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Review

Circulating vaccine-derived poliovirus and its implications for polio surveillance and eradication in Nigeria: A review of the literature

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This review reports on circulating vaccine-derived poliovirus (cVDPV) and its implications for polio surveillance and eradication in Nigeria, a review of the literature. It also describes the potential implications of VDPVs in the final stages of global polio eradication. As the global eradication of wild poliovirus nears, the world health organization (WHO) is addressing challenges unprecedented cVDPV in public health. A circulating vaccine-derived poliovirus is a strain of poliovirus, genetically changed from its original strain contained in oral polio vaccine (OPV) and is an indication that far too many children remain unvaccinated or under-immunized. cVDPVs are not a new phenomenon only that poliomyelitis cases due to VDPVs are generally rare and have occurred in various parts of the world. The emergence of a vaccine-derived poliovirus that can circulate in the population shows that too many children remain under-immunized. Nigeria indeed is fighting an unusual outbreak of polio caused by mutating polio vaccine; the only remedy is to keep vaccinating children. cVDPVs in the past have been rapidly stopped with 2 - 3 rounds of high-quality immunization campaigns with OPV. The ongoing outbreak in 18 northern states of Nigeria's 36 states is only appearing in areas where people are refusing to be vaccinated or where there is not enough oral polio vaccine (OPV). Recent outbreak of cVDPV in Nigeria has implications for the Global Polio Laboratory Network (GPLN) procedure for VDPV detection. It is an indication that far too many children remain unvaccinated or under-immunized. It also 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. This resurgence of polio by international spread is also a setback to the Global Polio Eradication Initiative that had successfully decreased the number of polio-affected countries to only 9 in 2002. All countries are at risk until polio has been completely eradicated. 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. One strategy to protect polio-free countries from reintroduction of wild poliovirus is by requiring proof of polio vaccination for all incoming travelers from polio-endemic countries. Heightened immunization campaign for children was a necessity to stop the endemic from spreading. In conclusion, in all other countries with ongoing WPV or VDPV transmission, serious limitations in accessing and vaccinating children remain the major impediments to polio eradication. In Nigeria, the key to success will be to scale-up throughout the country the communication, social mobilization, and operational improvements that were achieved in some areas of northern Nigeria. The best way to overcome the outbreak of vaccine-related polio virus will be to increase immunization coverage, making sure that all children get the vaccine.

Key words: Polio eradication, poliovirus, poliomyelitis, vaccination, circulating vaccine derived poliovirus (VDPV).

INTRODUCTION

As the global eradication of wild poliovirus nears, the world health organization (WHO) is addressing challenges unprecedented VDPV in public health (Kew et al., 2005). In 1988, the world health assembly resolved to eradicate polio worldwide. 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 fewer than 2,000 reported cases in 2005 and polio remains endemic to only four countries (Afghanistan, India, Nigeria and Pakistan) (CDC, 2005c).

VDPVs are defined as poliovirus isolates having >1% nucleotide sequence divergence in the ~900 nucleotide (nt) region encoding the major capsid protein, VP1 or polioviruses with >1% VP1 nucleotide sequence differrence from the parental Sabin vaccine strain of the same type (CDC, 2005a; Kew et al., 2002, 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 strain of poliovirus, genetically mutated from the strain contained in oral polio vaccine (OPV). 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). 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, 2001; Abdulraheem and Saka, 2004; Adu et al., 2007; GPE, 2007; Agbeyegbe, 2007). However, poliomyelitis cases due to VDPVs are generally rare.

VDPVs differ from the majority of vaccine-related isolates by having genetic properties consistent with prolonged replication or transmission. Because poliovirus genomes evolve at a rate of approximately 1% per year, vaccine-related isolates that differ from the corresponding OPV strain by more than 1% of nucleotide positions (usually determined by sequencing the genomic region encoding the major viral surface protein, VP1) are estimated to have replicated for at least 1 year after administration of an OPV dose, substantially longer than the normal period of vaccine virus replication of 4 - 6 weeks. Poliovirus isolates are divided into three categories, identified by the extent of VP1 nucleotide sequence divergence from the corresponding Sabin OPV strain: (1) OPV -like viruses (<1% divergent), (2) VDPVs (1–15% divergent) and (3) WPVs (>15% divergent) (CDC, 2005c, 2008b).

VDPVs are further divided into three categories: (1) iVDPVs isolated from persons with primary Immunodeficiencies who have prolonged VDPV infections after exposure to OPV, (2) cVDPVs that emerge in communities with inadequate OPV coverage, that is, circulating VDPVs (cVDPVs) with transmission resulting in more than one patient with paralysis and (3) ambiguous VDPVs (aVDPVs) which are clinical isolates from persons with no known immunodeficiency and environ-mental isolates whose ultimate source has not been identified or VDPVs isolated from non-immunodeficient persons, non-AFP patient sources or a single AFP patient whose case cannot be assigned to the other two VDPV categories (CDC, 2005c, 2006).

The emergence of a vaccine-derived poliovirus that can circulate in the population shows that too many children remain under-immunized (GPEI, 2008). A fully-immunized population with OPV will be protected from all strains of poliovirus, whether wild or VDPVs (Bellmunt et al., 1999; Halsey et al., 2004; Kew et al., 1998; Khetsuriani et al., 2003; MacLennan et al., 2004; Minor, 2001; WHO, 2004a). 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; Okonko et al., 2008). 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. Nigeria established surveillance for acute flaccid paralysis according to

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WHO guidelines published in 1993 (WHO, 1998). Key performance indicators of the surveillance include a sensitivity of at least one non-polio-related case of acute flaccid paralysis per 100 000 people aged <15 years annually with two adequate faecal specimens collected within 14 days of the onset of paralysis for 80% of cases of acute flaccid paralysis (WHO, 1998).

The revised international health regulations, IHR (2005) (WHO, 2005), entered into legal force on June 15, 2007. These regulations provide the legal framework for coordination of the international effort to reduce or prevent international spread of diseases of public health concern. IHR (2005) (WHO, 2006) lists polio as one of the diseases of public health emergencies of international concern. Preventing importation of polio into polio-free countries is therefore a test case for the revised inter-national health regulations (Hardiman and Wilder-Smith, 2007; Wilder-Smith, 2008). Compared to the previous IHR (1969), IHR (2005) has moved away from the definition of fixed maximum measures relating to specific diseases and instead focuses on the issuance of context-specific recommenddations made either on a temporary emergency basis (a temporary recommendation) or routinely for established ongoing risks of disease spread (a standing recommenddation) (Wilder-Smith, 2008).

Substantial progress has been achieved toward the World Health Assembly goals of 1988 (CDC, 1999a, b) and with the circulation of wild poliovirus eliminated in most of the world, attention has focused on examining the potential for vaccine-derived poliovirus to circulate where wild poliovirus has disappeared (CDC, 2001).

According to Hull (2008), current unanswered questions include the following; is single dose of IPV or OPV immediately before departure of travellers adequate? Are boosters needed? Why not include countries with imported wild or vaccine-derived poliovirus (VDPV) outbreaks? Can polio-free areas of polio-endemic countries (example, Kerala) be exempted? Must records be certified? Can fraudulent vaccinations be detected or prevented? These unanswered questions are also contributory to the spread and circulation of wild or vaccine-derived polio viruses globally as highlighted in this review. Data on importations clarifies any need for requiring vaccination of travelers entering polio-free countries (Hull, 2008). However, two additional obstacles to global eradication involve vaccine-derived polioviruses (VDPVs).

Polio outbreaks continue to be associated with circulating vaccine-derived polioviruses (cVDPVs) 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 (CDC, 2005c). Overcoming these obstacles of VDPVs is challenging. High rates of OPV coverage will prevent all poliovirus spread, including spread of VDPVs, but will not prevent establishment of prolonged VDPV infections in certain persons with B-cell immunodeficiencies (that is, having defects in antibody production). Inevitable gaps in vaccination coverage will give rise to cVDPVs as long as OPV use continues. These findings underscore the critical need to strengthen strategies to prevent emergence of VDPVs and to stop all OPV use once wild polioviruses (WPVs) are eradicated (CDC, 2005c, 2006, 2007, 2008b, 2009). This review therefore reports on circulating vaccine-derived poliovirus (cVDPV) and its implications for polio surveillance and eradication in Nigeria: a review of the literature. It also describes the potential implications of VDPVs in the final stages of global polio eradication.

WHAT ARE VACCINES?

Vaccines are polysaccharides and protein molecules, whole or subunit, synthetic or natural that is capable of stimulating the production of antibodies or specific cellular responses when introduced into a vertebrate host. Since most of the causative agents of infectious diseases contain surface and inner proteins which the host immune system responds to, these same causative agents that produce the disease, provide the raw material for vaccine production after the required laboratory manipulations (Adu, 2008). The concept of vaccination was first established by Edward Jenner in 1796 (Jenner, 1978; Adu, 2008).

