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Review

A case for developing antiviral drugs against polio

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ABSTRACT

Polio eradication is within sight. In bringing the world close to this ultimate goal, the Global Polio Eradication Initiative (GPEI) has relied exclusively on the live, attenuated oral poliovirus vaccine (OPV). However, as eradication nears, continued OPV use becomes less tenable due to the incidence of vaccine associated paralytic poliomyelitis (VAPP) in vaccine recipients and disease caused by circulating vaccine-derived polioviruses (cVDPVs) in contacts. Once wild poliovirus transmission has been interrupted globally, OPV use will stop. This will leave the inactivated poliovirus vaccine (IPV) as the only weapon to defend a polio-free world. Outbreaks caused by cVDPVs are expected post-OPV cessation, and accidental or deliberate releases of virus could also occur, but there are serious doubts regarding the ability of IPV to control outbreaks. Here, we argue that antiviral drugs against poliovirus be added to the arsenal. Anti-poliovirus drugs could be used to treat the infected and protect the exposed, acting rapidly on their own to contain an outbreak and used as a complement to IPV. While there are no polio antiviral drugs today, the technological feasibility of developing such drugs and their probability of clinical success have been established by over three decades of drug development targeting the related rhinoviruses and non-polio enteroviruses (NPEVs). In fact, because of this history, there are known compounds with anti-poliovirus activity in vitro that represent excellent starting points for polio drug development. Stakeholders must come to understand the potential public health benefits of polio drugs, the feasibility of their development, and the relatively modest costs involved. Given the timelines for eradication and those for drug development, the time for action is now.

Contents

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1. Polio eradication

The Global Polio Eradication Initiative (GPEI), a partnership led by the World Health Organization (WHO), Rotary International, the US Centers for Disease Control and Prevention (CDC) and the United Nations International Children's Emergency Fund (UNICEF), is the largest, most expensive international public health project ever undertaken. Most would agree that the GPEI has been quite successful. When the program was launched in 1988, endemic wild poliovirus transmission occurred in more than 125 nations with an estimated 350,000 persons, mostly children, developing paralytic disease each year. While there have been ups and downs, delays and setbacks, by the end of 2007 the annual paralytic poliomyelitis case count due to wild poliovirus had fallen to about 1300 and only four countries, Afghanistan, India, Nigeria, and Pakistan, remain with endemic poliovirus transmission (Polio Eradication, 2008a).

The GPEI strategic plan is based on improvement of routine immunization for all children, supplemental mass oral poliovirus vaccine (OPV) immunization activities in areas with ongoing poliovirus transmission, comprehensive acute flaccid paralysis surveillance, and a high-quality global laboratory network for isolation and characterization of polioviruses.

The GPEI has relied exclusively on OPV, an inexpensive and easily administered live, attenuated vaccine (Table 1). OPV is generally safe and has been very effective under most circumstances. However, in parts of India, specifically Uttar Pradesh and Bihar, OPV has failed to provide protection against paralytic polio. Moreover, at a low frequency, about 1 per 750,000 vaccinees, OPV itself can cause paralysis (vaccine-associated paralytic polio, VAPP) (Strebel et al., 1992). Normally, OPV viruses are excreted in the stool of healthy vaccinated individuals for up to 8 weeks. Vaccine-derived polioviruses (VDPVs), which may circulate among non-immune persons in poorly vaccinated communities for years (termed circulating vaccine-derived polioviruses, cVDPVs), have the potential to revert to neurovirulence and cause paralytic disease. Also, in immunodeficient individuals with defects in antibody production, such as agammaglobulinemia, vaccine-derived polioviruses (termed immune-deficiency-related vaccine-derived polioviruses, iVDPVs) can be excreted for years (Martín, 2006). The first recognized outbreak of paralytic poliomyelitis caused by a type 1 cVDPV occurred on the island of Hispaniola in late 2000 (Kew et al., 2002). This outbreak demonstrated that cVDPVs can acquire replicative capacity and virulence comparable to wild poliovirus and that these properties are associated with only a few nucleotide changes in the OPV genome (Kew and Nottay, 1984; Almond, 1987; Kew et al., 2005).

At the current global level of OPV use, it is estimated that there will be between 250 and 500 new cases of VAPP and at least one polio disease outbreak due to a VDPV worldwide each year (Duintjer Tebbens et al., 2005). While the benefits of OPV outweigh the risk of VDPV-induced disease when wild poliovirus transmission levels are high, as wild poliovirus transmission is eliminated, new polio cases will emerge as a result of the continued use of OPV. Thus, the very vaccine that has been so crucial to the eradication effort will eventually become the primary source of poliovirus in the community and of paralytic disease.

