CHAPTER 8

CONCLUDING REMARKS

The genetic pattern of the poliovirus transmission is permitted by the rapid rate of mutation (Liu, Zheng et al. 2000; Shulman, Handsher et al. 2000), which has caused poliovirus to be one of the most rapidly evolving viruses known (Nottay, Kew et al. 1981; Gavrilin, Cherkasova et al. 2000; Liu, Zheng et al. 2000). The overall rate of virus evolution is determined by several factors, including the replication error rates, the virus population size and growth rate, the frequency of genetic bottlenecks and the mechanism of genetic exchange (Domingo and Holland 1997). Wimmer et al. has estimated error rates to be 10^4 to 10^5 per site per replication (Drake 1993; Wimmer, Hellen et al. 1993). Estimates of the rates of the total nucleotide substitution of which most are synonymous in the coding region accumulate at overall rate of approximately 10^{-2} substitution per site per year (Georgescu, Delpeyroux et al. 1995; Bellmunt, May et al. 1999; Gavrilin, Cherkasova et al. 2000; Kew, Morris-Glasgow et al. 2002; Jorba, Campagnoli et al. 2008). Evolution rates appear to be similar across all three poliovirus serotypes and between wild and vaccine-derived polioviruses. Many poliovirus clinical samples are recombinants (Cammack, Phillips et al. 1988; Kinnunen, Huovilainen et al. 1990; Liu, Zheng et al. 2000), and frequently heterotrophic recombinants are from trivalent OPV recipients (Georgescu, Delpeyroux et al. 1994). The recombination is most common in the 3D gene of the non-capsid region and less common in other regions (Georgescu, Delpeyroux et al. 1995). Molecular clock can be used to estimate the dates of the common ancestors to WPVs as in the case of Chapter 3 and VDPVs (Jorba, Campagnoli et al. 2008).

Rapid evolution appear to occur during replication in the human intestine and genomic evolution has help to facilitate molecular epidemiologic studies, permitting the identification of imported cases (Chiba, Murakami et al. 2000) and VDVPs (Gavrilin, Cherkasova et al. 2000; Cherkasova, Yakovenko et al. 2005) and to resolve different lineages during outbreaks (Shulman, Handsher et al. 2000; Shimizu, Thorley et al. 2004) as in the case of this study.

In an attempt to answer these questions, the molecular epidemiological characteristics of polioviruses associated with outbreaks of VDPVs, wild polioviruses and identification of suspected VAPPs in Africa after 2000 were investigated. This involved reporting of 1091 cases of wild polioviruses in 2005 in Africa, including 10 imported cases of India genotype to Angola, 13 cases identified in the DRC and 19 cases reported in Namibia (Chapter 2 and Chapter 3). In this study we have described the distribution and molecular epidemiology of wild-type 1 poliovirus SOAS genotype in southern Africa. The SOAS strains identified in Angola, the DRC and Namibia were unique to Africa and is estimated to have circulated at least since 2005 in Angola. Both the 2006 Namibia outbreak and the DRC outbreaks were caused by the SOAS genotype, but were introduced from neighbouring Angola most likely through frequent cross-border movement among population groups living on both sides of the border. So far the SOAS genotype appears to be limited in Africa to these three countries. Since 2006 no wild-type viruses have been reported in Namibia and it thus appears that the transmission of wild-type polioviruses had been effectively controlled by the subsequent mass vaccination campaigns. New polio cases have, however, been recently reported in both Angola and the DRC suggesting that poliovirus circulation in the other 2 countries may still be occurring.

The Angola outbreak was caused by a genotype previously identified in India, while the outbreaks from the Namibia most likely originating from Angola. This is the first time that AFP cases associated with the Indian genotype were identified in Africa. This emphasises the vulnerability of regions with suboptimal vaccination coverage for importation and reintroduction of wild-type polio virus from the remaining endemic countries.