Types of polio vaccines

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 poliovirus 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 & 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.

Biologic properties of VDPVs

The critical biologic properties of VDPVs are their capacity to cause paralytic polio in humans and their potential or demonstrated capacity for sustained circulation.

VDPVs have lost key attenuating mutations and resemble WPVs biologically (CDC, 2005c, 2008b). All known cVDPVs (except those from China), but no iVDPVs, are recombinants with nonstructural protein sequences derived from species C enteroviruses, a property associated with poliovirus circulation (CDC, 2005c, 2008b). Most VDPVs are antigenic variants of the Sabin strains, but antigenic evolution appears to be faster in iVDPVs than in cVDPVs. Unlike cVDPV isolates, iVDPV isolates commonly contain mixed VDPV populations. These biologic distinctions (and the differing conditions favoring iVDPV and cVDPV emergence) have helped in recognition of the likely origins of man ambiguous VDPVs (aVDPVs) (CDC, 2005c, 2008b).

Risk factors for VDPV emergence

In all other countries with ongoing WPV transmission, serious limitations in accessing and vaccinating children remain the major impediments to polio eradication. The type 2 cVDPV outbreaks in Nigeria, DRC and Ethiopia reveal striking lapses in routine and supplementary immunization activities (SIA) vaccination in parts of those countries because cVDPVs are biologically similar to WPVs in terms of infectivity and pathogenicity. In Nigeria, the key to success will be to scale-up throughout the country communication, social mobilization and operational improvements that were achieved in some areas of northern Nigeria (CDC, 2009).

The key factors favoring cVDPV emergence and spread are the same as for WPV circulation are, low OPV coverage, poor sanitation, high population densities and (usually) tropical conditions. In all but the remaining polio-endemic areas, immunity to polio is no longer acquired from natural infection; immunization is the only current means to prevent the spread of emerging VDPVs or imported WPVs (CDC, 2005c, 2009). Although OPV is not recommended for immunodeficient patients, it is often inadvertently administered because certain primary immunodeficiencies (example, common variable immunodeficiency [CVID]) develop later in life. Certain persons with CVID who excrete iVDPVs had onset of polio several years after the implicated OPV dose was administered and three have demonstrated no signs of paralysis. Survival of patients with primary immunodeficiencies can be extended in upper- and middle-income countries by intravenous immunoglobulin therapy; however, for patients in low-income countries, such therapy often is too expensive and difficult to obtain (CDC, 2005c, 2009, WHO 2009a).

The benefits of Oral Polio Vaccines far outweigh the risk of a cVDPV

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. Poliomyelitis can be prevented by adequate immunization of children. Polio vaccine is given, by mouth, to protect (immunize) against Polio (or Poliomyelitis). It is usually given at two months, three months and four months, with a reinforcing dose (a booster) before school, usually between 3 and 5 years of age and again, before leaving school, between 15 and 19 years old. Boosters thereafter are not normally necessary, unless traveling to an area where polio is common, or likely to be exposed to people with polio. The vaccine contains live virus particles which have been altered (attenuated), to stop them from producing the effects of the actual disease. The idea is to fool the body's defence system into thinking it is under attack by the virus, and to produce defence mechanisms (antibodies) which will fight off the Polio virus if it is encountered in the future.

Advantage of OPV at birth (Zero doses)

The scientific strategy of any immunization programme is to secure protection before infants are at risk of developing a disease. In developing countries, the majority of cases of paralytic poliomyelitis reported in outbreaks occur in children under 5 years of age (WHO, 1993a). Both the community-based and hospital based data in polio endemic areas show that more than three quarters of the paralytic cases occur in children younger than 2 years of age (Onadeko and Familusi, 1990). The importance of providing vaccine as early in life as possible before exposure to wild virus occurs was high-lighted by type 1 polio outbreak in 1988 in Republic of Oman (Sutter, 1991) and in 1990 in Bulgaria (EPI, 1992b). In these countries, a zero dose was not part of the National schedule and doses of OPV were routinely administered at 3, 5, and 7 months of age. Early immunization would have prevented cases in each of these outbreaks. Today in both countries the national schedule includes a birth dose of OPV (in Bulgaria this is for high risk groups) and the next dose is given by 2 months of age.

Since 1984, the Global Advisory Group to WHO has recommended a zero dose of OPV in polio endemic countries (EPI, 1985). Among neonates who received a dose of OPV, 70 - 100% will develop local immunity in the intestinal tract and 30 - 50% will develop serum antibodies to one or more poliovirus types (Halsey and Galazka, 1985). The beneficial effect of zero dose of OPV given at birth was demonstrated clearly in studies conducted in China. It was found that a higher percentage of infants fed a dose at birth had antibodies against all the 3 types of poliovirus at younger ages (Dexiang, 1986). Studies carried in India and Brazil, also showed that the serological response was good in infants beginning immunization at birth during the first 4 weeks of life as in older children (John, 1984). No harmful effects have been demonstrated from early administration of OPV (WHO, 1993a). Injection-associated poliomyelitis provides an additional incentive for a dose of OPV at birth

and for early completion of immunization series. As maternal antibody titres wane, susceptibility increases.

Therefore it is desirable to complete a primary series of OPV/DPT immunization by 4 months of age, during which the risk of post-injection poliomyelitis is extremely low. If a dose of OPV cannot be given at birth or within the first 2 weeks of life, a fourth dose of OPV should be given at same time as measles vaccine or at any contact with the health system that is 4 weeks after the third dose (Abdulraheem and Saka, 2004).

IMMUNOLOGICAL RESPONSE TO POLIOMYELITIS INFECTION

lgM and lgG appear in serum about 7-10 days after infection (Ashkenazi and Melnick, 1962) following natural exposure. Sufficiently high levels of lgM and 1 gG can block poliovirus entry into the CNS. Passive immunity is transferred from mother to fetus via the placenta. The concentration of type 1 and 2. lgG neutralizing antibody in the newborn is approximately equal to that of the mother. Type 3 titres are somewhat lower than those of the mother suggesting differential trans-placental transfer of this serotype (Ananthakrishnan, 1988; Gelfand, 1959; Wright and Cohen-Abbo, 1991). The rate of decay of maternal antibody is constant; its half-life is estimated at about 30 days (rang 21 - 50 days) and these data have been confirmed by studies from developing countries (WHO, 1993b). Poliovirus also induces the development of secretory lgA antibody (Ogra, 1968). The persistence of secretory lgA antibody may be related to the virulence of the infecting virus and to the number of virus particles presented to the intestine and nasal mucosal (Abdulraheem and Saka, 2004). Appreciable levels of secretory lgA antibody have been detected in the nasopharyngeal secretions of individuals 10 - 15 years after natural with type 1 poliovirus (Ogra and Karzon, 1971; Abdulraheem and Saka, 2004).

Immunity induced by OPV

The immune response to OPV closely parallels that of natural infection. The administration of OPV results in secretory lgA antibody in the nasopharynx and intestine approximately 1 - 3 weeks after immunization. Secretory antibody activity has been observed to persist for as long as 5 - 6 years (Ogra, 1984). Local secretory lgA antibody induced by OPV is considered to be important in protectting the individual and in reducing the rate of transmission of wild polioviruses by immune persons. Colostrum produced in the first 3 days after childbirth contains secretory antibody, which might interfere with the immune response to OPV (Abdulraheem and Saka, 2004).

Several studies have shown that among breastfed infants, who are fed OPV in the first 3 days of life, 20 - 40% developed serum antibodies and 30 - 60% excrete vaccine virus (Halsey and Galazka, 1985), which may circulate among the populace. During the 1970s less-than-optimal responses to trivalent OPV in developing countries became apparent when reports of low rates of seroconversion to poliovirus types 1 and 3 began to appear in the medical literature (Ghosh, 1970; John and Jayabal, 1972; Oduntan, 1978; Abdulraheem and Saka, 2004).

Literature review of data from developing countries for the past 35 years revealed that 32 studies reported the response of at least 20 children to 3 doses of trivalent Sabin-derived OPV which contained at least 10^6, 10^5 and $10^{5.5}$ $TCID_{50}$ of types 1, 2 and 3 poliovirus respectively (Patriaca, 1991). The precise cause of seroconversion rates type 1 and 3 in some parts of the developing world is not clear. Available data suggests that type 2 vaccine virus and enteric pathogens often interfere may be partially overcome by modifying the absolute and relative dosage of the 3 Sabin vaccine virus types (Patriaca, 1988).

