaccination in July 2004 (Agbeyegbe, 2007). Despite the severe challenges, a major milestone to poliovirus eradication has been the disappearance of indigenous wild poliovirus type 2 which was last found in West Africa in 1997, and last found anywhere in the world (in Uttar Pradesh, India) in 1999 (WHO, 2001). Thus, in Nigeria, as in other parts of the world, the only current exposure to poliovirus type 2 is from use of the live, attenuated oral poliovaccine (OPV).

However, in recent years a new dimension of risk was identified with the discovery of highly divergent vaccine-derived polioviruses (VDPVs) (Adu et al., 2007). In September 2002, a type 2 VDPV was isolated from an incompletely immunized 21-month-old boy from Plateau state, in north central, Nigeria. The VDPV isolate differed

from the Sabin type 2 (Sabin 2) OPV strain at 2.5% of VP1 nucleotides, and had 3D^{pol} sequences derived from a source distinct from any of the Sabin strains (Adu et al., 2007).

Over the past 4 years, there have been localized outbreaks of cVDPV in Hispaniola, Philippines and Madagascar. Retrospective studies have confirmed occurrence of cVDPV in Belarus, Poland, Egypt etc. All cVDPV occurred in an environment of poor OPV coverage. Currently, the most urgent priority is to stop wild poliovirus circulation in Nigeria and other countries in Africa, and strenuous efforts are being made to close the large gaps in immunity to poliovirus in the continent (CDC, 2006b, 2007). Type 2 polioviruses are most readily controlled because of the high immunogenicity of the Sabin 2 component of OPV and the marked tendency of Sabin 2-related viruses to spread to and minimize contacts (Sutter et al., 2004). OPV has been the vaccine of choice for the more than 190 countries which have eliminated polio. OPV remains the only vaccine used by the Global Polio Eradication Initiative to interrupt all wild poliovirus transmission, globally (GPEI, 2008).

Vaccine Derived Polioviruses (VDPVs)

VDPVs are defined as poliovirus isolates having >1% nucleotide sequence divergence in the ~900 nucleotide (nt) region encoding the major capsid protein, VP1 (CDC, 2005a; Kew et al., 2005). This definition follows from the rapid rate of nucleotide sequence evolution in poliovirus (~1% per year) and the normal period of poliovirus excretion of less than 3 months (Alexander et al., 1997; Kew et al., 2005). A vaccine derived polioviruses (VDPVs) is a rare strain of poliovirus, genetically mutated from the strain contained in OPV. The OPV contains a weakened or attenuated version of poliovirus, activating an immune response in the body. A vaccinated person transmits the weakened virus to others, who also develop antibodies to polio, ultimately stopping transmission of poliovirus in a community. Between October 2001 and April 2002, five cases of acute flaccid paralysis associated with vaccine-derived poliovirus (VDPV) type 2 isolates were reported in the southern province of the Republic of Madagascar (Rousset et al., 2003). All cVDPVs occur in an environment of poor or low routine/mass immunization OPV coverage, poor sanitation, tropical condition and crowding (WHO, 1997, 2000; Abdurraheem and Saka, 2004; Adu et al., 2007; GPEI, 2007; Agbeyegbe, 2007).

Similarities of VDPV to wild polioviruses

- i.) Capacity for sustained person-to-person transmission.
- ii.) Significant paralytic attack rate.
- iii.) Highly neurovirulent in transgenic mouse model.
- iv.) Replicates at 39.5°C.
- v.) Undergoes recombination with non-polio entero-

viruses (NPEVs) during circulation

Categories of VDPVs

Two well defined categories of VDPVs have been recognized: (1) immunodeficiency-associated VDPVs (iVDPVs) associated with chronic poliovirus infections (Bellmunt et al., 1999; Halsey et al., 2004; Kew et al., 1998; Khetsuriani et al., 2003; MacLennan et al., 2004; Minor, 2001; WHO, 2004a), and (2) circulating VDPVs (cVDPVs) associated with polio outbreaks in areas with low rates of OPV coverage (Kew et al., 2002, 2005; Liang et al., 2006; Rousset et al., 2003; Shimizu et al., 2004; Yang et al., 2003). A third category, ambiguous VDPVs (aVDPVs) include clinical isolates from patients with on recognized immunodeficiency and not associated with an outbreak (Cherkasova et al., 2002; Georgescu et al., 1997; Korotkova et al., 2003), and environmental isolates whose ultimate sources have not been identified (Blomqvist et al., 2004; CDC, 2005a; Shulman et al., 2000).

