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Supporting Risk-Based Decision-Making to Minimize Facility-Associated Re-Introduction of Poliovirus: Phase I

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ABSTRACT

Sandia National Laboratories and Gryphon Scientific, as supported and directed by the CDC Center for Preparedness and Response (CPR), studied the process of risk assessment and risk-based decision-making in facilities expected to continue possessing poliovirus strains. The first phase of the study was conducted in anticipation of developing a tool to support decision-making processes for poliovirus containment to minimize the risk of facility-associated re-introduction of poliovirus.

The study results supported the starting assumption that risk management of poliovirus will be aided by more rigorous and consistent risk assessment and that experience-based risk assessment is, by itself, inadequate to understand risk in a post-eradication world. These results were derived from review of poliovirus literature, oversight documents, current and expected practices, and from discussions with affected facilities. Based on these results and on additional discussions with facilities, the study team recommends development of a quantitative risk assessment tool as well as improving access to and the quality of data for informing risk-based decision-making.

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EXECUTIVE SUMMARY

Under the direction of the U.S. Centers for Disease Control and Prevention Center for Preparedness and Response (CDC-CPR), Sandia National Laboratories and Gryphon Scientific are studying the process of assessing poliovirus risk and choosing risk-reducing measures in anticipation of developing a tool to support risk management for poliovirus containment activities to meet the requirements of the WHO Global Action Plan[1] (GAP III). This tool would be intended to aid facilities working with poliovirus and poliovirus-containing material, including research, public health, and diagnostic laboratories, and vaccine production facilities, in conducting assessments to identify and mitigate biorisks presented by polioviruses. This tool could also benefit country-specific (i.e., national authorities on containment (NACs)) and international authorities by providing a common approach and vocabulary to discuss risk assessment and risk-based decision making for those involved in global eradication activities. While Phase I of this study focused on U.S. facilities, the applicability of this work is, without doubt, global and the intent for further phases is to assure alignment and relevance for the global community.

We started with the assumption that risk management of poliovirus will be aided by more rigorous and consistent risk assessment and risk-based decision-making. Moreover, we posit that current experience-based risk assessment is, by itself, inadequate to understand risk in a post-eradication world. We envision supporting and improving poliovirus risk assessment capacity via a quantitative risk-based decision-making tool.

Methods

We sought to understand both the context within which poliovirus facilities evaluate and respond to risks, as well as the information and oversight guidance available to inform these efforts. This included:

- Review and annotation of over 150 papers relevant to poliovirus public health, safety and risk, dating between 1940 and 2018;
- Detailed review of the World Health Organization's Global Action Plan (WHO GAPIII) and GAPIII-derived guidance for references to and expectation for risk assessment and facility-based risk assessment;
- Cataloging example practices that can, in professional judgement and conversations with facilities, be expected to contribute to reduce the risk of facility-associated re-introduction of virus;
- Discussions with seven U.S. facilities housing (or considering housing) poliovirus type 2 (including research, public health, and diagnostic laboratories; and a candidate vaccine production facility) about their risk assessment and risk-reducing practices, as well as about their opinions regarding the benefit and necessary functions of a risk assessment tool.

Using these inputs, we evaluated:

1) the current process(es) used for risk assessment and risk mitigation decisions,

2) the level and nature of risk assessment and risk-based decision-making required by oversight bodies,

[1] WHO Global Action Plan to minimize facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of oral polio vaccine use – GAPIII

3) the nature and quality of information currently available for input and guidance in risk-based decision-making, and

4) the utility of and requirements for a more robust risk assessment tool designed to further improve and standardize risk mitigation in these laboratories.

Conclusions

In brief, we found that:

- The WHO and others have identified incidents with highest potential for facility-associated re-introduction of virus into the community as: 1) (asymptomatic) infection and shedding from an exposed worker and 2) release of poliovirus beyond the laboratory boundary (Dowdle & Wolff, Post-eradication poliovirus facility-associated community risks, 2006) (Dowdle, et al., 2006) (Dowdle W. R., Wolff, Sanders, Lambert, & Best, 2004).
- Due to widespread vaccination and the potential for silent infection among those vaccinated, the current frequency of facility-acquired infections is unknowable. The silent nature of laboratory-acquired infections will likely skew experience-based perception of poliovirus, possibly leading to underestimates of risk.
- GAPIII and GAPIII-derived guidance, by design, rely heavily on facilities to make their own decisions on risk and risk management.
    - Facility-specific risk assessment is prescribed by GAPIII in over 40 unique instances across nearly all functional areas of poliovirus risk management.
    - More detailed guidance such as that provided by the WHO Containment Advisory Group makes explicit reference and deference to facility-specific risk assessment to define risk-based decision-making around control measures.
- Limited poliovirus-specific information to help facilities choose best practices is provided by GAPIII, GAPIII-derived guidance, or the literature:
    - In a review of over 150 papers relevant to poliovirus public health, safety and risk, the majority addressed public health aspects of poliovirus (vaccination, eradication, diagnostics) while fewer provided information relevant or specific to facility containment.
    - Oversight documents, such as GAPIII, outline the biorisk management system to implement but, by design, do not specify more detailed procedures to control facility-associated risks.
- Risk-based decision-making at facilities varies in content, contributors, and rigor. All processes observed were experience-based.
- All facilities agreed that a more robust, consistent risk assessment approach could supplement and benefit existing risk-based decision-making. Facilities thought it likely that previously unknown factors and pathways contributing to risk might be identified through a more standardized methodology.
- Facilities are willing partners in maintaining eradication; however, their capacity to meet GAPIII facility infrastructure requirements is limited. In addition, facilities expressed the view that evolving oversight is confusing and can be frustrating.
- A more robust and standardized approach to risk-based decision-making should:

- Provide a baseline standard for risk assessment and risk-based decision-making quality across poliovirus facilities.
- Reduce the burden on facilities for conducting good risk assessments.
- Address weaknesses in experience-based risk assessments, especially for a projected future that no one has yet experienced.
- Identify previously unrecognized risk factors that could lead to loss of containment.
- Allow facility-specific calculations while using pre-populated and consistent data sources to drive those calculations.
- Enable the assessment of emergency scenarios identified in GAPIII.
- Integrate into existing risk-based decision-making processes.
- Compare risks from facility-associated reintroduction with those of vaccination, long-term shedders, and unrecognized PIM.
- Allow anonymous data sharing to inform best practices and ongoing guidance from oversight bodies.

Recommendations

Recommendation 1. Regardless of whether tool development is undertaken (Recommendation 2), **improving quality of and access to data** to inform facility-specific risk-based decision-making will benefit poliovirus containment efforts. Options include, but are not limited to:

- Development, in collaboration with poliovirus experts, of data sources on poliovirus properties and poliovirus manipulations that influence risk to provide consistent data agreed upon by the community.
- Identifying, consolidating and cataloging practices according to their (experience-based) potential for risk reduction to aggregate the options available.
- Identifying gaps in guidance available on risk-reducing practices and developing new guidance to fill those gaps.

Recommendation 2. **Develop a quantitative risk-based decision-making tool** using four phases before deployment.

- Step I: Data collection. Significant granular data is necessary to inform quantitative risk calculations. These data will come from additional literature review and stakeholder re-engagement from poliovirus-specific work, the life sciences, and other industries, as needed, and significantly reduce the amount of time that tool users need to enter data by "front loading" site-independent data.
- Step IIA: Model development. The study team will select and build the model(s) most aligned with available inputs and desired outputs. Step IIA will occur concurrently with Phase IIB so that the model and interface will be aligned.
- Step IIB: User Interface development. Concurrently with Step IIA, a visual display of model outputs will be designed for ease of understanding and manipulation. We will convene a small stakeholder focus group from which to gather feedback on usability of the interface.

- Step III: Piloting. Once the model is developed and populated, a user group(s) will test the prototype tool. In addition to piloting the tool and determining usefulness to stakeholders, method(s) for training on how to use the tool will be tested and evaluated. Feedback will be used to fine-tune the tool and prepare it for more widespread deployment.

Summary

Eradication of poliovirus will be one of mankind's most important and significant public health achievements. However, facility-associated community re-introduction could jeopardize eradication efforts and result in a public health emergency. To assure appropriate containment, effective facility-specific risk assessment is essential. Relying, however, on experience-based risk assessment in a world (post-eradication) that no one has yet experienced limits the value of the risk assessment and could result in misguided mitigation efforts. Overcoming this challenge and improving risk-based decision making could be accomplished through two parallel efforts: (1) improving the access to and quality of data to inform risk assessments (of any type, experiential or otherwise), and (2) developing a quantitative tool to help standardize risk assessments and improve risk assessment rigor and sophistication.