Protective efficacy of polio antibodies

Extensive literature has accumulated concerning the protective effects of OPV against infection and against development of the paralytic disease. Early laboratory and field trials were reported in international conferences on live polio vaccines (PAHO, 1960).

Administration of the live poliovirus vaccines has indeed greatly reduced the incidence of poliomyelitis, often eliminating the pattern of expected seasonal increase in polio cases (PAHO, 1984). A study from the 1950s indicates that persons with low serum neutralizing antibody titres can be re-infected by wild virus (PAHO, 1960). Among 237 naturally immune persons with neutralizing antibody titres of 40 or lower observed during family episodes of wild poliovirus infection in Louisinia during 1953 to 1957, 98% were reinfected as determined by a fourfold or greater rise in serum antibody titre (Gelfand, 1959). Studies from Japan and England indicate that persons with low serum neutralizing anti-body titres post immunization can be reinfected when challenged with vaccine virus (WHO, 1993b). Person with low but detectable serum antibody are probably not in danger of developing clinical poliomyelitis.

However, they may be re-infected with poliovirus and possibly provide a source of infection for others who have not been vaccinated (Abdulraheem and Saka, 2004).

THE POTENTIAL ROLE OF ANTIVIRAL AGENTS IN POLIO ERADICATION

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 (WHA, 1988). This Global polio eradication initiative (GPEI) was launched by the World health assembly 20 years ago. The principal idea behind the GPEI was to eliminate polio worldwide by the

year 2000 by means of large-scale vaccination with the oral live attenuated polio vaccine (OPV) developed by Albert Sabin (Griffiths et al., 2006). The GPEI has resulted since 1988, in a decrease in poliomyelitis cases from 350,000 to <2,000 (Kimman and Boot, 2006; Arita et al., 2006). Although important progress has been made, polio remains endemic in several countries. Today, poliovirus (PV) is endemic in 4 countries (Nigeria, India, Pakistan and Afghanistan), whereas the virus was prevalent in >125 countries at the time the initiative was launched (Minor, 2004).

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. 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. 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 (CDC, 2001).

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 1980s-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 (CDC, 2001). When wild PV transmission was interrupted, the World Health Organization proposes ending the global routine OPV to prevent the risk for vaccine-associated paralytic poliomyelitis, chronic infection of immunodeficient persons, and the reestablishment of poliomyelitis through circulating vaccine-derived PV (Aylward et al., 2005).

Also, the current control measures will likely be inadequate to deal with problems that may arise in the post-polio era. According De Palma et al. (2008) a panel was convened by the National Research Council to evaluate the potential for an antiviral drug as one of the tools to minimize poliomyelitis risk after OPV cessation. The panel concluded that the use of antiviral drugs may be essential in the polio eradication strategy. This conclusion of the panel was that it would be appropriate, and possibly essential, to develop antiviral drugs for PV infection, as an additional tool to address the problems that might arise in the "postpolio" era (Couzin, 2006). Antiviral agents do not confer immunity but could be used prophylactically as well as therapeutically. They could protect inactivated polio vaccine (IPV) recipients from PV infection, limit spread until immunity can be ensured and help clear vaccine-derived PV from persistently infected persons (MacLennan et al., 2004). The ideal drug would be safe, inexpensive, easy to use, stable, and manifest broad activity toward PV strains.

A substantial number of small molecule compounds have been reported as potent inhibitors of the replication of picornaviruses *in vitro* (De Palma et al., 2008) and these include: capsid-binding agents; protease inhibitors; protein 3A inhibitors; nucleoside analog; protein 2C inhibitors; and compounds with unknown mechanism of action.

Capsid-binding agents: Pleconaril (Sterling Winthrop, New York, NY, USA) and pirodavir (Janssen research foundation, Beerse, Belgium)

These agents inhibit attachment or disassembly of the viral particle after receptor binding (McKinley et al., 1992). Two of the most extensively characterized series of capsid-binding agents are the so-called WIN compounds and a series of pyridazine analogs. The prototypes of these series are pleconaril and pirodavir respectively (Hayden et al., 1995; Florea et al., 2003; De Palma et al., 2008). Pleconaril is still being used successfully on a compassionate basis for treating life-threatening enterovirus infections in children. Notably, it was effective in stopping virus excretion in a child persistently infected with PV, when combined with gamma globulin–mediated virus clearance. In another trial with a persistently infected person, however, treatment produced no benefit (Rotbart and Webster, 2001; Buttinelli et al., 2003; MacLennan et al., 2004; De Palma et al., 2008). According to De Palma et al. (2008) pleconaril and pirodavir, as well as a pirodavir analog (R78206) (Andries et al., 1994) inhibited PV2 and PV3 replication with EC_{50} values <2 µmol/L and TIs of 60 to >179. However, only R78206 exhibited inhibitory activity against PV1. Pirodavir proved 5- to 20-fold less active on PV1 replication, and pleconaril was inactive up to the highest concentration tested. Intranasal pirodavir (R77975) was active in some clinical trials of human experimental rhinovirus infections, but lack of therapeutic efficacy and metabolic instability after oral administration halted further development (De Palma et al., 2008).

Pleconaril has undergone extensive clinical evaluation for enteroviral infections. The compound is relatively potent in inhibiting PV2 and PV3 replication, but has no activity against PV1, which limits its potential for PV. Besides pleconaril and pirodavir (analog), several other potent capsid-binding agents have been reported (De Palma et al., 2008). According to De Palma et al. (2008), the pirodavir analog R78206 also displayed potent, broad-spectrum activity against PV. As was the case with rupintrivir, pirodavir did not appear to offer sufficient potential for treating HRV infection and was not further

developed. The compound, however, was well tolerated; thus, pirodavir (and its analogs) may, alone or combined with other antiviral agents, open perspectives for treating PV infection. One major problem with pirodavir and its analog, however, is the poor pharmacokinetic profile after systemic dosing due to hydrolysis of the ester bond. Orally bioavailable analogs of pirodavir were developed at Biota (Melbourne, Victoria, Australia) but appeared to have a limited activity toward PV strains (Barnard et al., 2004).

Protease inhibitors: Rupintrivir (AG-7088, Pfizer, New York, NY, USA)

This is a second approach to inhibiting PV replication. It works by targeting the virus-encoded proteases 2A and/or 3C enzymes that cleave the single polyprotein, encoded by the PV genome, into mature proteins. Rupintrivir is an irreversible inhibitor of the 3C function (Witherell, 2000; Patick et al., 1999; De Palma et al., 2008). Despite some successful trials in patients that were experimentally infected with HRV, rupintrivir was not able to mitigate disease severity in studies of natural rhinovirus infection, and clinical development was stopped (Patick, 2006; De Palma et al., 2008). According to De Palma et al. (2008), further efforts by Pfizer resulted in the development of compound 1, an inhibitor with a similar mechanism of action and with an excellent oral bioavailability (Patick, 2006). Both compounds inhibited all 3 PV strains with EC_{50}s <1 µmol/L and TIs of >322 to >19,230. Rupintrivir was the most potent compound of the selected series with EC_{50} values in the nanomolar range (5 - 40 nmol/L) against each of the 3 tested PV strains (De Palma et al., 2008). As depicted in a study by De Palma et al. (2008), rupintrivir, the most active compound in the CPE reduction assay, caused a 6-$\log_{10}$ decrease of infectious virus production at 100 µmol/L, and reduced virus progeny formation 10–1,000-fold at concentrations of 10 - 100 nmol/L.

According to De Palma et al. (2008), rupintrivir and its analog compound 1 emerged as highly potent and broad-spectrum anti-PV compounds without any signs of cytotoxicity up to the highest concentrations tested. The *in vitro* activity of these protease inhibitors against PV is comparable to their activity against various strains of HRV, the virus against which the compounds were originally developed (Patick et al., 1999, 2005). Given the excellent oral bioavailability (Patick et al., 2005) and its favorable pharmacokinetic profile, compound 1 may be an attractive candidate for further study for the treatment and prophylaxis of PV infection.

Protein 3A inhibitors: enviroxime

Enviroxime discovered in 1980, is a benzimidazole derivative that inhibits the replication of enteroviruses and rhinoviruses *in vitro* by targeting the nonstructural protein 3A (DeLong and Reed, 1980; Florea et al., 2003; De Palma et al., 2008). According to De Palma et al. (2008), previous in vivo studies with enviroxime, however, have shown toxicity and only weak to moderate activity, due to poor solubility and pharmacokinetics. It inhibited the replication of all 3 strains of PV, with EC_{50} values of 35 - 200 nmol/L and TIs of 290 - 1,657 (Wyde et al., 1988; Higgins et al., 1988; Miller et al., 1985; Phillpotts et al., 1981). Structural derivatives of enviroxime such as the C_2- and vinylacetylene analogs were reported to have a better oral bioavailability and pharmacologic profile (Victor et al., 1997a, b) and may therefore be considered as leading candidates for further development (De Palma et al., 2008). Enviroxime exhibits potent anti-PV activity, but was not developed because of unfavorable pharmacokinetics (De Palma et al., 2008). However, a further exploration of the potential of enviroxime analogs could be worthwhile, in an attempt to improve the activity, selectivity, and in particular, the pharmacokinetic profile (Victor et al., 199a, b; De Palma et al., 2008).