Immunodeficiency-associated Vaccine derived polioviruses (iVDPVs)

iVDPVs refers to vaccine derived polioviruses which is associated with chronic poliovirus infections (Adu et al., 2007). This can be excreted over prolonged periods (>6 months) by a small proportion of immunodeficient persons exposed to OPV. World Health Organization iVDPV registry identified only 30 persons excreting iVDPV since the introduction of OPV in 1961 - 1962. Persons with B-cell immunodeficiencies are mostly at risk for iVDPV infections. The first reports of iVDPV came from high-income developed countries (e.g. the USA, Western Europe and Japan) with high OPV coverage (Bellmunt et al., 1999; Halsey et al., 2004; Kew et al., 1998; Khetsuriani et al., 2003; MacLennan et al., 2004; Minor, 2001; WHO, 2004a).

Recent reports include middle-income countries while no iVDPVs have been reported from low-income develop countries where survival rates for persons with B-cell deficiencies are low. Although OPV is not recommended for immunodeficiency patients, that is often inadvertently administered because certain primary immunodeficiencies [e.g. common variable immunodeficiency (CVID) develop later in life]. Exposure is usually from receipts of OPV, though 3 of the known iVDPV infections occurred in immunized persons (Bellmunt et al., 1999; Halsey et al., 2004; Kew et al., 1998; Khetsuriani et al., 2003; MacLennan et al., 2004; Minor, 2001; WHO, 2004a).

Circulating Vaccine-derived Polioviruses (cVDPVs)

This also refers to vaccine-derived polioviruses that are

associated with polio outbreaks in areas with low rates of OPV coverage (Adu et al., 2007). Circulating cVDPV cause polio outbreaks during extensive circulation in populations with poor vaccine coverage and hygiene. Low vaccination coverage increases the proportion of non-immune persons in a population; this increases the potential for VDPVs to circulate. cVDPVs have produced several localized polio outbreaks, episodes in different countries such as Belarus (type 2, 1965 - 66), Poland (type 3, 1968), Egypt (30 cases of type 2, 1988 - 1993), Hispaniola (25 cases of type 1, 2000 - 2001), Philippines (3 cases of type 1, 2001), Madagascar (5 cases of type 2, 2002) and 8 independent outbreaks in 8 countries; Egypt, Haiti, Dominican Republic of Congo, Philippines, Madagascar, China, Indonesia and Cambodia have been associated with cVDPVs. A single isolates of vaccine/nonvaccine recombinant type 2 VDPVs were obtained under similar epidemiologic conditions in Peru in 1983 and Parkistan in 2000 (Kew et al., 2005). Prospective and retrospective studies of > 3,600 Sabin isolates have detected 1 additional drifted virus in immunodeficient patient in Argentina (EPI/SEARO/WHO, 2007). The largest documented outbreak (46 polio cases) occurred in the Indonesian Island of Madura (Bellmunt et al., 1999; Halsey et al., 2004; Kew et al., 1998; Khetsuriani et al., 2003; MacLennan et al., 2004; Minor, 2001; WHO, 2004a).

Genetic studies stored isolates suggest that a type 2 cVDPV circulated endemically in Egypt for 10 years (approximately from 1983 to 1993). Outbreaks of cVDPV have been associated with all 3 poliovirus serotypes. 2 independent type 2 cVDPV outbreaks occurred in Madagascar in 2002 and 2005 possibly signaling a higher potential for the emergence of type 2 cVDPVs (Adu et al., 2007).

In very rare instances, the virus in the vaccine can mutate into a form that can paralyze. When the virus regains the ability to circulate, it is called a circulating vaccine-derived poliovirus cVDPV). As with naturally occurring polioviruses, the only protection against cVDPV is full vaccination. The spread of a cVDPV shows that too many children remain under-immunized (GPEI, 2008). A fully immunized population will be protected from all strains of poliovirus, whether wild or vaccine derived (Bellmunt et al., 1999; Halsey et al., 2004; Kew et al., 1998; Khetsuriani et al., 2003; MacLennan et al., 2004; Minor, 2001; WHO, 2004a).

