Laboratory Containment of Poliovirus in the United States Phase II (Poliovirus Type 2)

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Outline

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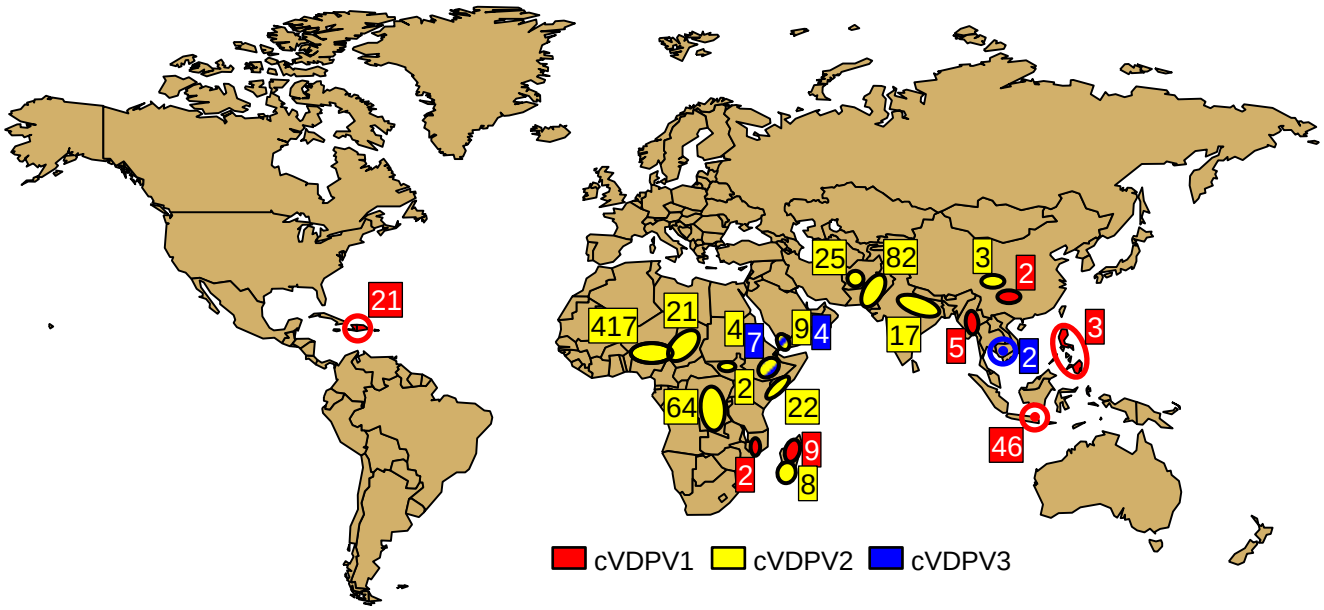
Last WPV Cases by Serotype

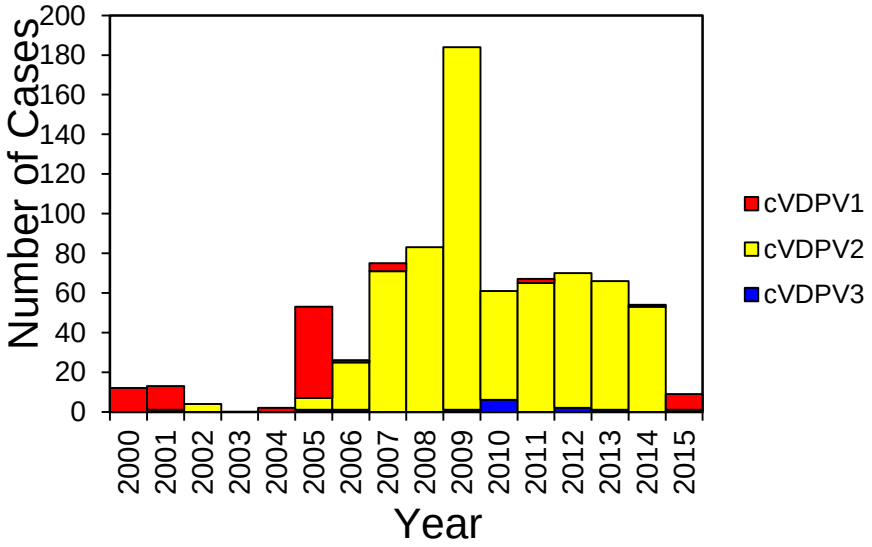
- USA
  - WPV2: before 1965 (indigenous)
  - WPV3: 1968 (indigenous)
  - WPV1: ~1970 (indigenous); 1979 (imported)
- Americas
  - WPV2: 1989, Peru (indigenous)
  - WPV3: 1990, Mexico (indigenous)
  - WPV1: 1991, Peru (indigenous)
- Global
  - WPV2: October 1999, India (indigenous)
  - WPV3: November 2012, Nigeria (indigenous)
  - WPV1: 22 December 2015, Pakistan (indigenous)