The current GPEI plan calls for discontinuation of routine OPV use once it can be assured that wild poliovirus transmission has been completely interrupted globally. At such time, the public health benefits of immunization with OPV will no longer outweigh the burden of disease due to VAPP and cVDPVs. Countries using OPV must decide whether to switch to inactivated poliovirus vaccine (IPV) or stop polio vaccination altogether. Because IPV is much more expensive than OPV, this will pose a major barrier to its universal use by the world's poorest nations. Governments of poor nations may divert their attention and limited resources to other pressing health needs. If IPV is not successfully incorporated into routine childhood immunization on a global basis at the time of OPV cessation, a rapid rise in susceptibility to poliovirus infection, especially among infants and young children living in impoverished circumstances, is inevitable.

2. Current armament is not enough—new weapons needed

Developing strategies to respond to and control poliovirus outbreaks during the final stages of eradication and in a post-eradication era present significant challenges. First, there is the unpredictability of outbreaks. As VDPVs continue to circulate, there will be a high probability of outbreaks of paralytic disease in the first several years after OPV cessation, but their incidence and magnitude are unknown. Second, threats of accidental or deliberate release of wild type polioviruses and VDPVs from vaccine manufacturing sites, research labs and diagnostic labs will persist well into the future. A third challenge is the nature of the response to a polio outbreak post-OPV cessation. While OPV might otherwise represent the preferred vaccine for outbreak control, there will be a reluctance to re-introduce OPV viruses into the environment. This leaves IPV as the only defense currently available.

Use of IPV carries no risk of generating VDPVs or causing paralytic disease. IPV provides excellent individual protection against polio disease and has been shown to induce a high level of immunity in young infants in developing countries (Cuba IPV Study Collaborative Group, 2007; Asturias et al., 2007; Dayan et al., 2007). However, unlike OPV, IPV must be given parenterally, requires a minimum of two doses spaced ideally at least 2 months apart to induce humoral immunity, and does not induce sufficient mucosal immunity to protect against poliovirus replication and subsequent virus shedding and transmission. Several studies exploring altered dose regimens, adjuvant use and intra-dermal delivery are ongoing in hopes of improving the vaccine's effectiveness. Nevertheless, IPV is far from ideal, and perhaps alone, inadequate for outbreak control.

New tools are clearly needed to improve the response capability, and its effectiveness, in the face of a polio outbreak in the post-eradication era. The ability to rapidly and effectively contain an outbreak is essential.

The role of antiviral drugs in polio outbreak control was considered at a recent workshop sponsored by the National Research Council (NRC) entitled "Exploring the Role of Antiviral Drugs in the Eradication of Polio". At the request of the CDC and WHO, the NRC established a committee to conduct a workshop to evalu-

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Table 1
A polio primer: basic facts about polioviruses and the polio vaccines

Classification and structure	Polioviruses are members of the Enterovirus genus, family *Picornaviridae*. There are three poliovirus species: types 1, 2 and 3. Virions are non-enveloped particles about 30 nm in diameter and consist of single-stranded, positive-sense RNA of about 7500 nucleotides encased by an icosahedral capsid formed by four viral proteins, VP1, 2, 3 and 4
Infection cycle	Virions gain entry to the cell by binding to CD155, followed by endocytosis. Upon internalization, the virion capsid disassembles or uncoats, releasing the viral RNA into the cytoplasm. The RNA contains a single long open reading frame and is translated using its internal ribosome entry site (IRES), producing a single large polyprotein. This polyprotein is processed into the mature viral structural and non-structural proteins by virus-encoded proteases. The nonstructural proteins migrate to cytoplasmic membrane vesicles where viral RNA replication occurs. Negative-sense RNA copies of the incoming positive-sense genome are synthesized, which then serve as templates for production of progeny positive-sense viral RNA genomes. Viral structural proteins associate with progeny RNA genomes, and virion assembly occurs in the cytoplasm. Virions are released from the cell by lysis
Epidemiology	Humans are the only natural host for polioviruses. Virus enters by way of the gastrointestinal tract and replicates locally. Virus is excreted in the feces of an infected individual for several weeks to several months. Transmission of the virus occurs by direct person-to-person contact and indirect contact with infectious saliva, feces, or contaminated sewage or water. Most infections are asymptomatic or result in febrile illness with transient diarrhea; about 0.5% of infections result in paralytic disease
Pathogenesis of paralytic disease	Virus spreads to Peyer's patches in the intestinal lining, then enters the bloodstream and seeds multiple organs. Infection of muscle cells leads to virus entry into motor end plates of neurons and upstream spread into the central nervous system. Destruction of motor neurons (those that control muscle movement) by the virus results in paralysis
Vaccines	IPV: Inactivated polio vaccine (IPV), originally developed in 1955 by Jonas Salk, consists of formalin-treated (killed) wild polioviruses of the three types. The vaccine is administered as a series of injections requiring trained personnel. The elicited immunity protects the individual from disease by blocking virus spread to the central nervous system, but does not prevent viral replication in the gastrointestinal tract and virus excretion. IPV carries no risk of vaccine-associated paralytic poliomyelitis (VAPP). OPV: Oral polio vaccine (OPV) was developed by Albert Sabin in 1961 and consists of live, attenuated polioviruses representing the three types. OPV is less expensive to produce and simpler to administer than IPV. While generally safe and very effective, OPV causes VAPP in roughly one healthy recipient per million vaccinees. Healthy vaccine recipients shed infectious virus in their stool for several months. These circulating vaccine-derived polioviruses (cVDPVs) may persist for years in communities with low herd immunity. On rare occasions, cVDPVs regain the ability to cause paralytic disease. OPV-vaccinated persons with defects in immunoglobulin production may excrete immune-deficiency-related vaccine-derived polioviruses (iVDPVs) for years
Control strategies	Most countries in the world have eradicated wild polioviruses through universal administration of OPV to children. A few countries in Scandinavia have used only IPV. In 2000, the USA halted the use of OPV and now uses exclusively IPV. Wild polioviruses continue to circulate in four countries (Afghanistan, India, Nigeria, and Pakistan), where mass vaccination with OPV remains the principal eradication strategy