Ambiguous Vaccine-derived Polioviruses (aVDPVs)

This also refers to vaccine derived polioviruses that are associated with clinical isolates from patients with on recognized immunodeficiency and environmental isolates whose ultimate sources have not been identified, and not associated with an outbreak (Blomqvist et al., 2004; CDC, 2005a; Cherkasova et al., 2002; Georgescu et al., 1997; Korotkova et al., 2003; Shulman et al., 2000). There

are reports of highly evolved VDPV that do not easily fit the above classifications. For instance, such strains were isolated from immunocompetent patients with vaccine-associated paralytic poliomyelitis (VAPP), a healthy contact of the VAPP case, and from sewage without any known source of excretion, they are called aVDPV. The sewage isolates have similar genetic and antigenic properties as iVDPVs, but measures to identify the infected persons have been unsuccessful (Bellmunt et al., 1999; Halsey et al., 2004; Kew et al., 1998; Khetsuriani et al., 2003; MacLennan et al., 2004; Minor, 2001; WHO, 2004a).

In addition, the finding that the Plateau/02 VDPV isolates had non-capsid sequences derived from nonvaccine enterovirus sources by Adu et al. (2007), suggests that it had been in circulation, as recombination with species C enteroviruses frequently but not invariably (Liang et al., 2006) occurs with circulating wild polio-viruses (Liu et al., 2003) and cVPDVs (Arita et al., 2005; CDC, 2005a; Kew et al., 2002; Rousset et al., 2003; Shimizu et al., 2004; Yang et al., 2003), but has not been observed with iVPDVs (Bellmunt et al., 1999; Kew et al., 1998, 2005; Martin et al., 2000; Yang et al., 2005).

Vaccine/nonvaccine recombinants are occasional found, but are rare among isolates with limited (<1%) capsid sequence divergence from the parental Sabin strain (Arita et al., 2005; Kilpatrick et al., 2004). Sequences of iVPDV isolates, by contrast, frequently have many mixed-base positions, indicative of multiple iVDPV lineages infecting the immunodeficient patients (Kew et al., 1998; Martin et al., 2000; Yang et al., 2005). As till date, Plateau/02 was not confirmed as cVDPV because no related VDPV isolates have been found in Nigeria or elsewhere, the VDPV was found in an area where conditions favour VDPV emergence and spread (Adu et al., 2007).

BIOLOGICAL PROPERTIES OF VDPVS

- i.) Have capacity to cause paralytic polio in humans.
- ii.) Potential or demonstrated capacity for sustained circulation.
- iii.) VDPVs have lost key attenuation mutations and resemble WPVs biologically.
- iv.) All known cVDPVs but no iVDPVs are recombinants with no structural protein sequences derived from species C enteroviruses, a property associated with poliovirus circulation.
- v.) Most VDPVs are antigenic variants of Sabin strains, but antigenic evolution to be faster in iVDPVs than in cVDPVs.

The frequency of VDPVS occurrence is represented in Table 1.

Implications of circulating vaccine-derived poliovirus

A circulating vaccine-derived poliovirus is a rare strain of

poliovirus, genetically changed from its original strain contained in Oral Polio Vaccine (OPV). The emergence of a vaccine-derived poliovirus that can circulate in the population shows that too many children remain under-immunized. A fully-immunized population with OPV will be protected from all strains of poliovirus, whether wild or VDPVs. Although quite rare, cVDPVs are not a new phenomenon and have occurred in various parts of the world. In the past 10 years worldwide: over 10 billion doses of OPV have been administered to more than 2 billion children; 9 cVDPV outbreaks have occurred in 9 countries, in communities with low OPV coverage, resulting in under 200 polio cases; during that period, more than 33,000 children were paralyzed by wild poliovirus while over 3.5 million polio cases were prevented by OPV. cVDPVs in the past have been rapidly stopped with 2 - 3 rounds of high-quality immunization campaigns with OPV. The solution is the same for all polio outbreaks: immunize every child several times with OPV to stop polio transmission, regardless as to the origin (GPEI, 2008).

The Nigerian VDPVS experience: when and how it started

Nigeria has the highest number of polio cases, accounting for 61% of global polio cases and 95% of cases in Africa according to the disease surveillance unit of the World Health Organization (WHO) (Adejia, 2007). Sixty-nine children in Nigeria have been partially paralyzed after weakened viruses from polio vaccines were inadvertently transmitted to people in unvaccinated regions in the north of the country (Adejia, 2007). According to McNeil (2007), officials of the World Health Organization (WHO) fear that news of the outbreak will be a new setback for eradication efforts in northern Nigeria, where vaccinations were halted in 2003 for nearly a year because of rumors that the vaccine sterilized Muslim girls or contained the AIDS virus. During that lull, polio spread to many new countries, although most have snuffed out the small outbreaks that resulted. Seventy (70) of Nigeria's last 1,300 polio cases stemmed from a mutant vaccine virus rather than "wild type" virus, which causes most polio (McNeil, 2007).