Nucleoside analogs: Ribavirin, valopicitabine and 4-azidocytidine

The nucleoside analog ribavirin is an antiviral drug with broad-spectrum activity against RNA and DNA viruses. It is used in combination with interferon in the treatment of hepatitis C virus (HCV) infection (Manns et al., 2006) and as an aerosol to treat respiratory syncytial virus infections in children (Sidwell and Barnard, 2006). As expected, ribavirin proved to be a weak inhibitor of PV replication with EC_{50} values of 50 - 60 µmol/L (TIs >1.6) (De Palma et al., 2008). Valopicitabine is the oral valine ester prodrug of another nucleoside analog, 2-*C*-methylcytidine. The 5-triphosphate of 2-*C*-methylcytidine is an inhibitor of HCV polymerase (Carroll et al., 2003). According to De Palma et al. (2008), clinical development of valopicitabine for the treatment of HCV infection was recently stopped, mainly because of gastrointestinal side effects. The compound was shown to exhibit relatively broad-spectrum activity against positive-sense single-stranded RNA viruses including inhibition of the replication of foot-and-mouth-disease virus (Goris et al., 2007; De Palma et al., 2008). It inhibits picornaviruses is also by inhibition of the viral polymerase. 2-*C*-methylcytidine inhibited the replication of PV strains with EC_{50} values of 3.9 - 29 µmol/L (TIs >3.4 - >25.6) in a study by De Palma et al. (2008). The adenosine analog of valopicitabine, as well as another nucleoside analog, 4-azidocytidine (a potent inhibitor of HCV replication) were also included in the study by De Palma et al. (2008). Thus, 2´-*C*-methyladenosine proved equipotent (≈5 µmol/L) against all 3 PV strains; whereas 4-azidocytidine proved inactive (De Palma et al., 2008).

Nucleoside polymerase inhibitors that have been developed for treating HCV infection may also have the potential to inhibit other single-stranded positive-sense RNA viruses. De Palma et al. (2008) demonstrated that the active component of the anti-HCV drug valopicitabine

inhibits the replication of all 3 PV strains. If such a drug becomes available for treating HCV infections, it could also be used "off-label" to treat PV infection. However, 4´-azidocytidine, a potent inhibitor of HCV replication (Smith et al., 2007), was devoid of anti-PV activity up to the highest concentrations tested. As reported before and confirmed by De Palma et al. (2008), ribavirin proved to be a relatively weak inhibitor of PV replication (TIs >1.8). Although ribavirin has limited activity against HCV when used as monotherapy, its potency is markedly increased when it is given in combination with pegylated interferon. According to De Palma et al. (2008) since extensive clinical experience exists regarding the use of ribavirin in treating HCV infection, it may be possible and beneficial to explore the potential of the combined use of ribavirin with drugs such as rupintrivir, pirodavir, or their analogs.

Protein 2C inhibitors: MRL-1237 and 2-(α-hydroxybenzyl)-benzimidazole (HBB)

These are inhibitors that target the enteroviral nonstructural protein 2C (Hadaschik et al., 1999; Shimizu et al., 2000; De Palma et al., 2008). According to De Palma et al. (2008), MRL-1237 showed antiviral activity against PV strains 1, 2 and 3 with TIs >19 while HBB appeared to be a weak inhibitor of PV replication with EC_{50}s of 200 - 300 µmol/L and TIs >1.3. These compounds have been less well characterized but still may form a starting point for the synthesis of more potent and selective inhibitors of PV replication. Unraveling the precise mode of antiviral activity and the molecular interaction with their antiviral target may allow structure-based drug design (De Palma et al., 2008).

Compounds with unknown mechanism of action: MDL-860

Compound MDL-860 was discovered as a broad-spectrum inhibitor of picornavirus replication, although the precise mechanism of antiviral activity has never been unraveled (Powers et al., 1982; De Palma et al., 2008). The anti-PV activity of MDL-860 proved comparable to that of the 2C inhibitor MRL-1237 (De Palma et al., 2008). Also, this compound have been less well characterized but still may form a starting point for the synthesis of more potent and selective inhibitors of PV replication (De Palma et al., 2008). According to De Palma et al. (2008), unraveling the precise mode of antiviral activity and the molecular interaction with their antiviral target may allow structure-based drug design (De Palma et al., 2008).

CURRENT AND FUTURE TRENDS ON THE ROLE OF POLIO VACCINES AND ANTIVIRAL AGENTS IN POLIO ERADICATION

The live, attenuated oral poliovirus vaccine (OPV), used for more than four decades to interrupt poliovirus transmission, and the vaccine of choice for developing countries, is genetically unstable. Reversion of the small number of substitutions conferring the attenuated phenol-type frequently occurs during OPV replication in humans and is the underlying cause of the rare cases of vaccine-associated paralytic poliomyelitis (VAPP) in OPV reci-pients and their close contacts (Kew et al., 2005). Whereas VAPP has long been recognized, two other adverse events have been identified more recently: (a) long-term excretion of highly evolved vaccine-derived polioviruses (VDPVs) in persons with primary immuno-deficiencies, and (b) polio outbreaks associated with circulating VDPVs in areas with low rates of OPV coverage. Developing a posteradication strategy to minimize the risks of VDPV emergence and spread has become an urgent WHO priority (Kew et al., 2005).

Vaccination simply does not provide high-level protecttion against poliovirus infection (Hull, 2008). Child-ren recently vaccinated with either oral poliomyelitis virus (OPV) or inactivated poliomyelitis virus (IPV) shed poliovirus following a challenge OPV dose (Onorato et al., 1991). Because secretory immunity falls rapidly, a high percentage of persons vaccinated years or even decades ago will become transiently infected when exposed to poliovirus and will excrete virus for weeks. Lower vaccine efficacy in developing countries further compounds the issue (WHO, 1996; Hull, 2008).

It should be noted, however, that the potential for an antiviral drug as one of the tools to minimize poliomyelitis risk after OPV cessation should be a welcome idea and most potent inhibitors of *in vitro* PV replication that has been identified include the 3C inhibitors rupintrivir and compound 1, the capsid binders R78206 and pleconaril, and the 3A inhibitor enviroxime. They act on different targets in the viral replication cycle (De Palma et al., 2008). These compounds could serve as scaffolds for the development of more potent and selective inhibitors of PV. The information available on their structure-activity relationship and their mechanism of action could be exploited as a solid base for developing a specific anti-PV therapy (De Palma et al., 2008). In a comparative study of a selected series of antipicornavirus drugs for their ability to inhibit PV replication *in vitro*, De Palma et al. (2008) reported that (1) certain drugs (example, rupintrivir) were specifically developed to treat rhinovirus and other infections and have never been evaluated for their ability to block poliovirus replication and (2) the selected compounds have never been compared in parallel by using the same technique against the 3 vaccine strains. Because of the high mutation rate of the viral RNA-dependent RNA polymerase, drug-resistant PV mutants have been readily selected in cell culture (Shimizu et al., 2000; Vignuzzi et al., 2005). The possibility that the use of antiviral drugs to treat polio would result in the appearance of drug-resistant variants cannot therefore be excluded (De Palma et al., 2008).

Table 1. The GPLN performance and initiatives during January 2006-June 2007.

	January - December 2006				January-June 2007			
		No. of PV isolates		% Samples		No. of PV isolates		% Samples
WHO Region	No. of Samples	Wild	Sabin vaccine-like	with NPEV isolated	No. of Samples	Wild	Sabin vaccine-like	with NPEV isolated
Africa	26,505	2,261	835	12.1	12,133	325	344	12.8
Americas	1,991	0	43	8.0	656	0	8	9.0
Eastern Mediterranean	22,948	212	963	19.0	11,356	42	501	17.0
Europe	2,814	0	152	4.8	1,229	0	55	2.0
South-East Asia	71,419	1,186	3,042	20.0	39,711	208	1,670	18.0
Western Pacific	13,662	1†	368	10.0	4,473	1†	81	7.0
Total	139,339	3,360	5,403	16.9	69,558	576	2,659	15.9

Source: CDC (2007a); WHO (2009c)
† Paralysis onset was outside of the region; in Nigeria in 2006 and in Pakistan in 2007

The use in combination of drugs with different modes of action will likely delay or prevent the emergence of drug-resistant variants. Moreover, the period of treatment during an acute PV outbreak would likely be much shorter than treatment regimens for such chronic infections as HIV or HCV, reducing the chance that drug-resistant strains will emerge (De Palma et al., 2008).