In Madagascar (Chapter 4), analysis of all poliovirus strains confirmed cases of cVDPVs in 2001/2002 and 2005 and suggest that the molecular epidemiological characteristics of each outbreak were different. The circulation of cVDPV in Madagascar differs from previous cVDPV outbreaks in that it was caused by both type 2 and type 3. This is the second time that type 2 cVDPV had caused an outbreak in Madagascar, and to our knowledge the first time that a type 3 cVDPV has been identified through AFP in Madagascar. The additional finding of type 3 cVDPV further emphasizes the serious implications for the Global Polio Eradication Initiative for stopping immunization once eradication has been achieved. In Madagascar and other countries affected by cVDPV outbreaks, OPV coverage rates were particularly low and nearly all of the case patients and contacts were unimmunized or incompletely immunized children (Kew, Morris-Glasgow et al. 2002) (Rousset, Rakoto-Andrianarivelo et al. 2003).

Following the Madagascar cVDPV, the DRC reported 32 confirmed cVDPV cases (Chapter 5). This is the first time that type 2 cVDPVs were detected in the DRC. The occurrence of VDPV outbreaks during the same period with WPV emphasize the need to maintain high OPV coverage and AFP surveillance in order to minimize the risk of emergence of VDPVs or of circulation of imported WPVs.

To summarise, Chapter 4, 5 and 6 reported vaccine-derived polioviruses (having > 1% VP1 nucleotide sequence divergence from the Sabin parental strain) from Madagascar, the DRC and Ethiopia since 2005 until 2011. Failure to interrupt these outbreaks jeopardizes the most significant achievement of the Polio Eradication Initiative to date, the global interruption of transmission of wild serotype 2 viruses since 1999. In terms of virology, the VDPVs show reversion of mutations associated with attenuation of the Sabin virus, and transmission now represents uninterrupted circulation and evolution of the wild serotype 2 parental strain.

In Ethiopia two outbreaks of both cVDPVs type 2 and cVDPVs type 3 were in this study. The era of wild polioviruses is rapidly drawing to a close. In a short time it appears likely that the only source of poliovirus infection worldwide will be from OPV. Successful navigation from the current pre-eradication era to the imminent post-OPV era and beyond requires surmounting an unprecedented series of public health challenges. The first step is the elimination of the last reservoirs of wild poliovirus circulation. Soon thereafter, implementation of the post eradication endgame strategy can begin. Implementation of this crucial phase of polio eradication requires a more detailed assessment of the risks of VDPV emergence in various settings (especially those at highest risk); a clearer understanding of the biological properties of VDPVs; reinforcement of global poliovirus surveillance; development of effective means to clear long-term iVDPV infections; establishment of appropriately formulated, sized, and positioned OPV stockpiles; and completion of poliovirus containment worldwide. Moving forward will continue to require the best efforts of the global public health and scientific communities.

The cVDPV findings have important implications for the Global Polio Eradication Initiative and for future policies about OPV immunization (Kew, Morris-Glasgow et al. 2002; Rousset, Rakoto-Andrianarivelo et al. 2003) (Yang, Naguib et al. 2003). OPV has been very effective in decreasing poliomyelitis cases, however its concerns regarding collateral effects has been increasing in recent years due to identification of cVDPV.

In Chapter 7, 10 cases of possible VAPP and one suspicious case of possible VAPP were identified. Sabin-like cases described in this chapter had mutation at the 5' NTR at position 480, 481 and 472 for Sabin 1, Sabin 2 and Sabin 3 respectively. The VP1 gene revealed similar sequences to that of their respective Sabin reference strain (data not shown). Recombination with either CAV24 and other Sabin-like strains have been confirmed in some of the cases. Relationship between all cases indicates an intense co-circulation and a rapid co-evolution between OPV strain and indigenous CAV24. As in Chapter 4, this report emphasise the rapid evolution between polioviruses and CAV24 by multi recombination events.

What need to be done:

The molecular data collected in this study has helped in dealing with the outbreak identified during this study, but there is still a need of studies to be conducted to estimate the potential for VDPV to persist among immunodeficient persons in the developing world. Such studies should measure the prevalence and duration of chronic poliovirus excretion in children with recurrent infections.

It has not yet been determined how often recombination occurs in the Sabin-like viruses identified in areas with low vaccine coverage in countries where VDPVs have not yet been identified.

Knowledge of the frequency of these events may help to further plan strategies to prevent emerging VDPVs from causing renewed outbreaks after termination of the oral poliovirus vaccination program.

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