The emergence of a circulating vaccine-derived poliovirus in Nigeria reaffirms that not enough children are protected from poliovirus (wild or vaccine-derived) and that much more must be done to reach all children with vaccine. Of the 69 children with cVDPV in Nigeria, 40% had never been vaccinated; 87% were under-vaccinated (three or fewer doses). Consistent with global recommendations, three rounds of trivalent OPV (the recommended vaccine for the type of cVDPV in Nigeria) were conducted in northern Nigeria after the first case was confirmed in 2006. The first round was conducted in November 2006 another in January 2007 and a further

Table 1. Frequency of VDPVS occurrence.

Country Episodes of cVDPVs in:	Type	Year	No. cases
Belarus	Type 2	1965-66	
Poland	Type 3	1968	
Egypt	Type 2	1988-1993	30
Hispaniola	Type 1	2000-2001	25
Philippines	Type 1	2001	3
Madagascar	Type 2	2002	5
Nigeria	Type 2	2006-2007	69
Nigeria: Case study			
States	Type	Year 2006	Year 2007
High risk states in Nigeria	cVDPV-2	No. cases	No. cases
Bauchi	cVDPV-2	1	2
Borno	cVDPV-2	4	2
Kebbi	cVDPV-2	1	1
Sokoto	cVDPV-2	0	1
Zamfara	cVDPV-2	1	1
Very high risk states in Nigeria			
Kaduna	cVDPV-2	2	5
Kano	cVDPV-2	23	13
Katsina	cVDPV-2	1	4
Jigawa	cVDPV-2	6	1

Source: EPI/SEARO/WHO (2007) and Adu (2008)

round in March 2007. These three rounds of immunization have reduced by more than half the number of cVDPV transmission strains and the geographical extent of the virus. In September 2007, an additional dose of trivalent vaccine was administered to children in the 13 high risk northern states, including those where the cVDPV continued to circulate.

In 2000 Bauchi/01 originally identified as Sabin 2 was isolated from Bauchi state, detected by REC primers (Kilpatrick et al., 1996, 1998) to be abnormal Sabin. Sequence studies showed <1% nucleotide change in VP1 but a vaccine/nonvaccine recombination in the capsid 3D region (Adu et al., 2003). In 2002 Plateau/02 VDPV was isolated from incompletely immunized 21 months old child. It was initially identified as Sabin by ITD. Sequences studies showed 22/903 (2.5%) nucleotide change in the VP1 region. Sequences upstream 620 of the 5'-UTR and downstream 5840 3C region derived from species C enterovirus unrelated to OPV. Ironically the VDPV did not circulate (Adu et al., 2007). The Plateau/02 VDPV isolated in Kanke LGA of Plateau state, North Central Nigeria. Plateau OPV coverage is 36% while Kanke LGA OPV coverage is 22%. It was quite possible that this VDPV was circulating but was not detected by surveillance (Recombination with type C enterovirus).

Type 2 cVDPV was observed in Nigeria 2005 - 2007, cVDPVs with 5 – 9 nt. changes in 2005 in Kaduna, Lagos, Sokoto and Zamfara States. A retrospective

observation was made on cVDPVs in 2006 and 2007. Noticed by clustering of Sabin 2 cases, not flagged by ELISA screen and 5 - 21 nt. differences from Sabin 2; the most divergent VDPV has 2.3% VP1 change (21/903 nt). There were circulation of many independent lineages of type 2 VDPV in Nigeria in 2005 - 2007; this was detected in 9 states. NIE type 2 cVDPV is characterized by multiple lineages, 9 states in Northern Nigeria and one isolate from Lagos, Southern Nigeria; 70 VP1 sequences (Adu, 2008). Determinants of neurovirulence and markers of attenuation have reverted or were changed or removed by recombination, 5 - 21 nt. differences from Sabin 2 in VP1. Most cVDPV are recombinants with human enterovirus C 3D coding region. The outbreak is significant, especially considering the low attack rate of type 2 polio compared to type 1. A new VDPV screening method is essential for type 2 and type 3 VDPVs, all cVDPVs were NSL in VP1 region using real-time PCR VDPV assay. Most preVDPV and VDPVs were NSL in 3D region using the real-time PCR VDPV assay. Type 2 VDPV has been detected in combination with wild polio in a few cases, and there are orphan cVDPVs. Most have recombined with wild polio/species C enteroviruses in the 3D region, typical of cVDPV. In 2006 and 2007, all the VDPVs except one found high risk (Bauchi, Borno, Kebbi, Sokoto, and Zamfara) and very high risk (Kaduna, Katsina, Jigawa and Kano) northern states where immunization coverage has been low. Aftermath of the OPV controversy: hidden rejection/Non-compliance (Adu, 2008).