ACRONYMS AND DEFINITIONS

Abbreviation	Definition
BSC	Biological safety cabinet
$CCID_{50}$	Cell culture infections dose 50%
CDC	United States Centers for Disease Control and Prevention
CEN	European Committee for Standardization
CWA	CEN Workshop Agreement
GAP	Global Action Plan
GPEI	Global Poliovirus Eradication Initiative
IPV	Inactivated polio vaccine
µm	Micrometer
OPV	Oral polio vaccine
PEF	Poliovirus Essential Facility
PIM	Potential poliovirus infected material
PPE	Personal Protective Equipment
PV	Poliovirus
SOP	Standard Operating Procedure
VAPP	Vaccine-associated paralytic poliomyelitis
VDPV	Vaccine-derived poliovirus
RA	Risk Assessment
WHO	World Health Organization
WPV	Wild poliovirus

1. INTRODUCTION

1.1. Study Purpose and Activities

Under the direction of the U.S. Centers for Disease Control and Prevention Center for Preparedness and Response (CDC-CPR), Sandia National Laboratories and Gryphon Scientific are studying the process of assessing poliovirus risk and choosing risk-reducing measures in anticipation of developing a tool to support risk management for poliovirus containment activities to meet the requirements of the WHO Global Action Plan[1] (GAP III). This tool would be intended to aid facilities working with poliovirus and poliovirus-containing material, including research, public health, and diagnostic laboratories, and vaccine production facilities, in conducting assessments to identify and mitigate biorisks presented by polioviruses. This tool could also benefit country-specific (i.e., national authorities on containment (NACs)) and international authorities by providing a common approach and vocabulary to discuss risk assessment and risk-based decision making for those involved in global eradication activities. While Phase I of this study focused on U.S. facilities, the applicability of this work is, without doubt, global and the intent for further phases is to assure alignment and relevance for the global community.

As proposed, the tool would:

1. take site-specific inputs entered by each facility, such as the control measures and PPE used in laboratories, the types of experiments conducted, their frequencies, and the virus concentrations and volumes used;
2. utilize an evidence-based, quantitative model of the risks posed by experiments, procedures, human practices, equipment and loss-of-containment scenarios to identify the areas of highest risk in each facility and, thus, those requiring prioritized risk mitigation;
3. utilize the quantitative model to calculate a ranked-ordered list of the riskiest accidents and scenarios a facility may face based on the specifics of each facility, and the relative risk of each one; and
4. enable users to add or subtract different experimental procedures and control measures to see how each one affects overall risk.

Figure 1 outlines the planned steps of the project before release of the tool to stakeholders. This report presents outcomes and analysis from the first three steps (Phase I).

Figure 1. Planned Steps for Poliovirus Risk Assessment Project

For Phase I , we sought to understand the context within which poliovirus is manipulated in facilities in the U.S. and the methods used to assess risk and make risk-based decisions for to minimize risk. Our activities included:

1. Compiling and annotating literature relevant to poliovirus survival in the environment; infection; disinfection; transmission; epidemiology; surveillance; diagnostics; eradication efforts; vaccines; and laboratory exposure, contamination, and containment. Additional data needed by the model will be gathered in future steps.
2. Reviewing current national and international poliovirus containment guidance and activities relevant to risk assessment and risk management,
3. Interviewing staff and visiting poliovirus facilities to ensure the planned tool will meet real-life requirements and use scenarios, which included the following::
    a. Gathering basic data on the types of experiments conducted.
    b. Identifying current practices and controls used in poliovirus facilities.
    c. Soliciting input for how facilities might use a tool to help make risk-based decisions for containing poliovirus.
4. Analyzing the above activities to determine the focus and scope of risk assessment and risk-based decision making approaches still needed to aid poliovirus facilities to reduce the risk of facility-associated reintroduction of virus.
5. Cataloging options for processes and practices to minimize the risk of facility-associated introduction of virus into the community.

6. Analyzing inputs on risk assessment and risk-based decision-making as they are relevant to the development and deployment of a software-based tool.

7. With the context from the data collection and analysis above, suggesting recommendations that might benefit risk-based decision-making by poliovirus facilities, as well as national and international authorities.

1.2. Structure of this Report

This is an interim report, providing highlights of Phase I activities, but more importantly, providing recommended next steps for the remaining phases of the proposed project. The report follows a structure moving from 1) context to 2) analysis, followed by 3) recommendations.

First, we provide background on the current and future environment in which work with poliovirus will occur, to provide context for the analysis and recommendations that follow. (Sections 2 through 4) Section 5 of the report focuses on our results: 1) analysis of gaps in information critical for risk assessment and risk management of poliovirus, and 2) requirements and inputs for the envisioned risk management tool. Section 6 provides conclusions and recommendations.

2. POLIOVIRUS & GLOBAL POLIO ERADICATION

2.1. Poliomyelitis & Poliovirus

Polio, or poliomyelitis, is a crippling and potentially deadly infectious disease [4]. The causative agent of poliomyelitis, poliomyelitis virus, was identified in 1908. The virus spreads from person to person and can invade an infected person's brain and spinal cord, causing paralysis. Poliovirus is classified as an enterovirus within the *Picornaviridae*. All three serotypes, 1, 2, and 3, of poliovirus can cause paralytic disease [5].

Poliovirus only infects humans and spreads through person-to-person contact. Infection begins when the virus is ingested and multiples in the throat and intestines [5] and can be transmitted by contact with the feces of an infected person and, sometimes, through droplets from a sneeze or cough.

Up to about 70% of people who get infected with poliovirus will not have any visible symptoms. Most symptomatic poliovirus infections cause flu-like symptoms (e.g., sore throat, fever, tiredness, nausea, etc.). These symptoms usually last 2 to 5 days then go away on their own. However, people who don't have symptoms can still pass the virus to others. An infected person may spread the virus to others immediately before and about 1 to 2 weeks after symptoms appear. The virus can live in an infected person's feces for many weeks. It can contaminate food and water in unsanitary conditions.

A smaller proportion of people with poliovirus infection will develop other more serious symptoms that affect the brain and spinal cord. Paralysis (~0.5% of infected persons) is the most severe symptom associated with polio because it can lead to permanent disability and death. Between 2 and 10 out of 100 people who have paralysis from poliovirus infection die because the virus affects the muscles that help them breathe. Even children who seem to fully recover can develop new muscle pain, weakness, or paralysis as adults, 15 to 40 years later (post-polio syndrome).

Features of poliovirus that enhance the risk of infection include:

- Stability in the environment:
    - Polioviruses are non-enveloped viruses (which are more resistant to disinfection and environmental conditions than enveloped viruses) and can remain infectious for several weeks in freshwater. Viable polioviruses may also be found in sewage and soil [2].
- Silent (asymptomatic) infection and shedding, even in vaccinated persons:
    - In most cases of infection with wild-type poliovirus (WPV), the infection is asymptomatic but the infected person can still shed virus. In persons vaccinated with oral poliovirus vaccine (OPV), the vaccine virus replicates in the intestine for several weeks, is excreted and can be spread to others in close contact [3].
- Ability to infect vaccinated persons:
    - Vaccinated persons can be asymptomatically infected with and shed WPV or OPV strains [2]. This happens more frequently in IPV-vaccinated persons [3].
- Potential presence of poliovirus in environmental and laboratory materials, not related to poliovirus diagnosis or research [6]:

- Poliovirus may reasonably expected to be present in some clinical and environmental samples from areas and times where WPV was circulating and OPV was in use.
- Poliovirus may also be found in viral stocks or other materials cultured in poliovirus-permissive cell lines from specimens collected from a time and place when poliovirus was in circulation.

2.2. Polio Vaccination

In the late 1940s to the early 1950s, polio outbreaks in the United States increased in frequency and size; polio crippled an average of more than 35,000 people in the United States each year. It was one of the most feared diseases of the twentieth century. Travel and commerce between affected cities were sometimes restricted. Public health officials imposed quarantines on homes and towns where polio cases were diagnosed.

The development of effective vaccines to prevent paralytic polio was one of the major medical breakthroughs of the 20th century. There are two types of vaccine that can prevent polio: inactivated poliovirus vaccine (IPV) and oral poliovirus vaccine (OPV). Only IPV has been used in the United States since 2000; OPV is still used throughout much of the world.

2.2.1. Inactivated Polio Vaccine (IPV or Salk strain)

The first polio vaccine, inactivated polio vaccine (IPV) was developed in 1955 by Dr. Jonas Salk. Also called the Salk vaccine, IPV consists of inactivated (killed) poliovirus strains of all three poliovirus types. IPV produces antibodies in the blood to all three types of poliovirus. In the event of infection, these antibodies prevent the spread of the virus to the central nervous system and protect against paralysis.