The need for adequate antiviral drugs against PV (most likely in combination with IPV) in the final stages of polio eradication is obvious. In a recent report from the World Health Organization (2006), an advisory committee concurred with the proposal to establish a "PV antiviral initiative," to take forward the key recommendations proposed during the National research council meeting on antiviral agents against PV (De Palma et al., 2008).

GLOBAL VDPV SURVEILLANCE

The Global polio laboratory network (GPLN) was established after announcement of the 1988 World health assembly resolution to eradicate poliomyelitis. Operating in all six World health organizations (WHO) regions, the network currently has 146 laboratories that test stool specimens from acute flaccid paralysis (AFP) patients for polioviruses. The virologic data provided by GPLN underpin the global polio eradication initiative, guiding decisions regarding where targeted immunization activities should be conducted based on confirmed wild or vaccine-derived poliovirus circulation. The data also are used to monitor progress toward polio eradication by documenting the genetic diversity and transmission links of viral isolates (CDC, 1997, 2000, 2001, 2002, 2003, 2004, 2005, 2006 and 2007). The GPLN performance and initiatives during January 2006 - June 2007 is shown in Table 1.

Concern has increased over the potential for VDPV epidemics since confirmation of a VDPV outbreak in Hispaniola in 2000 (Kew et al., 2002). Since the cVDPV outbreak in Haiti and the Dominican republic in 2000 - 2001 (CDC, 2005c), all polioviruses isolated in the WHO Global Poliovirus Laboratory Network from patients with acute flaccid paralysis have been characterized by one molecular method, to identify polioviruses by their genetic properties (usually using the polymerase chain reaction), and one antigenic method, to detect antigenic differences from the OPV strains (using either an enzyme-linked immunosorbent assay [ELISA] or panels of specific neutralizing monoclonal antibodies) (CDC, 2005c; Grassly et al., 2007). Isolates found to be genetically related to an OPV strain but with antigenic differences is possible VDPVs. VP1 sequencing is routinely performed on all possible VDPV and WPV isolates. Approximately 12,000 isolates from all WHO regions have been routinely screened for VDPVs since 2001 (CDC, 2005c; Grassly et al., 2007). Temporal or geographic clustering of vaccine-related isolates of the same serotype has prompted the detection and investigation of cVDPV outbreaks in eight countries (CDC, 2005c).

The recent outbreak of cVDPV in Nigeria has implications for the GPLN procedure for VDPV detection. All poliovirus isolates are screened using two com-plementary ITD tests (usually enzyme-linked immunosorbent assay [ELISA] using specific cross-absorbed antisera and diagnostic PCR using strain-specific reagents) (CDC, 2007). Isolates with discordant results from the two tests are flagged for sequencing for definitive identification of VDPVs. Follow-up clinical and epidemiologic investigations are used to categorize the VDPVs (that is, as cVDPVs, iVDPVs, or aVDPVs). This approach has successfully identified cVDPV outbreaks in five countries (Cambodia, China, Indonesia, Myanmar and the Philippines) since 2000 but failed to flag multiple type 2 VDPVs from Nigeria and type 2 and type 3 VDPVs from Madagascar (in 2001 and 2005) because they reacted as Sabin vaccine-like in both ITD tests (ELISA and PCR). In Nigeria, sequencing was performed because the temporal and geographic clustering of type 2 Sabin vaccine-like isolates suggested virus circulation (CDC, 2007). In Madagascar, the viruses had profiles that were not Sabin vaccine-like in a PCR-restriction fragment length polymer-

phism assay used in a multilaboratory collaborative study of Sabin vaccine-related polioviruses (Romanenkova et al., 2006). Although the GPLN screening procedure appears successful in detecting type 1 VDPVs, recent evidence suggests that it lacks sufficient sensitivity for detection of type 2 and type 3 VDPVs. A real-time PCR assay developed at a Global Specialized Laboratory appears to increase VDPV detection sensitivity for all types and is being evaluated for use by GPLN (CDC, 2007).

cVDPVS IN NIGERIA: WHEN, WHERE AND HOW IT STARTED

Vaccine-derived polioviruses (VDPVs) were detected from AFP cases in 2008 in seven countries. Of these, type 2 circulating VDPVs (cVDPVs) were identified in northern Nigeria, where transmission has continued since 2006 (158 cases in Nigeria to date) (CDC, 2007a, 2008a; WHO, 2009a) and in DRC and Ethiopia where new type 2 cVDPV outbreaks in 2008 were detected (two separate outbreaks of two and 14 cases in DRC and an outbreak of four cases in Ethiopia, to date).

Low OPV coverage following the elimination of at least one indigenous wild poliovirus serotype probably is critical for circulation of vaccine-derived polioviruses. Such conditions permit expansion of the cohort of children who are not immune to one or more poliovirus serotypes (CDC, 2000). The threshold rates of vaccine coverage needed to suppress circulation of vaccine-derived polioviruses are unknown but probably vary by poliovirus serotype and environmental factors (e.g., population density, levels of sanitation, and climate) (CDC, 2000). However, when OPV coverage rates are sufficient to prevent circulation of wild polioviruses, they probably are sufficient to prevent circulation of vaccine-derived polio-viruses (Wood et al., 2000; CDC, 2000).

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. Ongoing outbreak in 18 northern states of Nigeria's 36 states started in 2006 and was recently reported in September 2007 issue of Morbidity and Mortality Weekly Review of Centre for Disease Control and Preventions (CDC) in Atlanta (Adeija, 2007). Information on all cVDPVs in 2005-2009, 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. Reports on both the work of the global laboratory 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 of the wild type have been reported in the year 2008 as compared to 846 in 2007. Type 1 poliovirus, which has caused international outbreaks, has a higher paralytic attack rate than the two other types and is the eradication effort's primary target (Okonko et al., 2008).

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. Previous type 2 cVDPVs were detected in Madagascar in 2002 and 2005 and in Egypt in the 1980s - 1990s. 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 (Okonko et al., 2008).

GPLN has screened all Sabin vaccine-related isolates from AFP cases since 1999. During January 2006 - June 2007 (Table 2), vaccine-related isolates were observed in 7,311 specimens from AFP cases, including 7,190 (98.3%) categorized as Sabin vaccine-like viruses[†] and 121 (1.7%) categorized as VDPVs; 107 VDPVs were detected during cVDPV outbreaks, 12 were iVDPVs, and two were aVDPVs as shown in Table 2. iVDPVs were isolated from seven persons with primary immunodeficiencies during the same period. Three persons had type 2 viruses (detected in Iran, in Syria and in France in a child of Tunisian origin), one was coinfected with types 1 and 2 VDPVs (in Iran), and three had type 3 VDPVs (in Egypt, Iran, and Kuwait) as shown in Table 2. Six of the immunodeficient persons were paralyzed, and their viruses were detected through AFP surveillance; the seventh was not paralyzed and had iVDPV isolated in France during clinical investigations for a bone marrow transplant (CDC, 2007a). Type 1 aVDPVs were isolated from single AFP cases in Guangxi (where seven healthy contacts also had VDPVs) and Shanxi, China. aVDPVs also were detected in non-AFP sources: a healthy child in Shanghai, China (type 3) and sewage water in Israel (type 2) (CDC, 2007a).

Current updates on the cases and outbreaks of circulating vaccine-derived polioviruses (cVDPVs) and their dates of first cases and last cases from 2000-2009 is shown in Table 3. The cVDPV outbreaks occurred in Myanmar (four cases of type 1; data as of September 7, 2007) and Nigeria (68 cases of type 2; data as of September 7, 2007) as shown in Table 3; in 2006, two single-case importations of VDPVs from Nigeria were reported in Niger (Table 3). Four specimens from Nigeria yielded type 2 VDPV and wild poliovirus mixtures (two with wild PV1 and two with wild PV3). Two specimens from one AFP case in Cambodia in 2006 had type 3 VDPVs genetically linked to cVDPVs detected in 2005 (CDC, 2007a) as shown in Table 3.

ROLE OF IMPORTATION BY TRAVELERS IN CIRCULATION OF WILD POLIOVIRUSES AND VDPVs

In Bulgaria, an imported poliovirus was able to circulate for two to five months among minority populations. Surveillance data strongly suggest that wild poliovirus

Table 2. Number of Sabin vaccine-related isolates from persons with acute flaccid paralysis, by World Health Organization (WHO) region-Global Polio Laboratory Network, January 2006- June 2007.