WPV2 and VDPV2 Cases and Infections

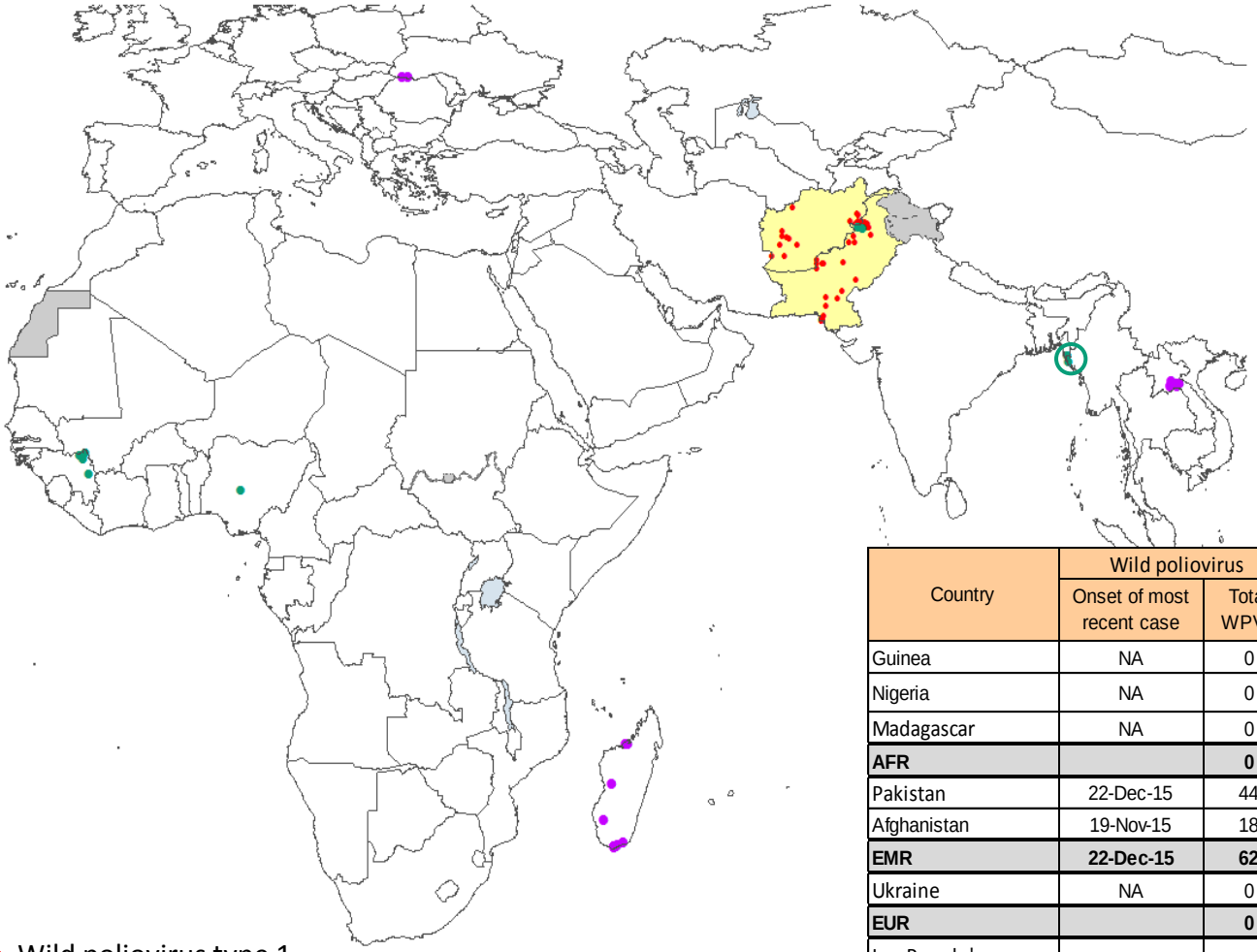
- Global Certification Commission certified WPV2 eradication on 20 September 2015
- VDPVs (vaccine-derived polioviruses) are genetically divergent phenotypic revertants of Sabin OPV strains ("feral" OPV viruses)
- VDPVs are phenotypically equivalent to WPVs
  - GAPIII Containment recognizes this equivalence
- Type 2 circulating VDPVs (cVDPV2) have repeatedly emerged since 2000
  - ~85% of cVDPVs are cVDPV2; ~95% since 2006
  - cVDPV2 has emerged and caused outbreaks in 24 countries
  - >1 M PV2 infections since 2000 from cVDPV2
- Type 2 immunodeficiency-associated VDPVs (iVDPV2) represent ~65% of total (n ~110) since 1961