Information on all cVDPVs in 2006 - 2007, including the cases in Nigeria have been available publicly since April 2007, and have been included in presentations at various polio eradication and global laboratory network meetings (GPEI, 2008). Reports on both the work of the global lab network and on VDPVs in general have been issued as standard every year. Since introduction of monovalent oral polio vaccine against type 1 (mOPV1) in Nigeria, wild poliovirus type 1 has declined: 58 cases have been reported this year as compared to 846 last year. Type 1 polio, which has caused international outbreaks, has a higher paralytic attack rate than the two other types and is the eradication effort's primary target (GPEI, 2008).

Wild poliovirus remains a greater threat to children in Nigeria than vaccine-derived virus. Since 2005, Nigeria has reported over 2000 polio cases due to wild poliovirus. In that same period, there have been 69 cases due to circulating vaccine-derived poliovirus (GPEI, 2008). Summarily, specific areas and children are still being missed by IPDs (particularly in hard to reach and non-compliance states); states in the polio high risk states are not making enough progress in RI outside the IPDs. More effort is needed to sustain the growth in RI services country-wide. Special attention to enhance the population immunity in the polio high risk states to check the outbreak of cVDPV is urgently required.

Lesson learned from Nigeria and Hispaniola Episodes

Nigeria continues to improve its polio immunization activities, both supplementary and routine to stop all polio transmission, including the cVDPV. The critical issue is to achieve high coverage during these activities by reaching all children. The cVDPVs in Nigeria are due to type 2 poliovirus, which was eliminated in the wild in 1999. It is the most responsive of the 3 types of poliovirus to OPV. Previous type 2 cVDPVs were detected in Madagascar in 2002 and 2005 and in Egypt in the 1980 - 90s. Enhancing routine immunization with trivalent OPV (targeting all 3 types of polio) in the northern states is the key to maintaining immunity against type 2 polio, as monovalent OPVs are increasingly used to eradicate type 1 and type 3 wild polioviruses.

- i.) Keep in mind that vaccine-derived polioviruses do exist.
- ii.) Maintain AFP indicators at pre-eradication levels.
- iii.) Maintain high coverage in every district and WHO laboratory networks.
- iv.) Maintain NIDs until adequate coverages are reached everywhere.

Factors enhancing VDPVs emergence

High use of OPV during mass campaigns

The use of 2 highly efficient vaccines, the Sabin live oral

polio vaccine (OPV) and the Salk inactivated polio vaccine (IPV) resulted in a dramatic decrease in polio-virus morbidity and led to the virtual disappearance of wild polioviruses from most of the world.

IPV: This consists of formalin inactivated wild-type polioviruses. It does not induce adequate immunity in the gastrointestinal tract and does not prevent cryptic virus circulation in communities. Life long immunity to poliomyelitis can be induced with a single dose of inactivated polio vaccine (IPV) administered at 5 or 7 months of age (Salk, 1984).

OPV: This consists of live attenuated poliovirus strains of 3 serotypes (I, II and III). It induces adequate immunity in the gastrointestinal tract and in population with high vaccination coverage, prevents virus circulation. The major shortcoming of OPV is its ability to cause rare cases of vaccine-associated paralytic poliomyelitis in vaccine recipients and unimmunized or non-adequately immunized contact persons.

Prolonged circulation of vaccine-derived poliovirus increases the likelihood of its reversion to a neurovirulent strain that could eventually assume the transmission characteristics of wild polioviruses. Most developed, polio-free countries in recent years have switched to the exclusive of IPV, but the great majority of children throughout the rest of the world are still being vaccinated with OPV. In countries that have already achieved eradication of poliomyelitis but are still using OPV, the only source of rare cases of paralytic poliomyelitis is the vaccine itself (GPEI, 2007, 2008). The risk of VDPV is higher in countries that have already achieved eradication compared to countries having cases of wild poliovirus.