	Sabin	VDPV*			
WHO Region	**vaccine-like†**	**cVDPV§ isolates**	**iVDPV¶ isolates**	**aVDPV** isolates**	**Total**
Africa	1,079	100	0	0	1,179
Americas	51	0	0	0	51
Eastern Mediterranean	701	0	12	0	713
Europe	207	0	0	0	207
South-East Asia	4,707	5	0	0	4,712
Western Pacific	445	2	0	2	449
Total	7,190	107	12	2	7,311

Source: CDC (2007a); WHO (2009c)
Key: * Vaccine-derived poliovirus: a poliovirus with ≥1% VP1 sequence difference compared with Sabin vaccine virus
† Either concordant Sabin vaccine-like results in ITD tests or <1% sequence difference compared with vaccine virus
§ Circulating VDPV. In Africa Region, 96 isolates were from 49 acute flaccid paralysis (AFP) cases in Nigeria and four isolates were fro two AFP cases in Niger, according to case counts as of June 30, 2007
¶ VDPV associated with a person with primary immunodeficiency
** Ambiguous VDPV isolates that cannot be categorized as either iVDPV or cVDPV

circulation ceased shortly after supplemental immunization activities with oral poliovirus vaccine were conducted (Kojouharova et al., 2003). According to Kojouharova (2003), Bulgarian authorities investigated the three cases of polio and their contacts, conducted faecal and serological screening of children from high-risk groups, implemented enhanced surveillance for acute flaccid paralysis, and conducted supplemental immunization activities. The three cases of polio studied had not been vaccinated and lived in socio-economically deprived areas of two cities. Four Roma children from the Bourgas district had antibody titres to serotype 1 poliovirus only, and wild type 1 virus was isolated from the faeces of two asymptomatic Roma children in the Bourgas and Sofia districts. Poliovirus isolates were related genetically and represented a single evolutionary lineage; genomic sequences were less than 90% identical to poliovirus strains isolated previously in Europe, but 98.3% similar to a strain isolated in India in 2000. No cases or wild virus isolates were found after supplemental immunization activities were launched in May 2001. No definitive conclusions were reached about the transmission path that allowed a strain very similar to those circulating recently in the Indian subcontinent to be imported into Eastern Europe. Before 2001, the last instance of wild virus-associated poliomyelitis in Bulgaria was recorded in 1991, when an outbreak that affected 43 cases, mostly Roma infants, was documented (EPI, 1992; Kojouharova et al., 2003).

Between 2003 and 2006, polio was imported by travelers (example, refugees, pilgrims, traders) to 24 polio-free countries (WHO, 2006). The origin of these importations was largely the 4 countries where polio transmission was never completely interrupted. The importations resulted in about 1,400 secondary cases (WHO, 2006). The resurgence of polio by international spread was a setback to the Global Polio Eradication Initiative that had successfully decreased the number of polio-affected countries to only 9 in 2002 (Wilder-Smith, 2008).

In July 2007, an Australian traveler imported polio from Pakistan to Australia (DPHA, 2007). He was a 22-year-old man who had immigrated to Australia and had traveled to his country of origin (Pakistan) to visit friends and relatives. Pakistan is one of 4 countries (Afghanistan, India, Nigeria and Pakistan) where polio is still endemic (Wilder-Smith, 2008). A diagnosis of polio was made shortly after his return to Australia. Australia was certified as polio-free in 2000 (Wilder-Smith, 2008). The Australian case comprised 1 imported case. Similarly, no paralytic cases followed the recent importation of a poliovirus from Chad into Switzerland (GPEI, 2007) or the 2005 Minnesota VDPV infections (CDC, 2005). The United Kingdom has been polio-free for decades despite close ties with India, Pakistan and Nigeria. Polio outbreaks (both wild and VDPV) occur where immunization coverage is low (Hull, 2008). The last major outbreak in Western Europe occurred in a Dutch religious group that refuses immunization (Hull, 2008).

The 2005 - 2006 global outbreak affected polio-free countries where polio immunization coverage had fallen after transmission was interrupted (Hull, 2008).

TRENDS AND THE IMPLICATIONS OF cVDPV: HOW FAR CAN WE GO?

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) (Adeija, 2007).

Table 3. Current Updates on the Cases and outbreaks of circulating vaccine-derived polioviruses (cVDPVs) and their dates of first cases and last cases from 2000 – 2009.

Country	Type	Years										Dates	
		2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	First cases	Last cases
Nigeria	VDPV-2	0	0	0	0	0	1	21	68	61	7	02/07/05	11/04/08
Ethiopia	VDPV-2	0	0	0	0	0	0	0	0	4	0	04/10/08	19/12/08
DR Congo	VDPV-2	0	0	0	0	0	0	0	0	14	0	22/03/06	15/12/08
Myanmar	VDPV-1	0	0	0	0	0	0	1	4	0	0	09/04/06	06/02/07
Niger** *	VDPV-2	0	0	0	0	0	0	2	0	0	0	28/05/06	03/10/06
Cambodia	VDPV-3	0	0	0	0	0	1	1	0	0	0	26/11/05	15/01/06
Indonesia	VDPV-1	0	0	0	0	0	46	0	0	0	0	09/06/05	26/10/05
Madagscar**	VDPV-2	0	1	4	0	0	3	0	0	0	0	2001	13/07/05
China	VDPV-1	0	0	0	0	2	0	0	0	0	0	13/06/04	11/07/04
Philippines	VDPV-1	0	3	0	0	0	0	0	0	0	0	15/03/01	26/07/01
DOR/Halti	VDPV-1	12	9	0	0	0	0	0	0	0	0	12/07/00	12/07/01
Total		12	13	4	0	2	51	25	72	18	7		

Source: Data in WHO/HQ as of 24 Mar 2009 (WHO, 2009d)
Key: **=Madagscar had 2 different outbreaks (2001/2002 and 2005)
**=Niger VDPVs are link to Nigerian outbreaks
=Circulating VDPV is associated with 2 or more cases of AFP.

In 2007, 68 children in Nigeria have been partially paralyzed after weake-ned viruses from polio vaccines were inadver-tently transmitted to people in unvaccinated regions in the north of the country. 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. As at 2007, about 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 in Nigeria of circulating vaccine-derived polioviruses (cVDPVs), a strain of the polio virus genetically changed from the original strain contained in the oral polio vaccine (OPV), is an indication that far too many children remain unvaccinated or under-immunized (Adu, 2008). It also 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. A study by Adu et al. (2007) on the first isolation of such recombinant polio virus in Nigeria confirmed the above facts. As at March 2009, there were 158 cVDPVs in Nigeria with two imported to Niger Republic. A study reported by Adu in 2008 showed that 40% of children with cVDPV never received the oral polio vaccine (OPV) while 87% received 1 or 2 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 2005. The first round was conducted in November 2006 another in January 2007 and a further round in March 2007 and more rounds in 2008 and 2009. 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 as well as in 2008 and 2009, 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 (Okonko et al., 2008).

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/non-vaccine recombination in the capsid 3D region (Adu et al., 2003). In 2002, Plateau/02 VDPV was

isolated from incompletely immunized 21 months old child (Adu et al., 2007; Adu, 2008). It was initially identified as Sabin by intratypic differentiation (ITD) (Adu et al., 2007; Adu, 2008). Sequences studies showed 22/903 (2.5%) nucleotide change in the VP1 region (Adu et al., 2007; Adu, 2008).

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 nonstructural proteins (NSL) in VP1 region using real-time PCR assay (CDC, 2007a). In addition, GPLN plans to expand its use of real-time polymerase chain reaction (PCR) assays to reduce the use of virus cultivation in cell culture and minimize opportunities for breaches of poliovirus containment in the laboratory (CDC, 2007a).

Most preVDPV and VDPVs were nonstructural proteins (NSL) in 3D region using the real-time PCR assay (CDC, 2007a). 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 was found in the high risk states in Nigeria (Bauchi, Borno, Kebbi, Sokoto, and Zamfara) and in the very high risk states in Nigeria (Kaduna, Kastina, 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). To this end, until the transmission of wild poliovirus is interrupted globally, it will remain possible for poliovirus to be reintroduced into a country, as well as into other regions of the world already free from poliomyelitis (WHO, 2000; Kojouharova et al., 2003). Thus, countries in polio-free areas of the world therefore should maintain vigilance, identify and actively vaccinate underserved populations, and develop the mechanisms for rapid detection and appropriate response to such an event (Kojouharova et al., 2003).

According to Hull (2008), after poliomyelitis was imported into Australia, Wilder-Smith and colleagues (2008) call for proof of vaccination for travelers from polio-endemic countries.