cVDPVs, Worldwide, 2000–2015





Wild Poliovirus & cVDPV Cases[1], Previous 12 Months[2]



- Wild poliovirus type 1
- cVDPV type 1
- cVDPV type 2
- Endemic country

Country	Wild poliovirus		cVDPV	
	Onset of most recent case	Total WPV1	Onset of most recent case	Total cVDPV*
Guinea	NA	0	02-Oct-15	4
Nigeria	NA	0	16-May-15	1
Madagascar	NA	0	22-Aug-15	10
AFR		**0**	**02-Oct-15**	**15**
Pakistan	22-Dec-15	44	09-Feb-15	2
Afghanistan	19-Nov-15	18	NA	0
EMR	**22-Dec-15**	**62**	**09-Feb-15**	**2**
Ukraine	NA	0	07-Jul-15	2
EUR		**0**	**07-Jul-15**	**2**
Lao People's Democratic Republic	NA	0	18-Dec-15	7
WPR		**0**	**18-Dec-15**	**7**
Myanmar	NA	0	05-Oct-15	2
SEAR		**0**	**05-Oct-15**	**2**
Global	**22-Dec-15**	**62**	**18-Dec-15**	**28**

*cVDPV1 in Madagascar, Ukraine, Laos, cVDPV2 in all other countries.
NA: most recent case had onset of paralysis prior to rolling 12 months.

[1]Excludes viruses detected from environmental surveillance.
[2]Onset of paralysis 27 January 2015 – 26 January 2016

Data in WHO HQ as of 26 January 2016

Global Action Plan ("GAP III")

- WHO Global Action Plan to *minimize* poliovirus *facility-associated risk* after type-specific eradication of wild polioviruses and sequential cessation of OPV use
- Based on risk assessment and risk mitigation
- Endorsed by World Health Assembly, May 2015
- Survey/inventory of materials
- Type-specific, phased implementation
  - PV2 in 2016
  - PV1 and PV3 possibly as soon as 2019
- All "infectious" and "potentially infectious" poliovirus materials requested to be inventoried by end 2015
- Virus-specific: WPV/VDPV *vs.* OPV/Sabin
- Reduce number of facilities handling poliovirus to minimum

