The Genetics of Polio Eradication

Olen Kew
Division of Viral Diseases
Centers for Disease Control–Atlanta

Overview

• Background, molecular epidemiology
• Eradication milestones
  – Genetic indicators of progress
• Current challenges
  – Countries with unbroken wild poliovirus (WPV) endemicity
  – Reinfection countries
• Vaccine-derived polioviruses (VDPVs)
  – cVDPVs
  – iVDPVs
**Poliovirus Genomic Organization**

- Single ORF, "polyprotein" proteolytically processed
- Single-stranded RNA genome (~7500 nt) has mRNA polarity
- Recombination between capsid/noncapsid regions
- VP1 gene (~900 nt) sequences used for molecular epidemiologic surveys; wider windows (up to complete genomes) for high-resolution analyses

**Epidemiologic Properties of Wild Polioviruses (WPVs)**

- Three serotypes: PV1, PV2, PV3
- Paralytic attack rate: PV1>PV3>PV2
  - PV1: ~1 case/200 naïve infections
  - PV2: ~1 case/1000 naïve infections
  - PV3: <1 case/1000 naïve infections
- Transmissibility: PV1>PV2, PV3
- "Natural" prevalence: PV1>PV3>PV2
Biological Properties of Sabin OPV Strains

- Stability of *attenuated* phenotype: PV1 > PV2, PV3
- Replicative fitness in gut: PV2 > PV1 > PV3
- Immunogenicity: PV2 >> PV1 > PV3
- Secondary Spread: PV2 > PV3 > PV1
- cVDPV emergence: PV2 >> PV1 > PV3
- iVDPV emergence: PV2 > PV1, PV3
- Eradication order (tOPV): PV2 → PV3 → PV1

Eradication Milestones

- Eradication of WPV2
- Certification of three WHO Regions (AMR, 1994; WPR, 2000; EUR, 2002)
  - Regional WPV certifications have stood test of time
- Eradication of indigenous WPV1 and WPV3 in very challenging settings:
  - Very high biological risk (Bangladesh, Egypt,…)
  - Conflict countries (Somalia [twice!], Angola, Sudan,…)
  - Poor infrastructure (most of sub-Saharan Africa, Yemen, Cambodia,…)
- Platform for other immunization initiatives
Polio Eradication Progress
Estimated and Reported Polio Cases, 1985–2009

1988: WHA Resolution to Eradicate Polio
1997: Last Case from Wild Type 2 Poliovirus Uttar Pradesh, India

2009 (YTD)
1337 cases
1051 - 4 “endemic” countries
296 - 23 reinfected countries

Certified polio-free
Continuously endemic
Reinfected

1988
350,000 cases
125 countries

~40 cases/hr

* Data as of 12 November 2009

Source: WHO/IVB database
192 WHO Member States.
Global Poliovirus Surveillance

- Rapid poliovirus screening methods used in WHO Global Polio LabNet
- All WPV and VDPV isolates sequenced (VP1)
- Phylogenetic trees/maps sent to WHO monthly
- Trees reflect current conditions (≤60 days after case)
- Phylogenetic analysis used to distinguish "source reservoirs" from non-reservoir "indicator communities"
- Sequence data used to drive eradication Program (target reservoirs) and identify surveillance gaps
Global Polio Laboratory Network, 2009

Genetic Indicators of Eradication

- Declining genetic diversity
- Disappearing genotypes (>15% nt divergence)
  - Genotypes distributed geographically
- Disappearing clusters (~5% nt divergence)
  - Clusters are geographically localized (spot-mapped)
- Disappearing lineages (=chains of transmission)
  - Surviving lineages stretch over increasingly wide geographic areas
  - Competing lineages gone
Eradiation of Wild Type 2 Genotypes

Eradication of Wild Type 2 Genotypes

Type 2 Wild Poliovirus Genotypes: 1979–1999

SOURCE: WHO POLIO LABNET
Eradication of Wild Type 3 Genotypes

SOURCE: WHO POLIO LABNET
Eradication of Wild Type 3 Genotypes

Eradication of WPV3 from Egypt, 1994–2000

VP1 Sequence Relationships
Poliovirus Molecular Clocks

- **Natural evolution rate:**
  - ~1%/yr; clocklike accumulation of nt substitutions (sub)
  - 1–2 sub/week (full genome)
  - ~1 sub/6 weeks (VP1; routine global PV surveillance)

- **Multiple molecular clocks (~30-fold "tick" range)**
  - **Fast clocks:** high-resolution molecular epidemiology
    - Dating recent importations, VDPV emergences
    - PV genomic evolution in individuals
  - **Slower clocks:** deeper evolutionary relationships
    - Dating older importations, VDPV emergences (>15 yr)

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**Poliovirus Capsid Region Molecular Clocks**

- **A:** Total Substitutions
- **B:** Synonymous Substitutions
- **C:** Nonsynonymous Substitutions
- **D:** Synonymous Transversions
- **E:** Synonymous Transitions
Challenges: Endemic Countries