ate whether an anti-poliovirus drug would have utility in the late stages of the eradication effort and in the post-eradication era, how a drug might be developed and how it might be used. The workshop report, released in March 2006, concluded that there is indeed an important role for poliovirus antiviral drugs (NRC, 2006). The report indicated that adding a polio drug to the outbreak response toolbox would provide increased response flexibility and improved effectiveness. It was recommended that at least two mechanistically distinct polio antiviral drugs be developed, and it was urged that the development of such drugs be initiated immediately, citing the timelines for drug development and the urgency of the need.

Subsequently, in October 2006 at the 3rd Meeting of the Advisory Committee on Poliomyelitis Eradication (ACPE), the Task Force for Childhood Survival and Development (Task Force) proposed the establishment of a Poliovirus Antiviral Initiative (PAI) to implement the NRC recommendations. The ACPE supported this proposal and recommended that a plan of action be developed and resources be mobilized (Weekly Epidemiological Record, 2006).

In June 2007, the CDC acted on the ACPE recommendations by contracting the Task Force to facilitate development of effective polio antiviral drugs for global public health applications. In collaboration with the CDC and WHO, the Task Force will evaluate and assist others to evaluate compounds with suspected or demonstrated anti-poliovirus activity in cell culture, particularly those that have shown promise for prophylaxis or treatment of other picornavirus infections. Compounds for which there are human pharmacokinetic, safety, and tolerability data are of high priority. In support of Task Force activities, the CDC has developed a poliovirus test panel of nearly 50 strains representative of all three poliovirus types and important vaccine-derived (VDPV) strains. Laboratories with promising poliovirus antiviral drug candidates are invited to submit a request to the WHO for drug susceptibility testing to be done by the CDC against this virus panel. The National Institute of Allergy and Infectious Diseases (NIAID) has also indicated its strong interest in supporting efforts to develop antiviral drugs against polio and encourages inquiries into its various investigator-initiated research programs (Greenstone et al., 2007).

3. Antiviral drugs and outbreak control

The idea of antiviral therapy for polio is not new. In the 1950s, shortly after the success of poliovirus propagation in cell culture, several inhibitors of in vitro polio replication were identified, some of which were evaluated in animals (Brown, 1952; Brown et al., 1953; Cochran et al., 1954; Francis et al., 1954; Knox et al., 1957; Barrbera-Oro and Melnick, 1961). In the 1960s, Hans Eggers was a vocal advocate of the concept of antiviral therapy for polio (Field and DeClercq, 2004). However, with the emerging success of the polio vaccines, the idea of drug treatment for polio faded.

The public health initiative against polio has used only vaccination over the course of its 50-year history. Therefore, it may be difficult to envision how an anti-poliovirus drug might contribute to control of poliomyelitis. To understand the potential of a polio antiviral drug, it is first important to appreciate the general attributes of antiviral drugs that make them so well suited for

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rapid response and control of virus disease outbreaks. Under ideal circumstances, antiviral drugs are:

(1) *Easily administered*: Antiviral drugs can be designed as oral medications in the form of an oral tablet, liquid, or even a food bar, suitable for adults and children. This simple means of administration does not require the presence of trained medical personnel.
(2) *Fast acting*: Orally administered drugs achieve effective levels in patients within hours, acting immediately to reduce virus levels and virus shedding in infected individuals, and serving to immediately protect uninfected individuals from infection when used prophylactically.
(3) *Effective irrespective of immune competency*: Antiviral drugs act to prevent virus replication in immunocompromised individuals, and in vaccinated and non-vaccinated persons. Antiviral drug administration does not interfere with environmental surveillance or diagnostic monitoring of virus infection by molecular, immunologic or virological means.
(4) *Readily stockpiled*: The production of small molecule antiviral drugs, as opposed to biologics (vaccines, immunotherapeutics), typically involves a defined, readily transferable chemical synthetic process, and does not require specialized or dedicated manufacturing facilities. Once produced, the active pharmaceutical ingredient is generally quite stable and may be stored in bulk or as finished (formulated) drug product with no extraordinary storage requirements.
(5) *Rapidly deployable*: The distribution of a small molecule antiviral drug product requires no special shipping conditions, such as a cold chain. Stockpiled drug product may be deployed globally at a moment's notice through normal shipping channels and further distributed locally under variable conditions.