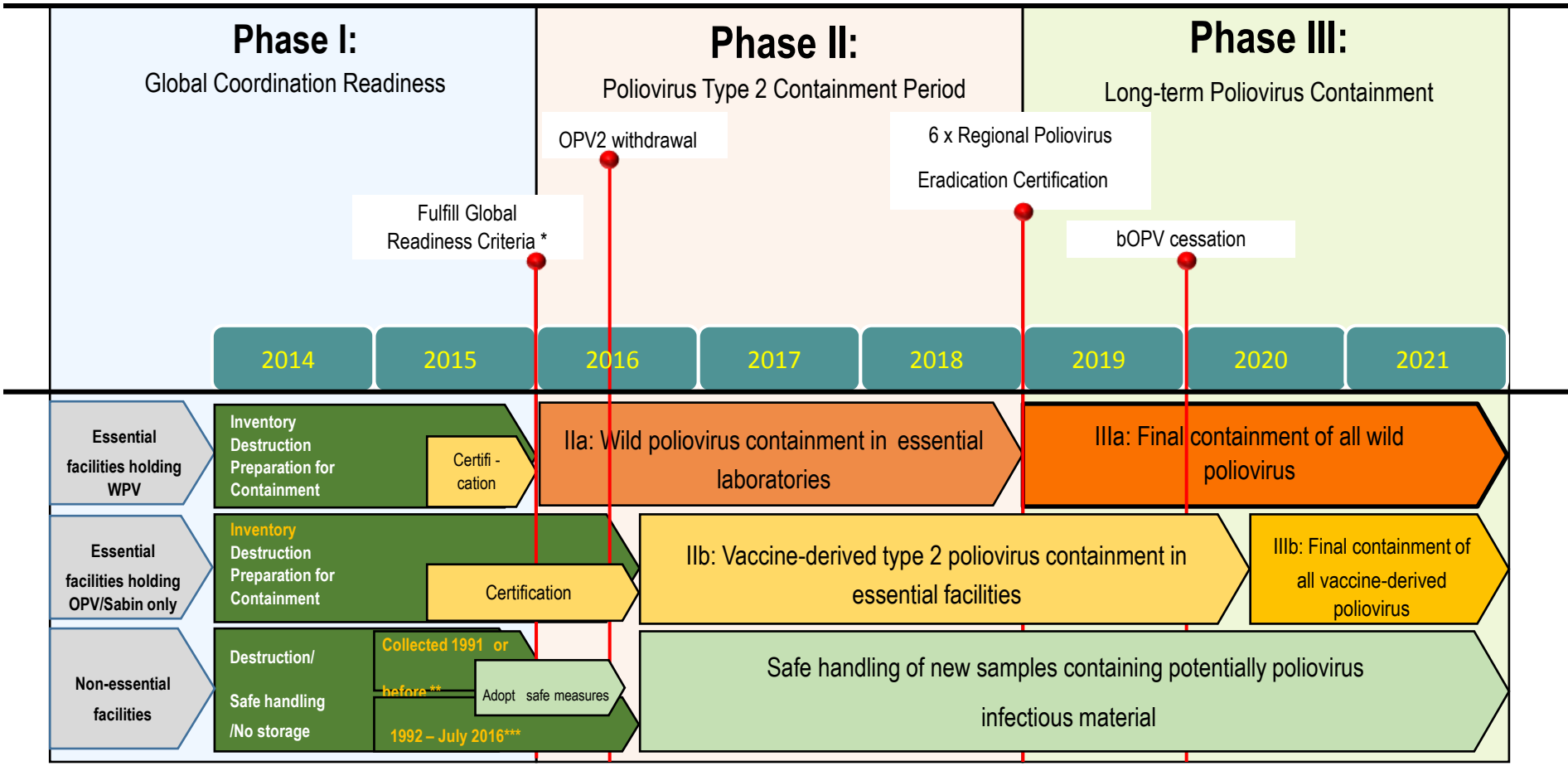

GAPIII

WHO global action plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of OPV use

http://www.polioeradication.org/Portals/0/Document/Resources/PostEradication/GAPIII_2014.pdf

Or *google* "gap iii polio"

Phases of GAPIII



- No containment
- Adoption of safe handling measures
- Containment of all WPV
- Final containment of all WPV

What Does “Containment” Mean?

- Destroy (and document): Autoclave, incinerate
- Transfer: To an “Essential” Laboratory Facility
- Contain: Become an “Essential” Laboratory Facility
  - Work with materials in appropriate containment space

Poliovirus "Infectious Materials"

- Presence of poliovirus confirmed and storage consistent with maintaining infectivity (stored at or below –20°C)
- Virus isolates identified as poliovirus by
  - Antigenic typing
  - Nucleic acid hybridization
  - rRT-PCR
  - Sequencing
- Specimens from person known to be infected
  - Example: stool from which a poliovirus isolate was obtained
- Specimens from infected experimental animals
  - Non-human primates
  - PVR-Transgenic mice

Poliovirus "Potentially Infectious Materials"