Although superficially attractive, their recommendation won't be extremely effective, will be burdensome for polio-endemic and polio-free countries, and is unnecessary. Documenting vaccination may slightly reduce, but will not eliminate, importations. Also, screening programs are likely to be costly and will not be simple to implement (Hull, 2008).

Lesson learned from Nigeria and other Episodes of cVDPV

Polioviruses are imported regularly, yet outbreaks are rare (Hull, 2008). Previous type 2 cVDPVs were detected in Madagascar in 2002 and 2005 and in Egypt in the 1980 - 90s (Okonko et al., 2008). 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. In addition, outbreaks of paralytic disease caused by circulating vaccine-derived polioviruses also could occur (WHO, 2002). High-risk communities are present in all European countries. All attempts must be made to reach minority children with immunization and other health services (Kojouharova et al., 2003).

The outbreak in the Dominican Republic and Haiti involved circulating poliovirus type 1; the cases in China and Egypt (and possibly infections detected by environmental surveillance in Israel) involved circulating type 2 vaccine-derived viruses (Shulman et al., 2000). The type 2 OPV strain is the most transmissible of the three poliovirus serotypes (Wood et al., 2000; Strebel et al., 1992). Because circulation of wild type 2 polioviruses probably has ceased worldwide (CDC, 1999a, b), the only type 2 polioviruses infecting humans and conferring type-specific immunity are likely to be those derived from OPV (CDC, 2000).

Australia will not be the last industrialized country affected by importation of polio. All countries are at risk until polio has been completely eradicated (Wilder-Smith, 2008). Because the outbreak reported by CDC (2000)

involved extensive person-to-person transmission of poliovirus, it differs from vaccine-associated paralytic polio (VAPP). Cases of VAPP are not linked epidemiologically or virologically to each other but are associated with separate recent exposures to OPV (Strebel et al., 1992). However, the early events associated with the circulation of vaccine-derived polioviruses may be similar to events associated with contact cases of VAPP: an unimmunized person is exposed to vaccine-derived poliovirus excreted by a recent OPV recipient (Strebel et al., 1992). Excreted vaccine-derived viruses often are more virulent than the original OPV strains (Minor, 1992). Low levels of population immunity may favor the selection and transmission of vaccine-derived variants with biologic properties indistinguishable from those of wild polioviruses.

Suboptimal vaccination in the Roma population contributed to the outbreaks in 1991 and 2001. Other outbreaks occurred in Europe among population groups with lower vaccination coverage in Spain during 1982–84 (Bernal et al., 1987), the Netherlands during 1992 – 93 (Conyn-van Spaendonck et al., 1996), and Romania during 1990 - 92 (Strebel et al., 1994). These examples show that, without appropriate control actions, population groups with lower vaccination coverage can sustain the circulation of wild polioviruses within a country for up to three years (Kojouharova et al., 2003).

Prompt vaccination of children at high risk within one month of the onset of paralysis in the index case and supplementary vaccination countrywide within two months may have prevented further spread of the virus strain within and outside Bulgaria. Considering that a sufficient pool of susceptible children was present in and around Bourgas at the time of onset of paralysis in the index case, it is unlikely that silent circulation of the virus could have occurred before February 2001. Molecular evidence that showed that none of the four isolates differed by more than two base pair mutations in the sequences analysed suggests a limited period of circulation in Bulgaria before the viruses were identified (Kojouharova et al., 2003).

The recent polio importation by an inadequately vaccinated traveler would add impetus to the revised International Health Regulations, IHR (2005) considerations (Wilder-Smith, 2008).

However, this case also shows that focusing on travelers from polio-endemic countries alone may not be sufficient (Wilder-Smith, 2008). Immigrants from developping countries to industrialized countries who subsequently return to their home countries to visit friends and relatives may also be at increased risk if traveling to polio-endemic countries, in particular as many may not have received adequate childhood vaccination including vaccination against polio (Leder et al., 2006). Targeting those visiting friends and relatives is therefore a potential additional strategy to reduce the risk for the worldwide spread of polio (Wilder-Smith, 2008).

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.

Increased awareness of the risk of poliomyelitis and implementation of active surveillance resulted in improvements in performance indicators for surveillance of acute flaccid paralysis in Bulgaria. Investigation of the outbreak rapidly identified the existence of greater-than-expected gaps in immunity among minority populations. The rapid implementation of the national vaccination campaign shows excellent collaboration between local health services, governmental services, the community network, the laboratory network, and international partner organizations. Although both rounds of national immunization days seemed to have achieved high coverage, additional supplemental immunization activities among high-risk minority children were conducted to provide multiple doses of oral polio vaccine to many children who had never been vaccinated (Kojouharova et al., 2003).

Countries at risk for polio importation because of low vaccination coverage should focus on improving their immunization programs, not vaccinating and screening travelers. Australia and other polio-free countries can best protect themselves against importations by supporting eradication efforts in polio-endemic countries (Hull, 2008).

MOLECULAR EPIDEMIOLOGY

Circulating VDPV 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).

Since 1995, countries in WHO's European region have been strengthening efforts to interrupt transmission of wild poliovirus. Supplementary immunization activities in individual countries, as well as synchronized supplementary immunization activities in 18 contiguous countries of the Eastern Mediterranean and European Regions of WHO ("Operation MECACAR") (WHO, 1998; Smith et al., 1998; Kojouharova et al., 2003), resulted in a dramatic reduction in the incidence of poliomyelitis. At the same time, surveillance of poliomyelitis improved in participating countries. In the European region, the last case of poliomyelitis caused by indigenous transmission of wild poliovirus was observed in Turkey in November 1998 (WHO, 2000; Kojouharova et al., 2003).

During 2000, circulation of type 1 vaccine-derived poliovirus in the Dominican Republic and Haiti was associated with 19 suspected polio cases (CDC, 2000). Nucleotide sequence relationships among Sabin 2-derived polioviruses isolated in China during the mid-1990s also were consistent with establishment of genetic lineages by person-to-person transmission (Zhang et al., 1998). However, the sequence diversity (4-5%) of the early isolates suggested that circulation had started several years before 1988. Although the precise duration and extent of vaccine-derived poliovirus circulation in Egypt is uncertain because of gaps in surveillance before 1990, regression analysis of the VP1 evolution rate suggested that all lineages derived from one OPV infection that occurred approximately during 1982, and that progeny from that initiating infection circulated in Egypt during 1982-1993 (EIBPVP, 2001). The estimate of the time of the initiating OPV infection is based on the assumption that the rate of VP1 evolution was nearly constant throughout the period of virus circulation.

Circulation of the Sabin 2-derived poliovirus occurred when OPV coverage probably was low in the affected communities. OPV coverage rates increased steadily in the mid-1990s, and no highly divergent vaccine-derived poliovirus isolates have been found in Egypt since 1993 (CDC, 2001; EIBPVP, 2001).

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 I (Rousset et al., 2003) as shown in Table 3. The first patient, an 11-year-old child from the urban district of Toliara, first experienced paralysis on October 29, 2001. Three other children, 6, 9, and 14 months of age from Ebakika village, in a rural district of Taolagnaro (250 miles east of Toliara), showed signs of poliomyelitis between March 21 and March 26, 2002. The last case-patient, a 20-month-old child from Ambanihazo village (6 miles north of Ebakika), came into contact with one of the three case-patients in Ebakika in March 2002, and symptoms developed on April 12, 2002 (CDC, 2002). None of the patients had been fully vaccinated against poliomyelitis (Rousset et al., 2003).

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 nonpolio enteroviruses is important. These VDPVs have major implications for the cessation of immunization with OPV after certification that wild PV has been eradicated (Rousset et al., 2003).

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 potntial for the emergence of type 2 cVDPVs (Adu et al., 2007).

Recent advances in genomic sequencing technology have lent its support to the monitoring and evaluation of vaccination programmes. Phylogenetic trees are invaluable tools for monitoring the progress of immunization activities. Viruses of the same genetic lineages cluster geographically together in a phylogenetic tree (Adu, 2008). The success of any immunization programme is dependent, to a large extent, on the quality and level of vaccination coverage. If Nigerian children are not to die unnecessarily form vaccine preventable diseases, the mechanism to improve the quality and raise the level of routine immunization coverage must be put in place (Adu, 2008). According to Adu (2008), various studies by Ibadan Polio lab under his leadership and in collaboration with Center for Disease Control and Prevention in Atlanta and the National Institute for Communicable Disease (NICD) in Johannesburg, South Africa, have used various molecular approaches to:

i.) Determine the source of imported viruses.
ii.) Follow the pathway of virus circulation.
iii.) Monitor the progress or lack of progress of the vaccination programme (WHO, 2002).
iv.) Identify reservoirs sustaining virus circulation (WHO, 2003).
v.) Detect gaps in surveillance.
v.) Show geographical distribution of the virus (WHO, 2004).