Given these general characteristics of antiviral drugs, the ideal poliovirus antiviral drug must, in addition, be exceedingly safe if it is to be used broadly, particularly in prophylactic or post-exposure prophylactic situations. The compound should show no evidence of genotoxicity, mutagenicity, teratogenicity, cardiotoxicity, hepatotoxicity or nephrotoxicity. The drug should exhibit efficacy in animal models of paralytic or lethal poliovirus infection at dosages that are below the maximum tolerated level. While oral administration is preferred, candidate antiviral drugs that are effective by injection may also be acceptable in certain situations. The pharmacokinetics of the candidate should allow for low frequency drug administration (e.g., once a day) to encourage higher patient compliance. Further, CNS drug exposure is desirable. Finally, the drug must be affordable.

4. How might a polio drug be used?

Currently, no poliovirus antiviral drug is available. However, if there were one, how might we use it? The above-listed general attributes of antiviral drugs portend multiple applications of a poliovirus drug in outbreak control both pre-eradication and post-eradication. Below, we discuss several possible situations in which an anti-polio drug might be used, including treatment, post-exposure prophylactic and prophylactic applications.

4.1. Treatment of individuals persistently infected with vaccine-derived polioviruses

A small number of persons with B cell immunodeficiencies have been identified who have excreted OPV viruses for months, even years, after vaccination (Kew et al., 1998; Martín et al., 2000; Khetsuriani et al., 2003; Martín, 2006). These persons have themselves an increased risk of VAPP, and further serve as potential reservoirs for re-introduction of OPV viruses, a risk that will markedly increase with declining levels of immunity in the population. Attempts to use therapeutic immunoglobulin and other non-specific treatments have failed to stop virus replication in the gastrointestinal tract in such individuals (Martín, 2006; MacLennan et al., 2004). The anti-picornavirus drug pleconaril (see below), while not optimized for activity against poliovirus, may have been successful in one instance (Buttinelli et al., 2003). Use of an appropriate, poliovirus-optimized antiviral drug, or a combination of two such drugs, is the only option for clearance of poliovirus infections in these individuals and reducing the risk to their non-immune contacts.

4.2. Treatment of infection and disease

There is no active treatment for acute paralytic poliomyelitis. Poliovirus replication and the concomitant destruction of neuronal tissue in the CNS peak within a few days of the onset of symptoms. It is unknown whether antiviral therapy would be able to halt or reverse disease progression if started early in the course of disease. However, the effectiveness of pleconaril in treatment of non-polio enterovirus (NPEV) experimental (Schiff and Sherwood, 2000) and naturally occurring human CNS infections (Bauer et al., 2002; Hayden et al., 2002; Utzig et al., 2003) provides reason for optimism that a similar, poliovirus-specific drug could prevent or reduce the long term complications of paralytic poliomyelitis.

4.3. Containment of outbreaks when used alone

In the event of a polio outbreak, one response contemplates the rapid deployment of a poliovirus antiviral drug to the affected area. Unlike vaccination, administration of a polio antiviral would be expected to provide immediate protection. Given the rapid onset of action of the drug, virus replication and shedding would be quickly curtailed in those already infected, and prevented in those not yet infected. This response in itself, if sufficiently swift and comprehensive, might be adequate to extinguish the outbreak.

4.4. Control of outbreaks when used in combination with IPV

While use of an anti-poliovirus drug would be expected to help to quickly contain an outbreak, its benefit requires continuous administration. For long-term protection, vaccination is preferred. However, vaccination does not provide immediate protection. For example, IPV requires two doses given a minimum of a month apart to be optimally effective. During this critical time between vaccination and the establishment of protective immunity, the so-called "immunity gap", individuals remain susceptible to infection and the virus can spread through the community and beyond. Administration of an antiviral concurrently with IPV would be a way to close this gap. Upon identification of an outbreak, a course of antiviral treatment administered to index cases, household contacts, people in immediate vicinities, or whole communities would provide immediate protection and shut down virus transmission within days during the time immunity is being developed as a consequence of IPV immunization.