- Presence of poliovirus unknown but collected in a *place and time* where WPV or cVDPV was circulating or OPV was used
- Storage consistent with maintaining infectivity (stored at or below –20°C or stored for less than one year at +4°C)
- Includes fecal specimens, sewage samples, or respiratory samples, extracted nucleic acid
- Working on risk assessment/management/mitigation language to minimize disruption in non-polio labs, especially for respiratory samples and extracted nucleic acid, which should be low risk

Containment applies to *all* laboratories, not just polio labs

(and not just virology/microbiology labs)

Why PV2 Containment Now? The tOPV to bOPV Switch; April 2016 (1)

- Continued use of tOPV (types 1, 2, and 3) has become inconsistent with polio eradication
- The GPEI increased use of bivalent OPV (types 1 and 3) to reduce interference by OPV2
  - Focused on eradication of WPV1 and WPV3
  - tOPV primarily used in routine immunization
  - Routine immunization rates remain low in many settings
  - tOPV campaigns became less frequent
  - cVDPV2 emergences became increasingly frequent
- Synchronized global tOPV to bOPV switch scheduled for April 2016 in countries using OPV
- At least one dose of IPV shall be used worldwide to maintain immunity to PV2
- No tOPV shall be given anywhere after April 2016

Why PV2 Containment Now? The tOPV to bOPV Switch; April 2016 (2)

- Excretion of OPV-related viruses expected to continue for ~3 months (until end-July 2016)
- Very little OPV2-related virus should be detected thereafter
- Apart from prolonged VDPV2 excretors, the main source of PV2 for reintroduction into the community would be the laboratory and vaccine manufacturers
- Similar considerations apply after total OPV cessation
- GAPIII addresses risks from WPV, VDPV, and OPV
- PV2 is top priority
  - Survey covers all three serotypes; sets stage for full Containment
  - Infectious materials can be identified by serotype
  - Potentially infectious, especially for OPV/Sabin, usually not identifiable by serotype
- GAPIII remains a work in progress

Critical Role of US in Global Containment

- 2002–03 US survey and subsequent global surveys found that 34% of all facilities storing WPV infectious or potentially infectious materials were in US
- CDC: Largest WHO Global Polio Reference Laboratory
- Many leading poliovirus research laboratories in US
- No poliovaccine production; ongoing vaccine testing
- Risks of poliovirus spread from US facilities low
  - High IPV coverage rates
  - Good sanitation/hygiene
  - But risk is not zero!
- Risk is much higher in developing country settings
  - cVDPV outbreaks underscore ongoing risk
- US must take leading role in implementing poliovirus Containment

What DHHS is Doing Now for Containment (1)

- Established Office of National Poliovirus Containment Coordinator (NPCC), September 2015
  - Based at CDC; logistical support primarily by CDC
  - Reports to NCC, through Office of Assistant Secretary for Health (OASH), through National Vaccine Program Office (NVPO)
- NPCC responsible for 2015–16 US National Survey
- NPCC Office includes
  - NPCC: Dr. Olen Kew, Technical POC, named 25 September 2015
  - National Poliovirus Containment Program Manager
  - Data Manager
- CDC Epidemiologist: Supported launch of surveys and coordinates with Programmer
- CDC-based Programmer: Set up and support web-based survey and data entry system