IPV triggers an excellent protective immune response in most people and because IPV is not a 'live' vaccine, it carries no risk of vaccine-associated poliomyelitis. However, IPV induces very low levels of immunity in the intestine. As a result, when a person immunized with IPV is infected with wild poliovirus (or attenuated strains, such as OPV), the virus can still multiply inside the intestines and be shed in the feces, risking continued circulation [7].

2.2.2. Oral Polio Vaccine (OPV or Sabin strain(s))

Oral poliovirus vaccines (OPV; made from attenuated live vaccine strains, also called Sabin strain(s)) are the predominant vaccine used in the fight to eradicate polio. There are different types of oral poliovirus vaccine, which may contain one, a combination of two, or all three different serotypes of attenuated vaccine strains. Each has their own advantages and disadvantages over the others.

The attenuated poliovirus(es) contained in OPV are able to replicate effectively in the intestine, but around 10,000 times less able to enter the central nervous system than the wild virus. This enables individuals to mount an immune response against the virus. Virtually all countries that have eradicated polio used OPV to interrupt person to person transmission of the virus [7].

For several weeks after vaccination the vaccine virus replicates in the intestine, from where it is excreted and can be spread to others in close contact. In extremely rare cases (at a rate of approximately 1 per 750,000 recipients) the live attenuated vaccine-virus in OPV can cause vaccine-associated paralytic poliomyelitis [8, 9]. Even more rarely, when there is insufficient coverage in a

community the vaccine-virus may be able to circulate, mutate and, over the course of 12 to 18 months, reacquire neurovirulence. This is known as a circulating vaccine-derived poliovirus [5].

2.3. Global Polio Eradication

In 1988, the World Health Assembly of the World Health Organization (WHO) resolved to eradicate polio worldwide [10]. Launched after the 1988 resolution, the Global Polio Eradication Initiative (GPEI), along with its partners, has helped countries to make huge progress in protecting the global population from this debilitating disease.

The GPEI website [11] states, "[t]he goal of the Global Polio Eradication Initiative is to complete the eradication and containment of all wild, vaccine-related and Sabin polioviruses, such that no child ever again suffers paralytic poliomyelitis."

Ongoing risks that are targeted by the GPEI [12], and the associated outcomes, include:

1. Completion of eradication to eliminate the risk of wild-type poliovirus (WPV) transmission
2. Cessation of the use of oral polio vaccine (OPV) to eliminate the risks of vaccine-acquired paralytic poliomyelitis (VAPP)
3. Implementation of poliovirus safe-handling and containment measures to minimize the risks of facility-associated re-introduction of virus into the polio-free community.

2.3.1. GAPIII – WHO Global Action Plan

The WHO Global Action Plan (GAPIII, [12]) was endorsed by the WHO Strategic Advisory Group of Experts on Immunization in October 2014 and the World Health Assembly resolution WHA68.3 in May 2015. The GAPIII Containment Certification Scheme (CCS) was endorsed by the WHO Strategic Advisory Group of Experts on Immunization in October 2016 [13].

GAPIII outlines critical steps for poliovirus essential facilities (PEFs)[2] that intend to retain materials either confirmed to contain or potentially containing type-specific WPV, vaccine-derived poliovirus (VDPV), or OPV/Sabin viruses, and steps for poliovirus nonessential facilities[3] that process specimens that contain or might contain polioviruses. National Authorities on Containment (NACs) will certify that the PEFs in their country meet the containment requirements described in GAPIII. After certification of WPV eradication, the use of all OPV will cease. Final containment, per GAPIII, of all polioviruses after polio eradication and OPV cessation is intended to minimize the risk for reintroduction of poliovirus into a polio-free world.

The title page of GAPIII explicitly states, "[t]o prevent reintroduction, the number of international poliovirus facilities will need to be reduced to the minimum necessary to perform critical function of vaccine production, diagnosis, and research."

[2] Poliovirus Essential Facility (PEF) = "Some countries will host a limited number of poliovirus facilities that serve critical international functions, including IPV and Sabin-IPV production, production and storage of mOPV stockpiles, vaccine quality assurance, diagnostic reagent production, virus diagnostic and reference functions, together with crucial research. (GAPIII, pg. 3) These are deemed poliovirus-essential facilities (PEFs).

[3] Poliovirus Non-Essential Facility = facilities housing poliovirus but not meeting the criteria (and certification) to be a PEF, above. Risk elimination in these facilities is achieved through destruction or transfer of poliovirus materials (wild-type and OPV/Sabin) (GAPIII, pg. 4).

GAPIII requirements are structured around biorisk management as described by CWA 15793, Laboratory Biorisk Management [14], as well as the principles of the WHO Laboratory biosafety manual, Third edition [15]. It is worth a side-note that both of these documents are currently undergoing significant revision[4].

The GAPIII Containment Certification Scheme (CCS) outlines a pathway for NACs validating and overseeing containment activities in PEFs. Appendix A lists the milestones and key preparatory activities involved in this pathway. There are four steps for a facility: 1) designation as a PEF, 2) certificate of participation (CP); 3) interim certificate of participation (ICC), if full GAPIII compliance cannot be achieved during poliovirus type 2 containment period, and 4) certificate of containment (CC), if facility is in full compliance with GAPIII and the country also meets secondary and tertiary safeguards.

A review of risk assessment framework specified by GAPIII and GAPIII-derived documents is provided in Section 5.

[4] CWA 15793 is undergoing conversion to ISO 35001. The final ISO document is expected to be released in Spring 2019. The WHO Laboratory Biosafety Manual is being updated to the fourth edition and is expected to be released in 2019. See also [18].

3. RISK ASSESSMENT & RISK MANAGEMENT: MINIMIZING POLIOVIRUS FACILITY-ASSOCIATED RISK

The focus of this study and report is to review risk assessment and risk management at poliovirus facilities, specifically aimed at minimizing the risk of facility-associated re-introduction of virus into the community. However, this effort is underway at the same time other eradication and containment efforts, including initiatives designed to eliminate the risk of WPV transmission and the cessation of the use of OPV. At times, the activities of each may influence or hamper the other initiatives. In this section, we first detail the components of the risk management process, and then detail how a potential tool could support, standardize, and improve that process at PV facilities.

3.1. Risk Assessment and Risk Management Process

Figure 2 visualizes a process of risk management comprising risk assessment, risk evaluation, risk control, and risk performance measurements. This approach was presented in an earlier report from Sandia National Laboratories to CDC evaluating risk assessment and risk management of biological select agents and toxins [16] and represents an aggregation and synthesis of the basic principles and steps for risk assessment and risk management models across a broad spectrum of hazards and industries.

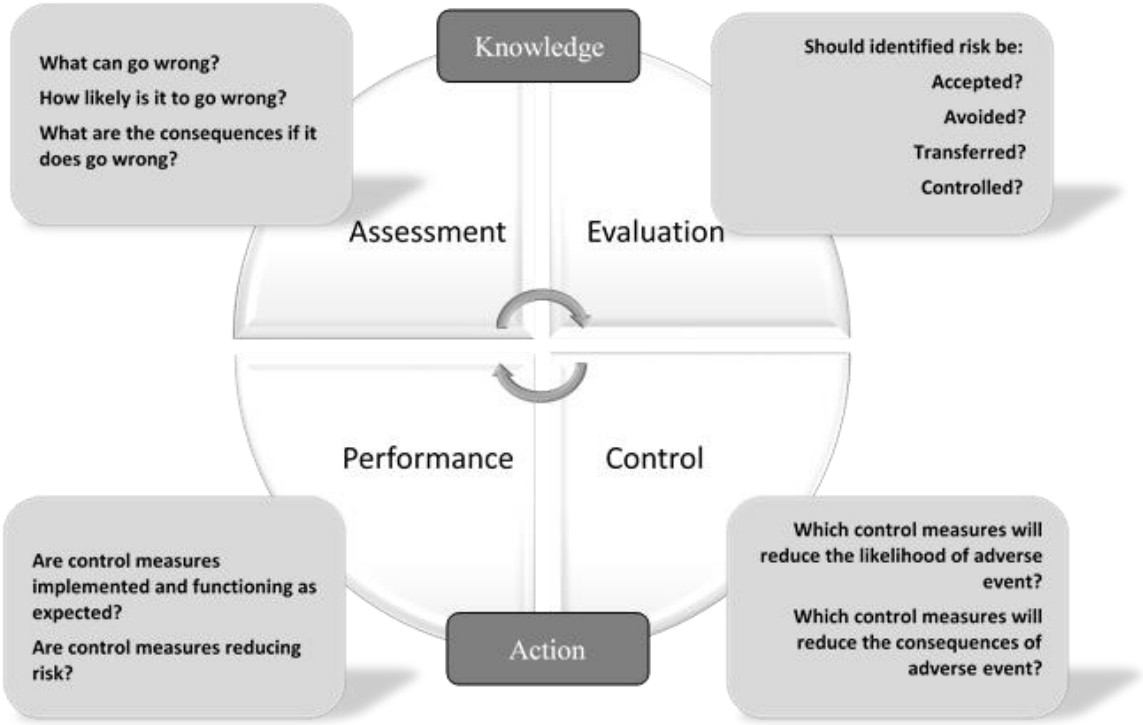

Figure 2 Visualization of Risk Management Process [16]

3.1.1. Risk Assessment

Risk Assessment is the process by which a defined risk is characterized. This includes hazard identification, situation definition, risk definition, and risk characterization [14, 17].