4.5. Containment of OPV

In the event that OPV (or monovalent OPV) is used in response to an outbreak, preventing transmission of the vaccine virus from vaccinees to other persons may be of critical importance. An antiviral drug could be used to limit the period of time for virus replication in

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those vaccinated and/or to control vaccine virus spread by deploying the drug in a protection zone around the OPV administered area, (i.e., using ring chemoprophylaxis to create a "firewall").

4.6. Improved vaccine manufacture biosecurity

OPV stockpiles will be maintained and IPV production will continue well into the future. While vaccine-manufacturing facilities will employ appropriate levels of biocontainment, given the large quantities of wild or Sabin polioviruses involved for the vaccine production, accidental release of infectious virus will always be a concern. It is anticipated that all workers will have received IPV. However, if infected, a worker may replicate and shed virus. Availability of an antiviral drug would provide an added level of biosecurity at vaccine manufacturing facilities in the event of worker exposures.

These examples demonstrate the potentially broad utility of a polio antiviral drug. Given the shortcomings of IPV in outbreak control and the versatile attributes of a polio antiviral drug, it is clear that efforts to develop such drugs must proceed immediately. Polio outbreaks will occur after OPV cessation, and the current response strategies may be insufficient to contain the virus.

5. Development of polio antiviral drugs: excellent starting points

The technological feasibility of developing poliovirus drugs and the probability of clinical success have been clearly established by over three decades of drug development targeting the related rhinoviruses and NPEVs. These latter picornaviruses cause significant, widespread human disease for which there are no vaccines. Illnesses caused by rhinoviruses and NPEVs represented potentially lucrative commercial markets, and consequently have the attention of pharmaceutical companies.

True pharmaceutical development of anti-picornavirus compounds took off in the late 1970s and early 1980s (Eggers, 1985; McKinlay, 1993; Carrasco, 1994). While poliovirus was never a therapeutic target of this movement, it was occasionally used as a test virus since it could be readily propagated in cell culture and there existed a mouse model of virus disease. Examples of those compounds for which significant anti-poliovirus activity was reported are mentioned below. However, as the real targets of these drug development programs were the NPEV and rhinoviruses, in no instance were compounds optimized against polioviruses. Efforts to develop broad-spectrum drugs against NPEVs and rhinoviruses centered for the most part on three virus-specific targets: proteins involved in viral RNA replication, the capsid, and the 3C protease.

5.1. Replication inhibitors

In the early 1960s, guanidine and the benzimidazole HBB were shown to be specific inhibitors of picornaviruses, including poliovirus (Barrbera-Oro and Melnick, 1961; Rightsel et al., 1961; Baltimore et al., 1963; Bablanian et al., 1966). Later, a more potent and selective compound, MRL-1237, was discovered (Shimizu et al., 2000). All appeared to act on viral replication protein 2C. Another benzimidazole series led by enviroxime (Wikel et al., 1980) was shown to inhibit viral RNA replication by blocking the initiation of plus-strand RNA synthesis through its interaction with viral protein 3A (Heinz and Vance, 1995). Enviroxime advanced to the clinic for NPEV and rhinovirus indications, but showed little efficacy and significant toxicity, at which point its development was stopped. However, enviroxime and derivatives do show anti-polio activity in cell culture (Table 2), so the question remains open as to whether these compounds would be suitable starting points for a poliovirus chemical optimization program.

5.2. Inhibitors of capsid disassembly

The most extensively studied picornavirus antiviral class, capsid inhibitors, block virus replication by preventing virus uncoating and the release of viral RNA from the capsid into the cell. By integrating into a specific hydrophobic pocket in virus particles formed principally by capsid protein VP1, the drug increases the stability of the virion to the extent that capsid disassembly is unable to occur. Capsid inhibitors of varying chemistries that have been identified over the years include rhodamine (1970), flavonoids (1982), chalcones (1985), oxazolinyl isoxazoles (1985), aralkylamino pyridines (1987), pyridazinamines (1992), phenoxyl imidazoles (1993) and pyridazinylpiperidines (1992) and their alkoxy benzoazole analogs (2005) (McKinlay et al., 1992; Carrasco, 1994; Rotbart et al., 1998; Brown et al., 2005).

Several capsid inhibitors have shown polio activity in both cell culture and animal models, Disoxaril (WIN 51711) was the first compound in this class to enter clinical trials (1990) for treatment of NPEV infections. In addition to being active in vitro against NPEVs, it also showed activity against human rhinoviruses and polioviruses (Table 2; Fox et al., 1986). Further, disoxaril showed oral efficacy in preventing poliovirus type 2-induced paralysis in mice (McKinlay and Steinberg, 1986). However, clinical studies were discontinued when crystallurea was observed in healthy volunteers at high dose levels. Ultimately, WIN 63843 (VP 63843; pleconaril) emerged from this series as a clinical candidate for the treatment of human NPEV and rhinovirus infections. Unfortunately, while pleconaril was shown to be safe and effective in treating NPEV disease (Bauer et al., 2002; Hayden et al., 2002: Utzig et al., 2003) and the common cold due to rhinoviruses (Hayden et al., 2003a), and continues in development for prevention of picornavirus respiratory infection-induced disease exacerbations in asthmatics (ClinicalTrials.gov NCT00394914), it shows little or no activity against polioviruses (Table 2).