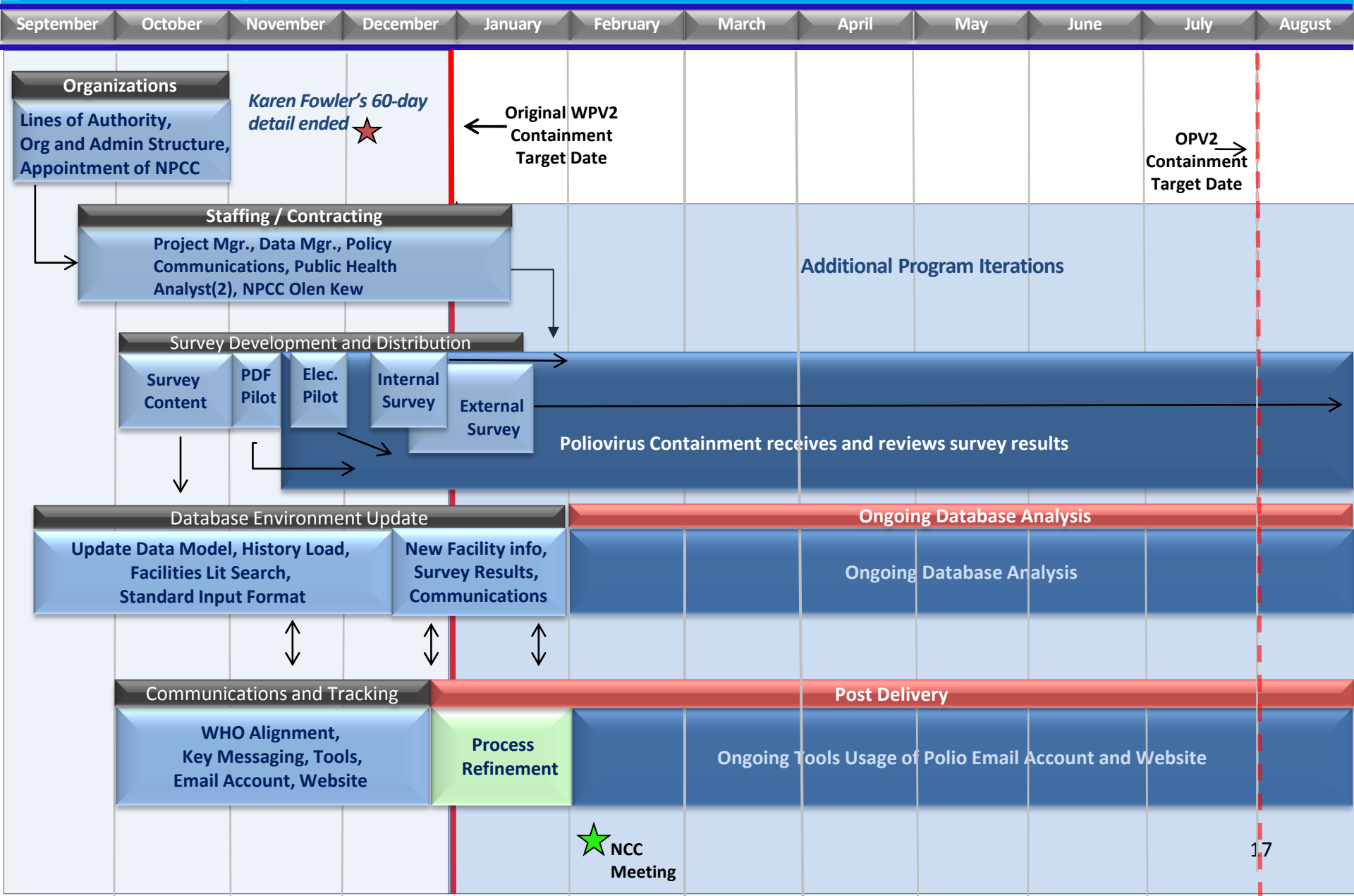
What DHHS is Doing Now for Containment (2)

- NVPO (Dr. Bruce Gellin) co-signed with NPCC a letter to Secretaries of key US Government Departments requesting support for Containment
- CDC developed a web-based survey instrument modified from WHO/PAHO template
- Two slightly different survey instruments were distributed
  - Internal CDC survey
    - Sent to 149 laboratories on 14 December 2015; requested return by 31 December 2015
  - External survey
    - Sent to 109 laboratories on 22 December 2016; requested return by 12 January 2016
    - Sent to Federal, academic, industrial, state and local government, and hospitals
    - Top-tier labs identified by results of 2002–03 survey
    - Very highest-tier labs known to have recently stored WPV2 were contacted directly by email and phone in addition to deployment of survey

U.S. Poliovirus Containment Program

2015 2016

As of: January 26, 2016



US NPCC Approach to Containment (1)

- Distribution of survey was prioritized by estimated risk
  - WPV2/VDPV2 infectious materials to be contained first
  - WHO target date of 31 December 2015 not achievable
  - Requested return ASAP from top-tier labs
  - Sent request directly to Laboratory Directors
    - Personal letters/emails to close colleagues
  - Facilities storing WPV2/VDPV2 potentially infectious materials will be second priority
- OPV2-related materials to be contained before 1 August 2016
  - Facilities storing OPV2/Sabin 2 infectious materials are third priority
  - Facilities storing OPV/Sabin potentially infectious materials will be fourth priority
- Priority categories will overlap in many facilities
  - Opportunity to contain all PV and be removed from list
- Potentially infectious materials will be prioritized by risk
  - Highest risk assigned to stool material, sewage