3.1.2. Hazard Identification

A "hazard" in biorisk assessment is generally the causative agent(s) for the disease to be controlled. In this case, the hazards would be known wild-type poliovirus (WPV), vaccine-derived strains (VDPV), and live vaccine strains such as OPV/Sabin . A profile of the characteristics of poliovirus, especially those influencing the risk of infection, is provided in Appendix B.

3.1.2.1. Situation Definition

The setting in which the hazard is found or used is equally important to effectively characterize risk. The type of facility, the manipulations that are used with the hazard, and other features may influence the likelihood of adverse events with the hazard occurring.

Facilities housing poliovirus can be generally divided into research, public health, diagnostic, and vaccine production laboratories, and separated based on their missions and typical poliovirus manipulations and hazards. Examples of common manipulations of PV or PIM in each facility including unique characteristics that might increase risk (e.g., large scale production in vaccine production labs) are listed in Table 1.

Table 1. Examples of Common Manipulations of Poliovirus or Potentially Infectious Material

Type of Facility	Example Types of Manipulations	Unique Features
Research	Virus culture & isolation Nucleic acid extraction Genetic sequencing Genetic modification	Many types of virus-containing samples Generation of new virus variants
Diagnostic	Virus culture & isolation RT-PCR Serologic testing CSF analysis	unknowns
Public Health	Virus isolation Genetic sequencing	Unknowns Samples from patients with asymptomatic infection
Vaccine Production	Amplification (large scale) Genetic modification	High concentrations of virus

Poliovirus may also be found in "poliovirus potentially infectious materials" (PV PIM) which include fecal, nasopharyngeal, or sewage samples collected in a time and place where wild polioviruses/vaccine-derived polioviruses (WPV/VDPV) or OPV-derived viruses were circulating, or where oral polio vaccines (OPV/Sabin) were in use. Non-polio[5] facilities with a high probability of storing such materials include those working with viruses such as rotavirus or other enteric agents, hepatitis viruses, influenza/respiratory viruses, and measles virus, as well as bacterial agents such as Salmonella species, Mycobacterium tuberculosis, and Streptococcus species. Poliovirus-permissive cell lines, including over 20 cell types from humans, non-human primates, mice, and

[5] PV PIM may be found in facilities with active work or collection of poliovirus-containing materials; however, poliovirus may be found with PV PIM in facilities that have never intentionally worked with or collected poliovirus.

hybrid cell lines, may also present a situation where poliovirus could be found. Other facilities could include those conducting nutrition research or collecting environmental samples.

3.1.2.2. Risk Definition

The risk of facility-associated re-introduction of virus into the community can be sub-divided into two more specific risks:

1. Risk of exposure of facility workers[6] to infectious poliovirus (infectious = capable of inducing symptomatic or asymptomatic infection with associated viremia and shedding)
2. Risk of release of poliovirus, intentionally or unintentionally, beyond the facility boundaries

Defining these risks separately, but characterizing both, assures both more comprehensive characterization of each risk as well as ultimate risk-based mitigation that is designed to protect the worker from laboratory exposure (#1, above), as well as protecting the community from exposure due to release from a facility, which could include exposure to, and secondary infection from, an infected worker (#2, above). If the focus is solely on protecting the worker, designed mitigation measures will be focused on primary containment (e.g., personal protective equipment, disinfection of surfaces, biological safety cabinets, etc.). Likewise, if the focus is only towards preventing release of materials, secondary containment (directional and filtered airflow, waste decontamination, robust and sealed facility boundaries, etc.) would be most likely to be prescribed. Protection of both worker and community is essential to address the risk of facility-associated re-introduction of virus.

3.1.2.3. Risk Characterization

"Risk" can be defined as a function of the likelihood of an outcome and the consequence of that outcome. Risk characterization identifies and enumerates both how, and the extent to which, specific hazards within specified scenarios contribute to risk [17].

In general, likelihood of a specific outcome is influenced by aspects of the scenario (e.g., the likelihood of worker exposure is less for an agent stored in a freezer than for the same agent being manipulated on a lab bench; the volume of materials handled will also influence the likelihood of worker exposure or release from the facility, especially in a spill scenario). Agent characteristics including environmental stability, route of transmission, etc. may also influence the likelihood of certain risks.

Consequence, generally, derives from the characteristics of the agent (e.g., an attenuated strain of an agent has generally lower consequence for an exposure than a fully-virulent strain). Factors of the host (person, whether worker or community member) figure into both likelihood (competence, experience, etc.) and consequence (susceptibility, vaccination status, etc.).

Taken together, the likelihood and consequence (i.e., risk) of a given agent (hazard; see 3.1.1.1, above) in a given situation (see 3.1.1.2, above) for a specific risk (see 3.1.1.3, above) can be characterized either qualitatively (e.g., high, medium, low risk) or quantitatively (e.g., a numerical value). Both qualitative and quantitative risk characterization have the most value in risk management when the characterization is compared to another characterization. For example, risk can be characterized for a situation with no control measures and then re-characterized with

[6] Facility workers may include other personnel within the facility boundary such as contractors, inspectors, visitors, etc.

consideration of specific control measures. The change in the level or numerical value can provide an idea of the risk reducing benefit of the control measure.

Risk characterization for the risks identified above (3.1.1.3) involving poliovirus will depend on the situation and the nature of the poliovirus being handled or retained at each facility, though, importantly, many of the potential generalized outcomes apply to most facilities, regardless of type (for example, exposure to poliovirus after a spill). These generalized outcomes can be modeled using a common approach, but tailored to each site using site-specific data (for example the frequency of experiments, and any site-specific mitigation measures).

As will be seen below, as eradication of poliovirus nears, the importance of accurate and precise risk assessment and risk-based decision making about mitigation measures for poliovirus containment Increases. This, in turn, drives the need to explore more robust and quantitative options for poliovirus risk characterization.

3.1.3. Risk Evaluation

Risk assessment, when based on a reproducible, documented, and robust procedure, should generate the same result for the same risk under the same operational circumstances, regardless of who conducts the assessment. Decisions about what to do about the characterized risk, however, may differ substantially depending on the decision-maker. The outcome of risk evaluation is an entity's decision whether to: 1) accept "as is," 2) avoid, 3) transfer, or 4) control the characterized risk. At this juncture in the timeline of poliovirus eradication, no entities should accept the pre-GAPIII risk of facility-associated re-introduction of virus into the community. The remaining options: 1) avoid (via destruction), 2) transfer, or 3) control per GAPIII require significant deliberation by facilities and by the national authorities where facilities are housed. Entities must consider, as part of their risk evaluation, other factors not included explicitly in a biorisk assessment. These factors could include the mission of the facility (for example, a public health laboratory will not be able to choose whether to receive a sample from a patient), community susceptibility or perception, regulatory environment, resource limitations, etc.

3.1.4. Risk Control

Risk control is a risk-based decision-making process to plan and implement measures that eliminate or reduce risk to acceptable levels. An interpretation of what GAPIII considers "acceptable" might be equivalent to the lowest risk possible while still functioning as a poliovirus-essential facility. In Section 5.4, we present options for risk control practices and procedures in facilities housing poliovirus-containing materials (known or potential). These options, while not exhaustive, are examples of risk control measures chosen based on the risk(s) to be addressed, the knowledge of the agent, and the situation in the facility. The measures presented are not weighted or prioritized based on which might address a "riskier" situation. The tool envisioned as an outcome of the larger study (described in Sections 5.5 and 6.1.2) would enable a lab to evaluate these (and other options) for their specific scenario and determine a priority order for risk control to minimize situations with more potential for facility-associated re-introduction of virus into the community, thereby targeting mitigation efforts toward where they matter most.