Pirodavir, another capsid inhibitor that was advanced to the clinic in the early 1990s for rhinovirus indications (Hayden et al., 1995), exhibits poor anti-poliovirus activity (Table 2). In a recent study, however, a closely related analogue of pirodavir, R75761, was found to be a potent in vitro inhibitor of all three Sabin strains of poliovirus (Thys et al., in press; Table 2). While this chemical series (pyridazinamines) suffers from poor oral pharmacokinetic properties, oxime ether derivatives have been used to address this issue (Watson et al., 2003). Pyridazinyl oxime ether compounds related to pirodavir that are metabolically stable and orally bioavailable are being developed for NPEV and rhinovirus indications. Within this series, BTA188 showed anti-poliovirus 1 activity, but proved inactive against the other serotypes (Table 2). The most advanced compound to evolve from this series, BTA798, currently in clinical trials for the rhinovirus common cold (Brown et al., 2005), remains to be tested for anti-poliovirus activity.

Capsid inhibitor SCH 47802, and its closely related analogue SCH 48973, originally being developed for NPEV infections, showed potent anti-poliovirus type 2 activity in cell culture, and when administered orally to mice, protected animals from poliovirus type 2-induced paralysis (Cox et al., 1996; Buontempo et al., 1997). Q2 These compounds have not been advanced to the clinic. However, one compound of the series, designated V-073, was found to have potent, broad-spectrum anti-poliovirus activity in cell culture (Table 2). Because of its good oral bioavailability, favorable pharmacokinetics, and safety profile in initial animal toxicology studies, V-073 is currently in preclinical development for polio indications (Collett, unpublished).

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Table 2
Anti-poliovirus activity of select compounds

Inhibitor class	Compound	Poliovirus activity (EC_{50}, μM)			Original indication (route of delivery)	Current Status
		PV1	PV2	PV3		
Replication	MRL 1237	5.3	4.6	3.8	Research	Research lead
	Enviroxime[a]	0.20	0.06	0.04	Rhino (oral/IN)	Discontinued at Phase 2
Capsid	Disoxaril[a]	1.8	0.10	0.10	NPEV (oral)	Discontinued at Phase 1
	Pleconaril[a]	10	1.1	0.22	Rhino/NPEV (oral)	In Phase 2 for rhino (IN)
	Pirodavir[a]	10	1.7	0.56	Rhino (IN)	Discontinued at Phase 2
	R75761[b]	0.03	0.003	0.02	Research	Research lead
	BTA188[c]	0.08	>4.6	>4.6	Rhino (oral)	Replaced by BTA798
	BTA798	nt	nt	nt	Rhino (oral)	In Phase 2 for rhino
	V-073[d]	0.02	0.05	0.02	NPEV (oral)	In preclinical for polio
3C Protease	Rupintrivir[a]	0.02	0.04	0.01	Rhino (IN)	Discontinued at Phase 2
	Compound 1[a]	0.26	0.31	0.06	Rhino (oral)	Discontinued at Phase 1

nt, not tested; IN, intranasal.
[a] DePalma et al. (2008).
[b] Thys et al. (in press).
[c] Barnard et al. (2004).
[d] Oberste et al. (in preparation).

5.2.1. 3C Protease inhibitors

The picornavirus 3C protease is responsible for processing of the viral polyprotein into mature viral proteins. Rupintrivir (also ruprintrivir), an intranasally administered, irreversible inhibitor of human rhinovirus 3C protease, exhibits potent, broad-spectrum anti-rhinovirus activity (Patick et al., 1999; Binford et al., 2005). Rupintrivir advanced to the clinic. In a natural infection study in patients, the compound failed to significantly affect virus reduction or moderate disease severity and thus was terminated for clinical development (Hayden et al., 2003b; Patick, 2006). A parallel effort to discover an orally bioavailable rhinovirus 3C protease inhibitor led to the identification of "Compound 1", which in humans was found to be safe and well tolerated at doses predicted to be sufficient for affecting virus replication (Patick et al., 2005). Currently, no further clinical development is planned for Compound 1. However, because of the conserved nature of the picornavirus 3C protein, both Compound 1 and rupintrivir were tested against the three Sabin strains and found to be potent inhibitors (Table 2). Compound 1, because of its good oral bioavailability, could in fact be a clinical candidate for the polio indication.

As the data provided in Table 1 indicate, there are a number of excellent starting points for development of an anti-poliovirus drug, from advanced preclinical candidates to compounds that have entered clinical development for other picornavirus indications.