Low vaccination coverage (by increasing non-immune population), including factors contributing to low coverage

Also low OPV coverage resulting into low levels of population immunity favored the selection and transmission of vaccine derived variants with biological properties indistinguishable from those of wild polioviruses in countries such as Nigeria, Afganistan, Somalia and Parkistan. Although quite rare, cVDPVs are not a new phenomenon and have occurred in various part of the world. Nonetheless, the benefits of oral polio vaccine far outweigh the risk of a cVDPVs (Kew et al., 2005).

Human altitudes and error

Human altitudes toward vaccination for example, false rumors in 2003, that the polio vaccine was unsafe leading to the shut down vaccination campaigns in northern Nigeria, which likely contributed to the outbreak of cVDPV,

the largest outbreak to date of poliomyelitis caused by VDPV. Ninety nine cases were reported from October 2005 to August 2007, with two additional related cases in neighbouring Niger. There were allegations that the polio vaccine can spread HIV (Kapp, 2004), which further strengthened the boycott and weakened the public's confidence in the vaccine (Agbeyegbe, 2007).

Also, it is a well-known and established fact that no vaccine is entirely safe, and even then, there exists the possibility of human error during administration of vaccine (Clements et al., 1999). However, despite questions of safety, vaccines have continually contributed to disease prevention and control (Plotkin and Plotkin, 1999). Strained relations between the West and Muslims in Northern Nigeria, some of whom identified positively with acts of terrorism (Nigeria World, 2001) provided an enabling environment for advocating boycott of polio vaccination (Agbeyegbe, 2007). Furthermore, deaths from a Pfizer drug trial had created lingering uncertainty in northern Nigeria about the safety of Western health initiative (BBC, 2004).

Political instability

In several countries particularly Afganistan and Somalia, part of Parkistan and Ethiopia political instability or armed conflicts make vaccination logistically difficult and unpredictable. In addition to this internal politics in the 2003 immunization boycott, were ramifications from the international political arena. Anti-western sentiments have increased among Northern Muslims fundamentalist following the September 11, 2001 attacks and America's war on terrorism (Freedom house, 2004; Agbeyegbe, 2007). Given the distrust and growing antagonism towards America, the involvement of the West in a program that benefits Muslims was viewed with suspicion (Dhimmi Watch, 2004).

Cultural and religious objections

Many Nigerians are blaming the outbreak on vaccination efforts; an attitude experts fear may ruin previous gains in eradicating polio in the country. Most of the anti-immunization campaigns in Nigeria have been predominantly Muslim north of Nigeria, and a number of Muslim clerics have been quoted in the Nigerian media as claiming that vaccines are dangerous and cause sterility or illness (Adejija, 2007).

Cultural and religious objections under vaccinations efforts, resulting in persistently low immunity in the population and consequently, a high incidence of vaccine-derived poliomyelitis. The 2003 boycott of national polio vaccination campaigns by some northern Nigerian states threatening the impending success of the global initiative (Agbeyegbe, 2007). Agbeyegbe (2007) examined the role of religion in the boycott, as reflected in the questioning of

the authenticity and the safety of polio vaccine by the Supreme Council of Sharia in Nigeria (SCSN). The influential Islamic preachers by raising questions on immunization and the safety of the OPV laid foundation for the boycott of the northern states of Nigeria from the national immunization programme (Gamii, 2004; Agbeyegbe, 2007) while some predominantly Muslim states in northern, Nigeria implemented the boycott (The Guardian, 2004). Due to the intensity of the religious divide, Muslims dismissed earlier efforts by the Federal Government to assure northern Muslims of the safety of the vaccines as not being credible since Muslims leaders had called vaccination unsafe (Csmonitor, 2004). Religion was however, a proximal factor in the 2003 boycott since principal advocates, SCSN, Jama'atu Nasril Islam (JNI) are Islamic organizations, and their primary concern was for Muslims in Northern Nigeria to boycott the immunization exercise (Ebonugwo and Ndiribe, 2004; Africa Action, 2004; Ishr, 2004; Agbeyegbe, 2007).