3.2. Benefits of Quantitative Risk Assessment

Quantitative risk assessment has several advantages over more qualitative processes which rely heavily on expert judgement and experience. Quantitative methods, that may be critical for continued containment of poliovirus after eradication, can:

- Mathematically account for differences in laboratory practices that involve different frequencies, titers, and volumes of infectious materials.
- model the impact on risk of linear relationships (e.g., an identical process involving 10 times the amount of virus can reasonably be expected to increase the opportunity for exposure to the virus by ten)
- model the impact on risk of more complex, non-linear relationships (e.g., the amount of virus available for ingestion from a small amount of contamination on a glove versus virus that is airborne after a large spill)
- allow direct and repeatable comparison of multiple risks and mitigation measures to choose the most cost-effective, risk-reducing measures
- explore the risk (and mitigation measures) of incidents that lie outside of biosafety practitioner's experience because they are rare or simply difficult to observe. Given that a rare event can be catastrophic in terms of consequence (touching off a global pandemic or simply leading to circulation of the virus again), these events can eclipse the risk of more commonplace events on which everyday biosafety is based.

A deeper exploration of these benefits relative to the current context of poliovirus containment can be found in Section 5.5.

4. STUDY METHODS

4.1. Literature review and annotation

We conducted a literature search to identify published papers that discuss one (or more) of several aspects of poliovirus, including information on poliovirus survival in the environment, infection, disinfection, transmission, epidemiology, surveillance, diagnostics, eradication efforts, vaccines, and laboratory exposure, contamination, and containment. The search began with a focus on frequently-cited relevant papers (for example, Dowdle, et al., 2006) [1]), and an exploration of works cited in these papers. New, relevant papers were identified and their citations were, in turn, searched for other relevant papers. Another original source of literature was a team-member's existing electronic archive of papers and other materials related to poliovirus. Finally, searches of key words on Google Scholar as well as the PubMed database yielded additional papers. Appendix C is a bibliographic listing of the papers reviewed. Appendix D includes a table listing years published, authors, titles, and brief notes summarizing the important elements of the work and sourced from the abstract, introductions, conclusions, and body of the papers. Entries on the tables were then ordered by year to provide a sense for the manner in which knowledge on poliovirus has been accumulated, and were color-coded by topic area and organized on a single master list as well as by individual topic, in order to facilitate study and review of the literature.

4.2. Current national and international poliovirus containment activities relevant to risk assessment and risk management

The study team gained familiarity with national and international poliovirus containment activities through two means: 1) reading publicly-available documents and literature published by organizations housing these activities, and 2) meeting with members of the United States NAC (US-NAC) and colleagues. Documents were reviewed to determine the requirements for risk assessment and risk-based decision making under national and international poliovirus containment authorities. The team also met with US-NAC representatives several times to exchange information relative to both the study and poliovirus containment activities.

4.3. Discussions with and Site-Visits at Potential Poliovirus-Essential Facilities (PEFs)

Engaging members of the United States poliovirus community served a critical role in ensuring that the study analysis and plans for a tool meets real-life use scenarios. Acquiring this subject matter expertise is essential to ensure that the project 1) includes realistic and rational assumptions about the risks associated with handling poliovirus and poliovirus-containing material, 2) identifies practices facilities have implemented, and 3) informs development of the tool or other options to be realistically and practically used to support ongoing risk mitigation processes.

The US-NAC, housed at CDC-CPR, initiated outreach to potential PEFs that were identified as housing Type 2 strains (WPV or OPV/Sabin). Facilities choosing to participate contacted the study team. For confidentiality considerations, the study team was not advised of the facilities contacted by the US-NAC and, once facilities contacted the study team, the US-NAC was not advised of their participation. Our understanding is that fewer than twenty facilities received an invitation to provide input to the study. Seven facilities contacted the study team and provided feedback. Site visits and discussions were held in person at three facilities; an additional four facilities were interviewed by phone.

Categories of facilities participating included research labs, public health labs, diagnostic labs, and a candidate facility for vaccine production. Participants in discussions generally included the laboratory director, poliovirus-specific laboratory manager, and biorisk management personnel.

The study team developed a discussion guide (Appendix E) to loosely organize discussion, but modified questions as warranted by the nature of the facility and time constraints, and participants were free to direct the discussion to other relevant topics. All discussions were open and congenial.

The study team hosted a web-forum at the end of the interview period to provide general observations from the interviews and visits and to receive feedback on the validity of those observations. Members of six of the facilities participated in the forum.

4.4. Catalog of Example Practices to Minimize Risk of Facility-Associated Reintroduction of Virus

Figure 3 presents a process for risk-based decision-making when choosing a mitigation measures. At the left of the figure, in orange, are listed the adverse events identified by GAPIII to be of concern for facility-associated re-introduction of virus: 1) worker exposure, and 2) release of poliovirus beyond the facility boundary.

On the far right of the figure, also in orange, are listed the potential adverse outcomes of exposure and/or release. For example, a potential outcome of worker exposure could be infection and viral shedding. A potential outcome of release could be direct community contact with poliovirus and resulting community infection.

The blue boxes in the middle of Figure 3 represent example actions that could interrupt the progression of the adverse event to the outcome presented. These are termed risk mitigation measures. For example, minimizing or eliminating poliovirus in a facility will reduce the likelihood of both exposure to and release of poliovirus and thus reduce or eliminate any of the outcomes listed on the right side of the figure.

Effective risk reduction does not rely on only one category of mitigation measure, but uses a layered approach so that weaknesses in one measure are covered by the strengths of another measure. The multiple blue boxes in Figure 3 indicate this layered strategy. If, for example, waste decontamination is not applied or effective, incident response could limit release beyond the facility boundary and prevent direct contact with the community or environment.

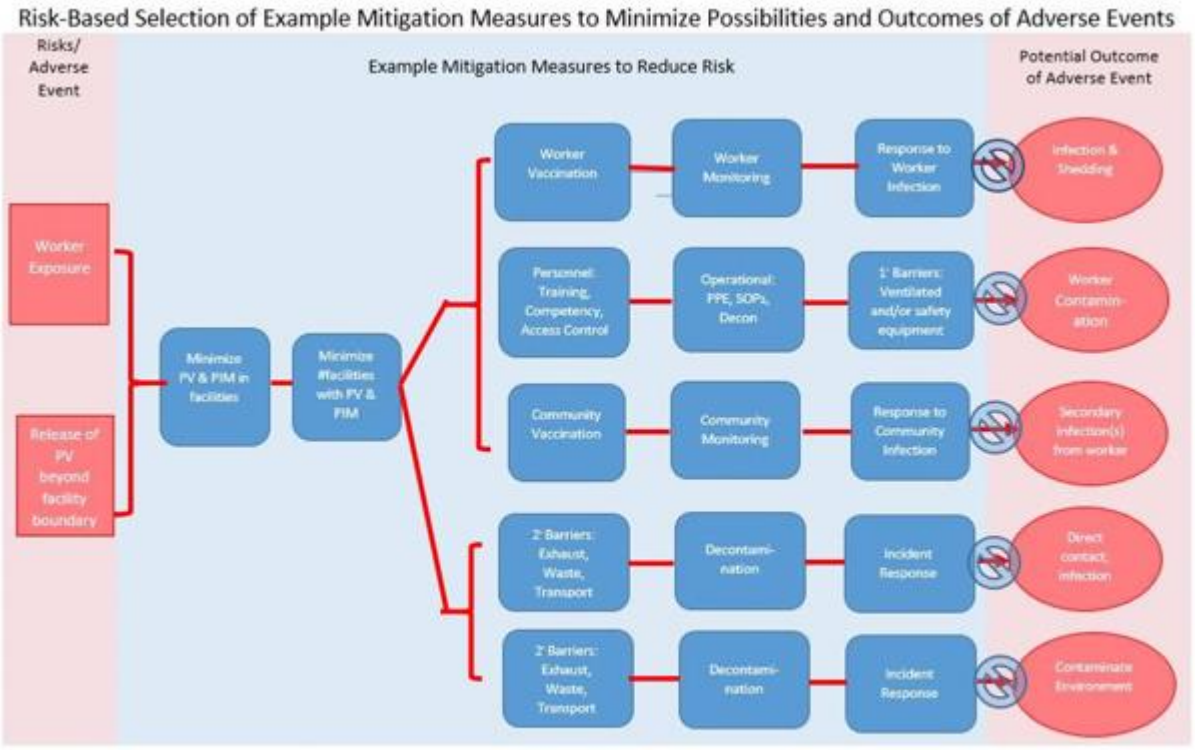

Figure 3. Schematic of Risk-Based Selection of Mitigation Measures to Reduce Risk