5.3. Other antiviral drugs

Several nucleoside analogs known to be inhibitors of viral polymerases, including ribavirin, 2′-C-methylcytidine 5′-triphosphate, 2′-C-methyladenosine 5′-triphosphate, and 4′-azidocytidine, were tested recently for activity against the three poliovirus serotypes in cell culture (De Palma et al., 2008). Ribavirin and the 2′-C methyl nucleoside analogs showed weak activity, with EC_{50} values ranging from 50 to 60 μM for ribavirin, 3.9 and 29 μM for 2′-C-methylcytidine 5′-triphosphate and 2′-C-methyladenosine 5′-triphosphate, while 4′-azidocytidine was inactive. There remain numerous additional nucleoside analogs, some approved drugs and others in development, which should be evaluated for anti-poliovirus activity. Moreover, holders of nucleoside analog libraries are encouraged to test, or have tested, their compounds for activity against polioviruses.

Pallansch-Cokonis and Ptak (2008) have evaluated the anti-poliovirus activity of antiviral drugs currently approved for unrelated viruses. Drugs tested included eight HIV nucleoside reverse transcriptase inhibitors, three HIV non-nucleoside reverse transcriptase inhibitors, nine HIV protease inhibitors, six HIV fusion/entry/coreceptor inhibitors, two HIV integrase inhibitors, four herpesvirus inhibitors, one influenza neuraminidase inhibitor, and interferon alpha. While interferon had potent activity against poliovirus in cell culture, as previously demonstrated (Muñoz and Carrasco, 1984), none of the other antiviral drugs showed activity against poliovirus.

5.4. Inhibitors of cellular targets

An alternative strategy to the development of poliovirus-specific antiviral drugs proposes to target normal cellular proteins that act as key factors in virus replication. For example, brefeldin A, which on acts on the cellular secretory pathway, is a potent inhibitor of poliovirus replication in cell culture (Irurzun et al., 1992; Maynell et al., 1992). More recently, inhibitors of heat shock protein 90 (Hsp90), such as geldanamycin and 17AAG, have been found to inhibit the replication of picornaviruses, including poliovirus (Geller et al., 2007). Moreover, these Hsp90 inhibitors reduced poliovirus replication in infected animals. Hsp90 chaperone appears to be important to the picornavirus assembly process (Geller et al., 2007). While these results are intriguing, concern for toxic effects from disrupting normal cell functions remains. However, in situations of short-term treatment, these safety concerns might be lessened.

Targeting the inhibition of cellular components for antiviral effects, instead of viral proteins directly, might be expected to reduce the likelihood of drug resistance emergence. In the case of Hsp90, this indeed appears to be the case (Geller et al., 2007). However, the rapid evolution of viruses resistant to cellular target inhibitors has been observed in several other cases (Aberham et al., 1996; Murata et al., 2001; Crotty et al., 2004).

6. Drug resistance and polio antiviral drugs

Development of resistance is to be anticipated for any antiviral drug that specifically targets a viral protein. Virus populations exist as quasispecies. Drug resistance is observed upon use of the drug on an otherwise drug susceptible virus population, during which minor pre-existing virus variants less susceptible to the drug are allowed to emerge as drug susceptible viruses are eliminated. In

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the case of positive strand RNA viruses, the error frequency giving rise to these variants in a virus population is typically about 10^{-4} to 10^{-5}. This was the observed frequency of virus variants resistant to picornavirus capsid inhibitors (Ahmad et al., 1987; Heinz et al., 1989; Groarke and Pevear, 1999). For the 3C protease inhibitor rupintrivir, the genetic barrier to resistance appears higher (Binford et al., 2007). In the case of capsid inhibitor resistant virus variants, all isolates studied to date, whether selected in cell culture by virus propagation in the presence of drug or isolated as treatment emergent variants from patients, have been found to be attenuated, or less fit by various criteria, than their drug-susceptible counterparts (Yasin et al., 1990; Groarke and Pevear, 1999; Ledford et al., 2005).

While it appears that the amino acid changes necessary to confer resistance to picornavirus capsid inhibitors come at a fitness cost, this may not be the case for all inhibitors. For example, naturally occurring amantadine-resistant influenza viruses and those that emerge during treatment appear to be as fit as drug-susceptible viruses. On the other hand, treatment-emergent oseltamivir-resistant influenza virus variants generally have reduced infectivity and transmissibility in animal models when compared with drug susceptible virus (Aoki et al., 2007; Ong and Hayden, 2007). In order to ascertain the potential consequences of antiviral drug resistance, the biological characteristics of resistant virus variants must be fully understood for each candidate antiviral.