Increasingly, some Muslims in the north are resisting compliance with some UNICEF and UN conventions being questioned for their incompatibility with the application of Sharia (Science in Africa, 2004). Whereas the undercurrents between Muslims and Christians in Nigeria as well as Western donors may have been sufficient to begin the controversy on the polio vaccine, other factors helped to sustain it. In October 2003, the Organization of Islamic Countries (OIC) issued a statement calling Muslim nations to speed up polio elimination in their countries. This position by the OIC counters claims that immunizations are an anti-Islamic practice (Marshall, 2003; Agbeyegbe, 2007).

Government negligence

The inability of the Nigerian government to acknowledge the risk involved in vaccination however negligible raises doubt about the sincerity of the government, and positions the boycotts of polio vaccination proponents as a more reliable source of information. The government does not appear to have positioned itself as a credible authority to implement immunization programs. No vaccine is fully safe, a perfectly potent and without risk of administering error (Clements et al., 1999). In 1991, WHO recommended post-immunization surveillance for any nations that implement national immunization programs (WHO, 1991). Beyond monitoring for adverse effects, some countries have established compensation schemes for injuries that result from vaccination (BBC, 2004). Such efforts by government do not necessarily raise suspicion about immunization programs but may rather raise the credibility of government with the public.

Lack of risk communication

Lack of risk communication is one of the factors affecting

polio eradication especially in Nigeria. Although, the boycott of immunization is no longer in effect, low participation during vaccination may persist reflecting a failure to implement risk communication (Agbeyegbe, 2007). The silence of the government over the alleged report by JNI and widely in the media that the government acknowledged the use of contaminated vaccines but claimed that the contaminated batch had been completely used, could be interpreted as indicative of the accurateness of the report. To address such situations, risk communication is increasingly becoming important in public health (Rudd et al., 2003; Rothman and Kiviiniemi, 1999).

Risk communication offers a two-way communication process that presents the expert opinions based on scientific facts to the public, and acknowledges the fears and concerns of the public, seeking to rectify knowledge gaps that foster misrepresentation of risk (Leiss, 2004; Aakko, 2004; Frewer, 2004). The information delivered to the public over the immunization boycott period was capable of affecting their risk perception. Public perception of risk shaped by variables such as bias, values, beliefs and experience may disregard facts and rational reasoning, and be entirely subjective. Individuals perceive risks which they are familiar with (polio cases) and have control over (refuse to submit to vaccination) as more acceptable than unfamiliar risk situations (infertility) over which they have no control over which the individual can exercise no control (compulsory vaccination) (Renn, 2004; Aakko, 2004; Frewer, 2004; Ropeik, 2004).

Prolonged circulation of vaccine virus (among existing gaps of non-immune population), including factors contributing to it

Tropical climate

Results of some studies indicate that circulation of vaccine-derived polioviruses in temperate countries may be limited in time and it is behaved that tropical climates are more conducive than ones to prolonged vaccine virus circulation reason (Abdulraheem and Saka, 2004; Adu et al., 2007; GPEI, 2007; Agbeyegbe, 2007). The World Health Organization has identified as the highest priority research evaluation of persistent vaccine-derived poliovirus circulation in tropical countries

Levels of sanitation

Low rates of OPV coverage coupled with poor sanitation, tropical conditions, and the prior eradication of the corresponding serotype of wild poliovirus are said to be the main risks factors for cVDPV emergence (Kew et al., 2005).

Population densities

Also, low rates of OPV coverage coupled with over-

crowding is said to be one of the main risks factors for cVDPV emergence (Kew et al., 2005).

Conclusion and Recommendations

As with the other epidemics in Egypt and Hispaniola, VDPV circulated in a province of Madagascar with low OPV coverage (CDC, 2001; Kew et al., 2002). Because a high OPV coverage rate helps prevent the circulation of both VDPVs and wild PVs, obtaining and maintaining high rates of immunization coverage are essential (Wood et al., 2000). Moreover, two recombinant VDPV lineages in Madagascar indicate that recombination is frequent between OPV and cluster C enteroviruses. Similar recombinant VDPVs have been implicated in the epidemics in Hispaniola and in the Philippines (CDC, 2001a, b). Determining whether the neurovirulence and transmissibility of these VDPVs could be the result of the recombination with non-polio enteroviruses is important. These VDPVs have major implications for the cessation of immunization with OPV after certification that wild PV has been eradicated.