What is inferred but not included in Figure 3 are all of the activities that comprise an effective mitigation measure, as well as the various procedures that might contribute to an adverse event. In our experience, the failures of mitigation measures often occur due to lack of attention to these details. In several incidents unrelated to poliovirus, for example, laboratory personnel performed inactivation procedures before releasing an agent from the laboratory, but did not take the additional critical step to validate that the inactivation procedure was actually effective under the specific conditions. Effective biosafety and biosecurity require answering not only "what" but "how." Answering, "yes, we inactivate our agents before removal" is incomplete without also including procedures and data demonstrating that inactivation of the specific agent by the specific procedure is indeed accomplished. In order to begin adding this critical detail to the risk-reducing practices needed to minimize facility-associated re-introduction of virus, we used the general approach outlined in Figure 4 to catalog candidate activities that may be necessary to move towards risk-reduction goals stated by Dowdle et al, [2]. These goals are:

1. Minimize WPV infectious and potentially infectious materials in laboratories
2. Minimize risk of operations in PEFs that:
    a. Might expose workers
    b. Might cause release of poliovirus outside PEF boundary
3. Minimize susceptibility of workers to infection and shedding
4. Minimize susceptibility of community to poliovirus spread

We used information collected, as described above, from reviewing the literature, oversight documents, discussions with and observations at poliovirus facilities as well as using our own biosafety and biosecurity experience and professional judgement to create this catalog, which is not exhaustive and includes only examples of candidate practices.

The results of this activity are provided in Appendix E (Catalog of Possible Practices to Minimize Risk of Laboratory-Associated Re-Introduction of Virus), an excerpt of which is provided and annotated in Figure 4.

Example Practices to Minimize Risk			Analysis of Risk-Informed Guidance Available to Implement Practices			
B Work Flow Category	C Work Flow Sub-Category	D **Example** Work Flow Practices	E Specific[1]	F GAP III	G Literature	H Observed (n=7) >5 3-4 <2 Not evaluated
A Minimize WPV infectious and potential infectious materials in facilities						
Identify and evaluate sources of WPV in facility	Identification & Classification	• Identify potential PV type and/or source of material	PV	2/2.4.1 2/3.1.1	Yang 1991; Van Loon 1993; De 1994; Van de Avoort 1995; Davies 2003; Savolainen 2003; Khan 2006	
	Inventory	• Record type and location of materials in inventory. • Assign accountability for materials.	SP	2/3.1 2/3.2 2/3.41		
	Archive/Store	• Determine if materials will remain in working stock. • If yes, aliquot, store, and inventory with working stocks. • If no, determine if materials will be archived or transferred or destroyed. • If archiving, aliquot, store, and inventory in archival collections. • See transfer and destruction, below.	PV	2/3.1.1	WHO Polio Lab Network 2002	
	Sequence	• Determine if materials will be genetically sequenced prior to transfer or destruction. • If sequence, following sequencing procedures.				

[1] SP = standard practice; application of practice/procedure is similar to practice with other similar pathogens
PV = practice requires unique knowledge and risk assessment of poliovirus
PV* = practice requires unique knowledge of poliovirus, but GAPIII does not provide information unique to poliovirus to guide application of practice

Figure 3. Excerpt of Appendix E

The catalog is divided into sections (A) representing the risk-reducing goals listed above. Within each section, the first three columns (B, C, and D), represent a general workflow of activities, in increasing granularity (left to right), that provide example practices to be performed to meet the risk-reduction goal of the section.

The columns to the right (E, F, G, and H) contain individual analyses of each risk-reducing measure based on the following criteria:

Specific (Column E): For each practice, the study team evaluated where knowledge unique to poliovirus was necessary to inform the risk assessment and risk-based mitigation selection and implementation of each procedure. For example, due to the environmental stability of poliovirus, disinfection and decontamination procedures must be more stringent than for many pathogens. Likewise, the potential for silent (asymptomatic) poliovirus infection of vaccinated personnel

requires different procedures than standard practices with pathogens where infection is more likely to be observed.

GAPIII (Column F): Each practice was mapped, if possible, to a GAPIII requirement. In addition, the GAPIII requirement was evaluated to determine if it provided guidance that was standard practice for most pathogens or if the GAPIII requirement provided poliovirus-specific information that would aid the facility in assuring poliovirus-specific mitigation. We determined procedures for which GAPIII indicated standard practices, but where, in the team's judgement, poliovirus-specific guidance to inform risk-based decisions on control measures was warranted for effective risk mitigation. These determinations are captured in the analysis presented in the Specific column (E).

Literature (Column G): For each cataloged practice, a literature citation was noted if we felt that the literature contributed to the poliovirus-specific information required to inform risk assessment and risk mitigation selection.

Observed (Column H): Lastly, we indicated if the procedure was observed or reported in the small sampling of laboratories working with poliovirus. the color of the box indicates that, in the discussions and site visits (n=7), the practice indicated was practiced by most (more than 5; green), some (2 to 5; yellow), few or none (1 or 0; red), or was not able to be evaluated (grey).

The intent of these analyses is to identify areas of risk mitigation where information to inform risk assessment and risk mitigation selection exists, and, more importantly, where this information does not exist. It is in these gaps where a robust, quantitative tool can provide the most aid to facilities to, ultimately, minimize facility-associated risk of reintroduction of poliovirus into a polio-free environment, the goal of GAPIII requirements.

5. RESULTS AND ANALYSIS

5.1. Literature Review and Annotation

Over 150 papers relevant to poliovirus public health, safety, and risk were identified, collected, and annotated. Publication dates ranged from 1940 through 2018, with the greatest numbers in the 1990s and 2000s, presumably linked to the resolution to eradicate polio in 1988 and to the discovery that the OPV vaccine presented an unanticipated threat to eradication efforts. Papers were categorized, generally, into topics of relevance to public health, safety, and risk management. While not a scientifically-valid survey, under this generalized categorization (Figure 5), more papers discussed vaccination and eradication, with infection, disinfection, laboratory containment, and handwashing being the least represented, but arguably most important for containment decisions. However, even though some of these critical topics have fewer references, this body of literature represents a solid foundation from which to derive evidence-based practices and data to inform a quantitative risk-based decision-making tool.

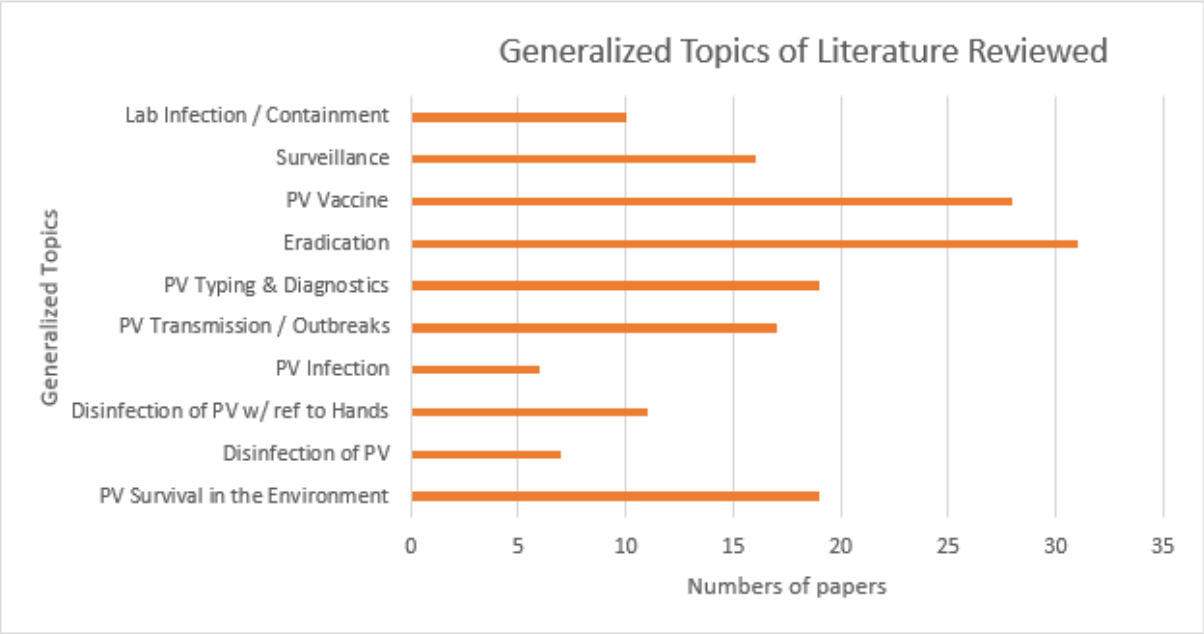

Figure 4. Generalized categorization of poliovirus literature review

5.2. Current national and international poliovirus containment activities relevant to risk assessment and risk management

5.2.1. GAPIII - 2015

The expectation by GAPIII that facilities are equipped to conduct risk assessments and to use those risk assessments in risk-based decision is clear. GAPIII states (pg 29):

> *"the organization is best placed to understand the risks associated with its work and can manage those risks in a number of ways acceptable to the national and international bodies responsible for facility oversight. This standard further assumes that poliovirus-essential facility personnel and management at all levels fully*

appreciate the enormity of the consequences of accidental or malicious poliovirus release in the post eradication/post-OPCV era and are prepared to demonstrate that the appropriate systems and controls are in place to manage those risks."