GPLN continues to provide important data to monitor progress toward polio eradication and to direct immunization and other services to areas of greatest need.

During 2006 - 2007, GPLN identified specific areas in Nigeria and India as the ultimate sources of wild poliovirus transmission occurring elsewhere, under-scoring the need to interrupt transmission in these areas to avoid jeopardizing the polio-free status of other countries. High vaccination coverage must be achieved and maintained in all WHO regions to prevent circulation of endemic or imported wild poliovirus or VDPVs (CDC, 2007). These efforts are with ultimate aim of detecting the viruses and the un-immunized children and of reaching every Nigerian child with the vaccine in order to stop the unnecessary suffering and untimely death resulting from these vaccine preventable diseases (Adu, 2008).

SUMMARY AND RECOMMENDATIONS

In 1988, the World Health Assembly resolved to eradicate poliomyelitis globally by 2000 (WHO, 1988). Substantial progress has been achieved toward this goal, (CDC, 1999a, b) and with the circulation of wild poliovirus eliminated in most of the world, attention has focused on examining the potential for vaccine-derived poliovirus to circulate where wild poliovirus has disappeared (CDC, 2001; EIBPVP, 2001). The finding that vaccine-derived polioviruses may circulate under suitable conditions presents an additional challenge to efforts to eradicate polio worldwide (WHO, 1988; CDC, 1999a; Wood et al., 2000).

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 168 cases due to circulating vaccine-derived poliovirus (GPEI, 2008). 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. 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 cVPDV is urgently required.

One strategy to protect polio-free countries from reintroduction of wild poliovirus is by requiring proof of polio vaccination for all incoming travelers from polio-endemic countries (Wilder-Smith, 2008). This was proposed by the Advisory Committee on Poliomyelitis Eradication in October 2006. The rationale is similar to that used for yellow fever, currently the only disease for which proof of vaccination may be required for travelers as a condition of entry to a country (Wilder-Smith, 2008). The proposal of the Advisory Committee of Poliomyelitis Eradication was discussed at the World Health Assembly in May 2007 (WHO, 2007). Although the main strategy for polio eradication continues to be attaining high vaccination coverage against polio in all countries, the 193 member states have also adopted the resolution to "continue to examine and disseminate measures that member states can take for reducing the risk and consequences of international spread of polioviruses, including, if and when needed, the consideration of Temporary or Standing Recommendations, under the International Health Regulations (2005)" (WHO, 2005; Wilder-Smith, 2008).

The potential of vaccine-derived polioviruses to establish and maintain circulation has important implications for developing an appropriate strategy for the cessation of vaccination with OPV after wild poliovirus eradication has been achieved (Wood et al., 2000). Potential vaccine-derived poliovirus circulation also under-scores the importance of maintaining high rates of poliovirus vaccine coverage worldwide. Countries using OPV should target communities with low vaccine coverage for intensified vaccination activities to prevent circulation of vaccine-derived and wild polioviruses. Countries using inactivated poliovirus vaccine should take steps to ensure high coverage rates in all communities to prevent the transmission of imported polioviruses (CDC, 2000).

Increased awareness of the risk of poliomyelitis and implementation of active surveillance resulted in improvements in performance indicators for surveillance of acute flaccid paralysis in Bulgaria. Investigation of the outbreak rapidly identified the existence of greater-than-expected gaps in immunity among minority populations. The rapid implementation of the national vaccination campaign shows excellent collaboration between local health services, governmental services, the community network, the laboratory network, and international partner organizations. Although both rounds of national immunization days seemed to have achieved high coverage, additional supplemental immunization activities among high-risk minority children were conducted to provide multiple doses of oral polio vaccine to many children who had never been vaccinated.

Several drugs, some of which have been (rupintrivir, pirodavir, valopicitabine, compound 1) or are being (pleconaril) studied in the clinical setting, are reported to have inhibited the *in vitro* replication of PVs to varying degrees. These drugs, used alone or in combination, may have potential for the treatment or prophylaxis of PV infections. These and other compounds may serve as starting points for the design of more potent PV inhibitors with favorable safety and pharmacokinetic profiles (De Palma et al., 2008). To date, few, if any, drug discovery programs for PV have been initiated. Therefore, research initiatives leading to the successful development of anti-PV drugs will have to rely on the current knowledge of existing picornavirus antiviral agents. Antipicornavirus compounds that reached clinical trials are scarce, and despite the fact that some of these drugs have demonstrated activity against certain picornavirus-associated conditions in humans, no specific antipicornavirus agent has yet been approved by the US Food and Drug Administration (FDA) (De Palma et al., 2008).

Immunization and vaccination remains one of the most cost effective strategies to prevent infectious diseases. The most effective and efficient way to protect the health of children is by immunization-before the risk of disease arises. Vaccination has succeeded in eradicating small pox in the world (Fenner et al., 1988; Adu, 2008). The Expanded Programme on Immunization (EPI) was approved by the World Health Assembly in 1977 (WHA, 1998 reviewed in Adu, 2008). The efficacy of vaccination and immunization in reducing the incidences of several diseases is clearly shown by the success story of measles control in developed countries of the world (Cutts and Markowitz, 1994; Adu, 2008). Even still more dramatic is the story of poliomyelitis. The oral polio vaccine (OPV) has reduced the number of wild polio cases from 350,000 in 125 countries in 1988 to 1,998 cases in four endemic countries in 2006 (CDC, 2008a; Adu, 2008). Unfortunately, twenty years after, this level of success has not been matched in Nigeria. In this country, vaccine preventable diseases such as measles and polio has continued to cause high morbidity and mortality among children and children have continued to be paralyzed by these vaccine preventable diseases (CDC, 2008b; Adu, 2008).

Nigeria indeed is fighting an unusual outbreak of polio caused by mutating polio vaccine; the only remedy is to keep vaccinating children. This vaccine 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 (Adeija, 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). Furthermore, the success of any immunization programme is dependent, to a large extent, on the quality and level of vaccination coverage. If Nigerian children are not to die unnecessarily form vaccine preventable diseases, the mechanism to improve the quality and raise the level of routine immunization coverage must be put in place (Adu, 2008).

However, Nigeria will continue to pose a high risk to international health until the new top political commitment is translated into field-level improvements in campaign quality. For example, >30% of children remain unvaccinated in Kano State. This has resulted in the ongoing co-circulation and international exportation of type-1 wild poliovirus (WPV1), type-3 (WPV3), and circulating vaccine-derived poliovirus (cVDPV) type2. The international risks posed by Nigeria are compounded by the current economic climate, which severely compromises the capacity of the international community to respond to any new international spread from the large areas of uncontrolled poliovirus transmission in the north of the country.

Consequently, only 1 of the milestones established at the beginning of the intensified eradication effort in early 2007 has been fully met; the others have been partly met. Milestones were not fully met as a result of: a) suboptimal efficacy of OPV in key areas of northern India where, despite implementation of multiple campaigns that achieved high immunization coverage, WPV1 transmission has not yet been completely interrupted; b) suboptimal campaign quality in Nigeria, parts of Pakistan, the Southern Region of Afghanistan and the 5 countries that have had prolonged transmission of imported virus, where coverage has not achieved the levels necessary to interrupt transmission of WPV and, in the case of Nigeria, a type-2 cVDPV; c) security-compromised areas in parts of Afghanistan and Pakistan where access to communities is limited during immunization campaigns. To continue progress towards more rapid detection of WPV and cVDPVs, the implementation of the algorithm for laboratory testing and incorporation of new diagnostic tools (such as real-time polymerase chain reaction) should be carried through to completion. The pursuit of an active research agenda by the eradication programme through the reconstituted Polio Research Committee, using new strategies to overcome obstacles to eradication, which include the use of mOPVs. In Nigeria, the performance of polio vaccination campaigns must improve markedly by the end of March 2009, and there must be independent, objective evidence that the proportion of "0-dose" children (that is, children who have never been immunized) has been reduced to <10% in all polio-infected states.

In conclusion, in all other countries with ongoing WPV transmission, serious limitations in accessing and vaccinating children remain the major impediments to polio eradication. The type 2 cVDPV outbreaks in Nigeria, DRC, and Ethiopia reveal striking lapses in routine and Supplementary Immunization Activities (SIA) vaccination in parts of those countries because cVDPVs are biologically similar to WPVs in terms of infectivity and pathogenicity. In Nigeria, the key to success will be to scale-up throughout the country the communication, social mobilization, and operational improvements that were achieved in some areas of northern Nigeria.

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