- Four countries have never eradicated indigenous WPV genotypes
- Key reasons differ
  - **India**: very high biological risks, large birth cohorts, low OPV immunogenicity, migration
  - **Afghanistan**: Active conflict, insecurity, hard-to-reach populations
  - **Pakistan**: Conflict areas, epidemiologic linkage to Afghanistan, local operational gaps
  - **Nigeria**: low OPV coverage in northern states, political impediments, local operational gaps

Northern India

- Key reservoirs: Uttar Pradesh (UP) (~180 million), Bihar (~100 million)
  - UP + Bihar birth cohort: ~500,000/month
  - Lower per dose efficacy of OPV
- Hyperendemic in 1998 (WPV1, 2, 3)
  - Most clusters eradicated
  - Both UP and Bihar have stopped WPV1 transmission (migrants, ping-pong of WPV1)
- WPV3 reduced to four lineages in 2005
  - WPV3 expansion with emphasis on mOPV1
- Decreasing WPV1 genetic diversity
Wild Poliovirus, India, 2008–09

2008
- P1= 67
- P3=462

2009*
- P1= 75
- P3=484

Genetic Linkages, WPV1, 2008–2009*

WPV1 – 2008
WPV1 – 2009
WPV1 – Sewage 2008
WPV1 – Sewage 2009

*as of 26th Oct, 2009
Pakistan/Afghanistan

- Widespread WPV 1, 2, 3 circulation in 1998
  - Multiple clusters
- Most WPV1 and WPV3 clusters eradicated
- Active conflict, attacks on UN staff, facilities, vehicles (especially AFG)
- Residual endemicity in conflict areas (south and along shared border in north)
- Single epidemiologic block
  - Migrating populations carry WPV from endemic zones to polio-free communities
  - Gradual decline in WPV genetic diversity
WPV1 Pakistan/Afghanistan, 2008–09

- Wide “immunity gaps” in northern states
  - Poor routine immunization
  - Low OPV coverage in mass campaigns
- Indigenous polioviruses eradicated by 2003 from more populous (high-risk) south
- Widespread, continuous WPV1 and WPV3 circulation in north
  - Anti-OPV rumors
- Major WPV exportations
  - WPV1: 2003, north, west, east; 2008, north, west
  - WPV3: 2008, east
- Revitalized national commitment, 2009
- Biological risks only moderate: expanding WPV diversity can be stopped by good OPV coverage
Decreasing WPV1 Diversity
Nigeria, 2008–09

Challenges: Re-infected Countries

- Poor infrastructure (most)
- Ongoing or recent conflict (Chad, Sudan, Somalia, Angola, DR Congo, …)
- National immunization programs fragile
- Inattention to polio after first successful nationwide control
  - Widening immunity gaps
  - Surveillance gaps (“orphan” lineages)
- Adjoin endemic areas (Chad, Nepal, …)

- Wild virus type 1
- Wild virus type 3
- Wild virus type 1/3

* Excludes viruses detected from environmental surveillance and vaccine derived polioviruses

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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Nigerian WPV1 Moves West

Nigerian WPV3 Moves East
• Continued use of OPV carries continued risks
  – 250–500 cases of VAPP/yr worldwide
  – Excretion of virulent derivatives by many healthy OPV recipients
  – cVDPV outbreaks in areas with low coverage
  – Chronic iVDPV infections among a subpopulation of persons with defects in Ab production (primary immunodeficiencies)

• Polio eradication means cessation of all poliovirus circulation (infection)
Attenuating Substitutions in Sabin OPV Strains

0 1 2 3 4 5 6 7 kb

Circulating Vaccine-Derived Poliovirus Outbreaks, 1988–2009

SOURCE: WHO POLIO LABNET
Type 2 cVDPV Outbreaks, Nigeria, 2007–2009

Immunodeficiency-Associated Vaccine-Derived Poliovirus Isolates, 1962–2009

SOURCE: WHO POLIO LABNET
Summary

- WPV genotypes eradicated since 1985:
  - All WPV2 (4/4)
  - 82% of WPV3 (14/17)
  - 85% of WPV1 (17/20)
- Decreasing genetic diversity within most genotypes
  - Disappearing clusters and lineages
- Major challenges:
  - Operations in conflict areas
  - Widening immunity gaps in some polio-free countries
  - Continuing emergence of cVDPVs and iVDPVs
  - Developing/implementing safe endgame strategies

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Thank You!
Wild Virus Polio Cases by Serotype, 2001–2009

Countries Currently Using IPV in National Immunization Programs
### Routine OPV3 Coverage
**UNICEF/WHO Estimates, 2006**

- **≤50%**
- **51-79%**
- **≥80%**

*source: UNICEF/WHO, 2006 Global Summary*

### Potential Antiviral Compounds

<table>
<thead>
<tr>
<th>Inhibitor Class</th>
<th>Compound</th>
<th>Poliovirus Activity ($EC_{50}$, µM)</th>
<th>Original Indication (route of delivery)</th>
<th>Current Status</th>
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<td>Rhino (oral/IN)</td>
<td>Discontinued at Phase 2</td>
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<tr>
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<td>Discarene</td>
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*source: UNICEF/WHO, 2006 Global Summary*