US NPCC Approach to Containment (2)

- Surveys will be launched in successive waves prioritizing from highest to lowest estimated risks
- Containment is an ongoing process
  - Immediate goal: PV2 Containment in 2016
  - Overall goal: All poliovirus containment (~2019)
- Analysis of results from internal CDC survey (especially) and first round of external survey will guide priorities for subsequent survey rounds
  - What other external laboratories should be contacted?
- Will take a collaborative approach as described in Introduction to GAPIII
  - Will continue to work with Laboratory Directors
- Will request assistance of Institutional Biosafety Office Directors for further follow-up
- May request additional high-level OASH/DHHS assistance as needed

Structure of 2015 Electronic Surveys

- Modular Organization
  - A. General Information
    - Institution, lab, who filled out the survey, capacity to store samples
  - B. Type of Stored Samples or Specimens
    - Specimen types, whether from place/year of interest
  - C. Specification and Inventory Information
    - Infectious and potentially infectious materials, estimated number
  - D. Disposition of Materials
    - Decision to destroy, inactivate, or transfer
  - E. Attestation Statement
  - Appendix A: Countries/years of last WPV, by type, and last use of tOPV
  - Appendix B: Definitions

Internal CDC Survey (1)

- CDC is the largest facility storing poliovirus infectious and potentially infectious materials
- Containment receives strong institutional support
- The Polio and Picornavirus Laboratory Branch (PPLB) within the Division of Viral Diseases is the major WHO Global Polio Reference Laboratory
  - Contains the largest poliovirus collection in the world, including
    - WPV2 isolates dating from the 1950s to 1999
    - cVDPV2 isolates through 2015
    - OPV2-related isolates to present
    - Poliovirus-infectious and potentially infectious materials from the US and abroad
- Other CDC laboratories store poliovirus potentially infectious materials
  - Historical US specimens; international specimens up to present
- 140 of 149 laboratories (94%) completed the survey by 28 January 2016

Internal CDC Survey (2)

- Only laboratories within the Polio and Picornavirus Laboratory Branch (PPLB) reported retaining WPV2/VDPV2 infectious materials
- Only PPLB and the CDC Viral Gastroenteritis Laboratory reported storing OPV2/Sabin 2 infectious materials
- Nine (9) laboratories reported storing WPV2 potentially infectious materials
  - Laboratories handling enteric specimens
    - PPLB
    - Gastroenteritis and Respiratory Virus Laboratory Branch
  - Laboratories handling respiratory specimens
    - Measles, Mumps, Rubella, and Herpesvirus Laboratory Branch
    - Influenza Division Laboratories
    - Bacterial Meningitis and Vaccine-Preventable Diseases Branch
- Ten (10) of these laboratories (except Bacterial Meningitis) reported storing OPV/Sabin potentially infectious materials

CDC Polio Lab (PPLB) Compliance

- All WPV2/VDPV2 were moved to a BSL-3 containment laboratory
- The laboratory is in compliance with GAPIII guidelines
- Vials retained by Polio Molecular Epidemiology Team
  - 2664 VDPV2 and OPV2/Sabin 2 from environmental samples
  - 2358 WPV2 and VDPV2 isolates from AFP cases
  - 56 VDPV2 transfected cells
- Vials retained by Polio Vaccine Development Team
  - 1857 WPV2 (primarily MEF-1 and derivatives; some VDPV2)
- 178,615 vials were autoclaved by 31 December 2015
  - NPEVs
  - OPV1, 2, and 3
  - Potentially infectious negative stool specimens
  - Specimens for years 1955-2007; will complete by April 2016