When discussing antiviral drug resistance in general, it is important to distinguish drug resistance in a situation in which the host immune system is chronically impaired by a persistent virus infection, such as is the case with HIV, from treatment-emergent resistance in acute, self-limiting virus infections that are naturally cleared by a normal unimpaired immune response, such as those caused by picornaviruses (polioviruses). In the antiviral treatment of HIV, drug resistant virus variants are able to propagate due in part to the relentless attack on the already compromised immune system. This is in stark contrast to picornavirus (poliovirus) infections and other acute self-limiting infections such as influenza, in which the use of antivirals serves to lessen the disease severity, shorten the duration of illness and reduce virus transmission, while the host immune response acts effectively to resolve the infection. Virus variants resistant to an antiviral drug emerge concurrently with a mounting host immune response to the infection. Drug resistant viruses are still susceptible to that immune response and consequently have little chance of surviving. In fact, in modeling studies of the dynamics of antiviral drug resistance that take into account the presence of a generally immunocompetent population, treatment-emergent drug resistance in the case of an acute, self-limiting infection is likely of little consequence (Wodarz and Lloyd, 2004). However, the B cell immunodeficient individuals persistently infected with poliovirus (iVDPV) are important exceptions to this scenario. In these cases, the use of a combination of two or more antiviral drugs that differ in their drug resistance profiles would improve the likelihood of preventing paralytic disease and eradicating virus from these patients.

7. Development of polio antiviral drugs: who, how long and how much?

As outlined above, there are several strong starting points for development of anti-poliovirus drugs. Compounds that already show some anti-poliovirus activity could serve as scaffolds for the development of more potent and selective inhibitors when entered into a poliovirus-specific optimization program. While research programs should be initiated, there are also late stage preclinical and early stage clinical drug candidates specific for poliovirus that should be advanced (e.g., V-073 and Compound 1, respectively).

Pharmaceutical and clinical development of a polio antiviral will require commitment by a drug developer. However, as there will likely be no commercial market for such a drug, there is scant interest from traditional pharmaceutical companies. The Task Force has proposed the establishment of a Polio Antiviral Initiative, structured as a public/private partnership, to provide the most efficient and least expensive means to develop antiviral drugs. The components and participants of such a partnership are under development.

Funding such an initiative presents another challenge. Financing by investors is unlikely since there will be little prospect of financial return on any investment. That means philanthropic individuals, organizations, and government agencies must become involved and come to understand the potential public health benefits of a polio drug, the feasibility of its development, and the actual costs involved. The NRC report estimated the cost of polio antiviral drug development from an IND to licensure to be $75 million over the course of 5 years and would include Phase 1 safety and pharmacokinetics studies involving normal human adult and pediatric volunteers, followed by efficacy-defining studies (NRC, 2006). If one considers the comparable development of a second antiviral, the overall costs would be in the range of $150 million.

To date, approximately $5.3 billion has been spent on the GPEI and it is estimated that about $2 billion more will be needed to finish the job (Polio Eradication, 2008b). Protecting this investment should be a global priority. Polio antiviral drugs represent an excellent cost-effective component to ensure a successful return on investment.

8. Closing comments

Polio eradication is within sight, but, like smallpox, the threat of polio will never go away. Protecting the estimated $7.3 billion, two-decade investment, and maintaining a polio-free world post-eradication, will depend on policies, defense strategies and emergency response capabilities available at the time of global eradication. These safeguards must defend against an accidental or deliberate re-introduction of the virus, and in the event of re-introduction, must be able to rapidly contain, control and eliminate the virus.

Use of antiviral drugs is a new concept to the polio field, which has so successfully used vaccination over the past 50 years to bring us where we are today. However, it is clear that finishing the job and maintaining a polio-free world will require more resources than are currently available for post-eradication outbreak control. In such a “vaccine-centric” field, it may be difficult to appreciate the potential of poliovirus drugs in the context of eradication and post-eradication defense. We hope that our discussion here has helped illuminate that potential. Polio antiviral drugs represent another tool for outbreak control used on their own and as adjuncts to vaccines. Admittedly, there are unknowns and uncertainties regarding the precise use of a polio drug. However, in the face of the numerous potential benefits that anti-poliovirus drugs could provide, these are insufficient rationale for not pursuing their development.

Polio antiviral development has a high probability of success. There are a number of excellent starting points that would allow drug development to occur within a relevant timeframe for a relatively modest financial commitment. Stakeholders must come to understand the potential public health benefits of polio drugs, the feasibility of their development, and the relatively modest costs involved. Given the timelines for eradication and those for drug development, the time for action is now.

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Conflict of interests

MSC is a principal in ViroDefense Inc. ViroDefense Inc, has been awarded a contract from the Task Force for Childhood Development and Survival to evaluate poliovirus antiviral candidate V-073, and is further participating in an NIAID program for provision of certain preclinical services. JN and JFM have no conflicts.

Uncited reference

Cox et al. (1986).

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