Most polio-free countries no longer immunize against polio. Thus, the global population was vulnerable to polio spreading from Nigeria. The resurgence of polio at a global level would not only mean the \$3 billion investment in eradication efforts will be over with, it will also leave the world at the beginning of another eradication effort requiring more financial commitment (WHO, 2004f). The most efficient means to close the immunity gaps in Nigeria and other countries in Africa is by implementation of high quality NIDs, coupled with strengthened routine immunization and sensitive AFP and poliovirus surveillance (Adu et al., 2007). Negotiation for days of tranquility (the suspension of hostilities in order to allow for vaccination) will have to remain an integral part of polio eradication activities for the foreseeable future.

The above mentioned factors have caused great setbacks in the eradication of polioviruses-both the wild types and the vaccine-derived. Nevertheless, only 4 countries where the virus remains endemic-Nigeria, India, Parkistan, and Afghanistan-account for 93% of the world's cases of poliomyelitis, unlike all other countries, they have never succeeded in interrupting the transmission of wild poliovirus. Furthermore, these countries are also faced with the problem of vaccine-derived poliovirus. Wild poliovirus remains a greater threat to children in Nigeria than vaccine-derived virus (GEPI, 2008).

Researchers were preparing vaccine alternatives to combat polio outbreak. Monovalent vaccines (which protect against only one of the three strains) should be used in the areas where the virus is still circulating. But nationwide, the polyvalent vaccine (which protects against all three strains of poliovirus) should be aggressively used and coverage increased (Adu, 2007).

Immunization remains a widely used public health intervention and one of the most cost effective prevention

and control measure of poliomyelitis (WHO, 2004e). The smallpox vaccine made possible the global eradication of smallpox (Dittman, 2001). Rates of OPV coverage sufficient to block wild poliovirus circulation, will also be sufficient to prevent cVDPV emergence and spread (Adu et al., 2007). However, once wild poliovirus circulation has stopped, high rates of poliovaccine coverage must be maintained until global cessation of OPV use (WHO, 2004c).

The findings by many authors, that vaccine-derived polioviruses may circulate under suitable conditions prevents an additional challenge to efforts to eradicate polio worldwide. The threshold rates of vaccine coverage needed to suppress circulation of VDPVs are unknown but probably vary by poliovirus serotype and environmental factors (e.g. population density, levels of sanitations and climate) (Kew et al., 2005). However, when OPV coverage rates are sufficient to prevent circulation of wild polioviruses, they probably are sufficient to prevent circulation of VDPVs.

The ability to rapidly distinguish cVPDVs from iVPDVs will assume greater importance in the post-OPV era (WHO, 2004c), when any poliovirus detected 6 months after cessation of OPV use might signal continued poliovirus transmission. During this critical phase, virologic findings, particularly nucleotide sequence information, will be needed to test for links between any sporadic poliovirus infections that may be detected (Adu et al., 2007). Sustainable establishment of a global integrated virologic surveillance network and enhanced molecular characterization surveillance will provide greater insights into its circulation than would be possible with strictly epidemiologic tools. Tracking individual virus lineages will help in knowing the patterns of transmission and for cultural monitoring the progress of eradication effort. Studies will continue, as risks of cVDPV may change over time. Therefore, intensive virologic surveillance will be especially important in populous high-risk areas, such as Nigeria, which have been major reservoirs for wild poliovirus circulation (Adu et al., 2007). Intensifying polio eradication strategies, all children 0 - 15 years must be sufficiently immunized for high population immunity as well as bringing up a scientifically sound strategy to discontinue global eradication.

Although the polio immunization boycott in the northern states of Nigeria has now been fully suspended in Nigeria, and all 36 states of the nation are implementing the polio vaccination program, the risk of a global outbreak originating from Nigeria may remain. Sharing appropriate information can correct the public's misconceptions on OPV and increase its responsiveness to vaccination programs. In order to achieve this, the authorities should use risk communication strategies (Agbeyegbe, 2007). The successful use of polio vaccine (OPV) has helped to bridge the gap and this has contributed immensely to the limit of spread of the disease. In the study, it was found that most of the mother and guardian did not know how many OPV

(booster doses) their children have received. This indirectly showed the efficient coverage of national immunization programme. In view of these, concerted effort should be made by the government and WHO towards complete eradication of poliomyelitis. Parents and guardians should be educated on the need to allow their children to receive the normal schedule of OPV and booster doses given during national immunization programmes.

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