External US Survey

- CDC sent surveys to Directors of 109 top-tier external laboratories identified in 2002–03 survey
- Timeline of CDC external survey
  - Launch: 22 December 2015
  - Requested due date: 12 January 2016
- 37 of 109 (34%) external laboratories have completed the survey as of 28 January 2016
- Among the 37 external laboratories that completed the survey by 28 January 2016
- Six (6) report storing WPV2 infectious materials
  - Academic: 3
  - Government Public Health: 1
  - Industrial: 1
  - Biomedical research: 1
- Four (4) report storing OPV2/Sabin2 infectious materials

"Essential" *vs.* "Non-Essential" Facilities

- Essential: It is essential that facility retains live poliovirus materials
  - Vaccine (IPV and OPV) manufacturers
  - Vaccine testing laboratories (QC, serologic studies)
  - Key reference laboratories
  - Key laboratories performing essential research to directly inform endgame and post-eradication decision-making
- Non-essential: It is *not* essential that facility retains live poliovirus materials
- Diagnostic labs—can perform diagnostics regardless of specimen source
  - Global Polio Laboratory Network (GPLN) will continue routine diagnostic work under BSL-2 conditions
  - Detection of OPV viruses or VDPV implies presence in community; laboratory does not contribute significant additional risk
  - GPLN continues shift to all-molecular detection methods

Technical Requirements for Containment in Essential Facilities

- Biorisk Management
- Poliovirus inventory and information
- General safety
- Personnel and competency
- Good microbiological technique
- Clothing and personal protective equipment
- Human factors
- Healthcare
- Emergency response and contingency planning
- Accident/incident investigation
- Facility physical requirements
- Certification
- Decontamination, disinfection, and sterilization
- Transport procedures
- Security
- Certification

Lessons Learned

- Mid-December is not the best time to launch a survey due by the end of the year!
- High response rate at CDC result of strong institutional support
- Importance of regular follow-up
- Absence of statutory authority could limit compliance outside of Federal Government facilities
- Legitimate concerns by non-polio laboratories (laboratories handling and storing enteric and respiratory specimens) must be addressed by WHO, PAHO, and NPCC
- Effective engagement with lab directors, clear communication of overarching goals, and collaborative problem-solving are essential
- Many non-polio labs remain unaware of Containment
- Containment taps reservoir of good will toward polio eradication
- Awareness, a major objective of Containment, coupled with good microbiological practice, can mitigate risks
- Poor specimen records in many labs impede survey completion

Challenges (1)

- GAPIII is defined as an evolving document
- Some interpretations at WHO/HQ of GAPIII requirements and processes are far too prescriptive
- High-risk infectious materials and low-risk potentially infectious materials (such as respiratory specimens, nucleic acids) are grouped together for strict Containment
- Overly strict interpretation of GAPIII will impede compliance
- WHO is aware of these challenges and will empanel an expert Technical Advisory Group to help guide way forward
- Once clear, achievable guidelines are established for potentially infectious materials, we can contact Institutional Biosafety Office Directors for further assistance
- Process for issuing Certificates of Participation incompletely defined

Challenges (2)

- Potentially infectious materials, especially of OPV/Sabin variety, present challenges for outreach
- Respiratory virology/microbiology labs have particular concerns about how poliovirus Containment might adversely impact their vital work
- Academic labs, with frequent student turnover, present special challenges to specimen management and containment
- Absolute poliovirus containment is not feasible
  - Undetected iVDPV excretion is likely to continue for some time
  - Poliovirus can be easily prepared by synthetic biology
    - GenBank sequence data exists in perpetuity
- The goal is major reduction of risk, which is feasible, if colleagues are constructively engaged

Next Steps for US External Survey

- Follow up on first-wave external surveys
- Internal CDC survey and results from top-tier labs will cover the large majority of labs thought to store WPV2/VDPV2
  - Containment of these viruses will sharply reduce PV2 risk
- Analysis of results from internal CDC survey (especially) and first round of external survey will guide priorities for subsequent survey rounds
- Launch successive survey waves, prioritizing from highest to lowest estimated risks
- Challenge: Potentially infectious materials
  - Non-poliovirus labs, non-virus labs are *not* generally aware of poliovirus containment
  - Many store potentially infectious materials
  - Enteric virology/microbiology labs would have the next highest-risk specimens
  - Respiratory specimens carry much lower risk

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- CDC/Center for Global Health/Global Immunization Division
- National Vaccine Program Office
- Task Force for Global Health