GAPIII explicitly mentions facility-conducted risk assessment as a pre-requisite for determining appropriate risk mitigation strategies. In the GAPIII document, over 40 unique[7] references to "risk assessment" exist. Phases I and II (as defined by GAPIII) of poliovirus containment require facilities to adopt and implement, "safe and secure working practices based on a risk assessment and the implementation of appropriate biorisk management systems" [GAPIII, p.11].

"Risk Assessment" is defined by GAPIII as, "a qualitative or semi-qualitative process undertaken by individuals with expertise in appropriate disciplines and backgrounds in response to an identified hazard." Annex 5 presents a "Risk Assessment Strategy" that is derived directly from CWA 15793, with no modification (Figure 7).

In addition to being used to, more broadly, guide adoption and implementation of safe and secure working practices, risk assessments must, per GAPIII, be specifically used to identify or guide:

- inclusion or exclusion of persons from facilities;
- good microbiological techniques;
- selection of personal protective equipment (PPE);
- consideration of human factors;
- health surveillance;
- procedures to adopt to ensure adequate first-aid during medical emergencies;
- facility planning, design, and validation;
- facility and equipment maintenance;
- selection and acquisition of equipment;
- equipment calibration, certification, and validation;
- decontamination strategies;
- physical security controls; personnel reliability measures.

[7] References to "risk assessment" are essentially identical in Annex 2, 3, and 6

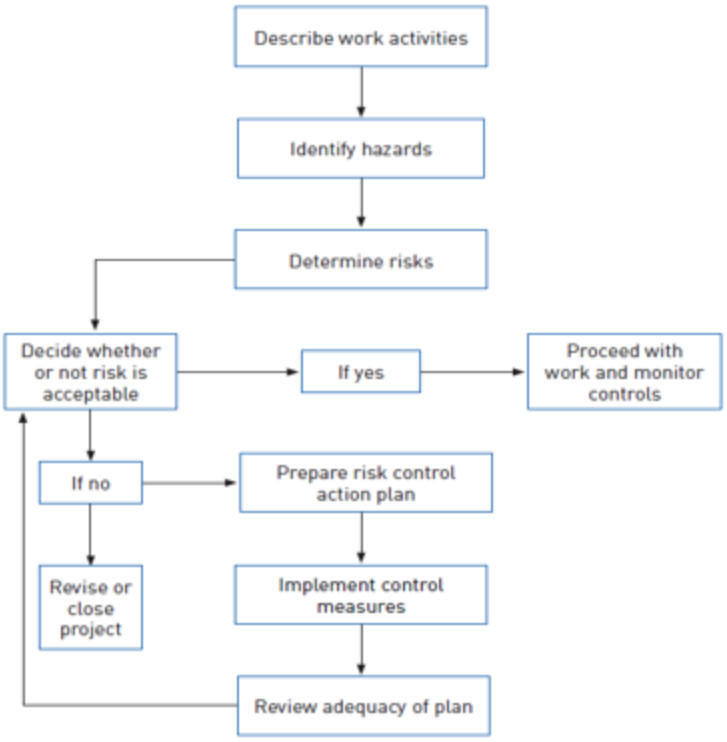

Figure 6. Risk Assessment Strategy provided by Annex 5 GAPIII.

Further, GAPIII specifies that risk assessment must be required by a facility's biorisk management policy and must be supported, financially and technically, by senior management, the biorisk management committee, and scientific management (and, though not explicitly called out, the biorisk management advisor8). Occupational health, facilities, security, and animal care managers should have input. Risk assessments must be documented, communicated, and updated to reflect changes that impact biorisk management or those that are instituted through continual improvement. Guidance for GAPIII Implementation - Containment Advisory Group

The Containment Advisory Group (CAG) is an advisory body to the Director-General of WHO, and makes recommendations on technical issues related to the implementation of GAPIII. The CAG has convened four times: June 2017, November 2017, January 2018, March 2018 (reports may be found at http://polioeradication.org/tools-and-library/policy-reports/advisory-reports/containment-advisory-group/). Examining the technical issues brought before the CAG and their recommendations further demonstrates a reliance on risk assessment to assure poliovirus containment. CAG reports make explicit reference and, perhaps more importantly, deference to facility-specific risk assessment:

> *June 2017: "GAPIII expects designated PEFs to develop very detailed risk assessments following recognized methodologies. However, multiple agencies will look at and evaluate these RAs, and considerable variations may be possible in terms of what are considered to be acceptable risk levels by different parties. CCS requires*

[8] A biorisk management advisor, per GAPIII, "should be regarded as an advisory position and not one directly responsible for managing biorisk."

an independent review of the RA in case of deviations from GAPIII requirements for issue of an ICC. Given the criticality of risk assessments and potential for differing interpretation, expectations on RAs for containment certification may benefit from the development of RA guidance, possibly by the WHO secretariat. However, guidance on RAs is already available from different sources, and WHO's mandate is to support GCC and NACs, not PEFs."

In March/April 2018, Guidance for Non-Poliovirus Facilities to Minimize Risk of Sample Collections Potentially Infectious for Poliovirus was published after endorsement by the CAG [6]. This guidance states that, "[a]ll facilities that propose to retain PV PIM collections should prepare a thorough risk assessment, with the objective of minimizing risks of release of PV back into polio-free communities." In addition, this guidance states, "[r]igorous risk assessments should be conducted and documented for all procedures that will be used with PV PIM faecal samples or sewage concentrates to identify strategies to minimize risks of inadvertent release."

The above review demonstrates that "risk assessment" is considered an imperative and integral component of the strategy to minimize facility-associated risk of reintroduction of virus. GAPIII and GAPIII-supporting guidance infer, either explicitly or implicitly, that the facility knows its processes best and is equipped to make the "right" risk-based decisions. However, the discussions with poliovirus facilities demonstrated confusion and inconsistent approaches to risk assessment and risk control measures (see Section 5.3, below).

5.2.2. Discussions with and Site Visits at Potential Poliovirus-Essential Facilities (PEFs)

The study team gratefully acknowledges the frank and open discussions with current poliovirus facility personnel. Detailed results of these discussions are included in aggregate in the table presented in Section 5.4, below (observation of procedures to minimize risks) and in Section 5.5, where the tool requirements gathered from stakeholders are outlined.

While the focus of the discussions was on risk-reducing practices and the functionality, value, and requirements of a more robust risk assessment tool, some general observations are warranted given the frequency in which they came up in conversation.

1. **Each facility considers different factors in risk management**. Those variations suggest that standardizing risk assessment and management would elevate risk-based decision making at most facilities. In our visits, we observed that what one facility emphasizes in risk management, another may deemphasize or overlook. Some of these variations are expected given that risk truly does vary between facilities, but the degree of variation suggests that some factors may be missed at some sites.

2. **The stringent facility requirements in GAPIII are dissuading many PV researchers from continuing their work**. What is not clear, though, is whether the loss of this research may threaten the knowledge base to achieve or maintain polio eradication.

3. **Facilities are confused about which requirements apply to what type of poliovirus material and activities**. The release of the PIM guidance during the course of our study appeared to alleviate confusion a bit, but it was unclear if facilities were correctly interpreting requirements. Most facilities have adopted a "wait and see" approach.

4. **Facility decisions that focus on engineering and facility controls, as required by GAPIII, will consume both financial and human capital** that 1) is not generally available under

current funding schemes and 2) might be more effectively spent on controls that minimize worker exposure and surveillance for and response to subsequent asymptomatic infection.

5.3. Evaluation of Information and Guidance Available to Implement Risk-Reducing Practices

As discussed in 4.4 above, Appendix E presents a catalog of candidate practices to minimize risks that could be associated with poliovirus-essential facilities, along with analyses of the information and guidance available for risk-based decision-making for these measures.

Many of the practices identified in Appendix E require unique knowledge of poliovirus characteristics and risks, much of which is not supplied by GAPIII. Likewise, many practices identified in GAPIII call for site-specific risk assessment (see Section 5.2.1, above). In general, the primary guidance specific to poliovirus in GAPIII is related only to some specific aspects of facility design and to vaccination and follow-up when an infection occurs or is suspect.

GAPIII does not provide specific information for decontamination procedures, best practices associated with common manipulations of poliovirus, and poliovirus-specific information on emergency response (except for response to a potential poliovirus exposure or infection).

While some practices have extensive poliovirus-specific literature available to support implementation (some of which is cited in the GAPIII document), for most practices, risk-based decision making and implementation appears to rely on the ability of facility personnel to combine their knowledge and expertise about poliovirus with standard practices for biorisk management to derive appropriate mitigation measures.

We did not conduct inspections or audits based on either GAPIII or the procedures listed, but retrospectively evaluated whether the practices were implemented (as observed or reported) by most, some, few or none of the facilities (or not evaluated). Very few practices listed were observed or reported by all. In general, those that were reported by all facilities involved identification and characterization of poliovirus-containing materials. Most labs also practiced some form of access control, although the criteria for access were not reviewed by the study team. With the exception of conducting (most) manipulations in a biological safety cabinet (BSC), very few of the GAPIII-specific facility requirements were in place.

Without exception, all of the personnel interviewed expressed some concern or confusion about implementation of GAPIII requirements and, in particular, the difficulty of identifying a potential silent infection in an immunized lab worker.

Although the facility infrastructure requirements of GAPIII are quite strict and will require entities seeking PEF certification to operate necessarily complex, sophisticated, and expensive facilities, many of the practices that may also benefit risk-reduction, as documented in Appendix E, are not defined and are left to the PEF to determine. Given that, in the post-eradication world, one infection from poliovirus will be considered a public health emergency, potentially inconsistent determinations and applications of risk mitigation warrants concern. Even within the context of an incident investigation, a facility must be knowledgeable and articulate about what might have happened to cause a release so that corrective and preventive measures can be applied to address future potential releases. That said, much of risk assessment and risk-based decisions on control measures must consider facility-specific information, thus, additional generic prescriptive measures are not the answer.

This evaluation demonstrates that PEFs could benefit from additional guidance on risk-based decision-making to most effectively minimize the risk of facility-associated reintroduction of virus to a (nearly) polio-free community. Given current gaps in knowledge and guidance, risk-based decision-making would greatly benefit from a more standardized and uniform, poliovirus-specific and evidence-based approach that addresses new challenges for containment in a post-eradication world.

5.4. Tool Requirements Gathered from PV Stakeholders

As envisioned, the software tool we propose to develop would be used by poliovirus essential facilities (PEFs) to conduct and support risk assessment and risk-based decision making. Broadly speaking, the tool would enable researchers and biorisk management personnel to input conditions and activities at the facilities for which the risk assessment is being conducted (including experiments, viral volumes and titers, available physical control measures, etc.), and the tool would output a visual, easy to understand assessment of risk as the lab is currently configured. Specifically, the tool would show the risk of loss of containment for each pathway, and would suggest potential risk reduction measures that could most reduce risk of loss of containment. Users would be able to enable/disable potential control measures or experiments, and the tool would provide a visual representation of how those changes in the facility affect overall risk.

To support these outputs and aid users, the tool would be pre-loaded with scientific and technical data (such as failure rates of PPE, human error rates, dose-response information, etc.) so that the PEFs would input data only on their specific experiments. This frontloading of data significantly reduces the workload for each facility, as they no longer have to gather these data themselves, and also increases the sophistication of the tool, improving the rigor and accuracy of the risk assessments conducted with it. At the same time, each facility would be able to input their own, customized facility-specific data (like frequency of experiments), to provide site-specific risk measurements tailored for their facility and work plan.

As envisioned, the tool would be quantitative and would contain an underlying, probabilistic statistical model of experiments and loss of containment scenarios. Quantitative models offer many advantages not available in qualitative models. First, quantitative models allow detailed comparisons between loss of containment pathways, to determine which are the biggest drivers of risk. Second, these models also enable detailed measurement of the risk reduction offered by various controls, enabling facilities to understand which measures have the greatest return on the investment needed to implement them. Lastly, quantitative models enable incorporation of human error in loss of containment pathways, to understand how human error drives risk. In our experience, human error can be a major driver of risk both because a single human error can negate multiple control measures, and because many loss of containment paths are frequently precipitated by a human error (for example, spills usually require a human motor mistake). Although qualitative models can include considerations of human error, quantitative models can provide more detailed and nuanced examinations of the relative importance of human error vs mechanical failures to prioritize investments in risk mitigation (for example, the relative importance of additional training vs the need for more barrier precautions). In addition, they can help ensure human errors not yet encountered in the real-world experience of the tool operator are properly weighed in the risk assessment.

Although the tool would have many benefits, it would also have some limitations. In general, data on the cause of accidents in life sciences laboratories is scarce and the tool would use data on human error from analogous incidents in other settings that have been well studied (such as nuclear power, transportation, etc). This limitation is one reason why we imagined that users would implement this

tool alongside their existing risk assessment procedures to identify heretofore unappreciated elements of risk or options for risk mitigation. However, because the tool would compare risks of various escape pathways, incidents and mitigation measures (instead of providing absolute risk estimates), the same underlying data would be used across many aspects of the tool, suggesting that the relative importance of each risk element would be valid even if the underlying data is off in absolute terms.

5.4.1. Purpose and Vision for The Tool and Requirements

In the sections that follow, we discuss the requirements we developed via discussions and site-visits with PV stakeholders from research and public health laboratories. A formal requirements assessment was required because this tool would be entirely new: no such system is in use by poliovirus facilities today (or for any infectious disease work). Even where risk assessment tools are in use in the life sciences, they are not widely applied in PV facilities, which are facing daunting and unique challenges. Performing a requirements study was necessary to understand how a tool could best work hand-in-glove with longstanding risk assessment methods, and what capabilities such a tool would need to best serve research and facility personnel.

Additionally, PV facilities are facing new containment and biosecurity requirements from GAPIII. Because several of these requirements exceed long-established measures that have successfully prevented any known facility-acquired infections, stakeholders are voicing reservations about the necessity of these requirements for biosafety purposes. A tool can be used to help stakeholders understand the true risk-reduction value of these new measures, providing evidence that they are essential and therefore should be implemented, given that a loss of containment event may threaten global eradication—even a single case of poliomyelitis will be considered a public health emergency. Such a tool should help reinforce the existing culture of containment that might otherwise be undermined by the perception towards seemingly unwarranted new requirements. To help develop this evidence, the tool must satisfy key requirements, such that it addresses critical questions held by the community.

5.4.2. Current Processes for Risk Assessment

Although discussed more extensively above, a few points about how PV facilities manage risk bear mentioning here. All PV facilities we talked to currently use risk assessments in their biorisk management approaches; however, those risk assessments vary widely. The most extensive RA involves a multi-month-long assessment that includes an evaluation of the risks inherent in each procedure and an assessment of any mitigation measure (be it administrative, materiel or procedural). The process is supported by working groups comprised of researchers, safety officers and institutional leadership, an investment of time and funding that cannot easily be replicated at most entities. The entity conducting this type of RA uses a Failure Mode Effects Analysis (FMEA) tool to assess all 16 elements of GAPIII and all failure modes. Another entity uses a similar, albeit less extensive process, by which the facility members evaluate each experimental procedure and develop mitigation measures that should be implemented, instead of a more holistic assessment of risk. Both entities use qualitative and experiential data to inform their assessments. Other laboratories use a qualitative laboratory review or use an institutional biosafety committee (IBC) or similar to review their research protocols, but similarly use professional judgement to assess the level of risk inherent with each protocol and identify risk mitigation measures via thought experiments. Across all facilities, biorisk management professionals typically review the risk assessments and ensure compliance with GAPIII.

5.4.3. Existing Risk Assessment Gaps

The current processes for risk assessments leave several gaps that may pose unacceptable threats to the maintenance of global eradication and the sustainability of ongoing PV research. The biggest gap is that almost all PV labs use an RA methodology that is based entirely on the experience of the personnel conducting it and, as discussed above, this experience may falsely minimize risks (both in terms of the probability that a loss of containment event will occur and the consequences should it occur) that may result in a loss of containment event sparking an outbreak in a post-eradication world. Also, experiential risk assessment necessarily undervalue very rare but catastrophic risks because they are not experienced by most researchers and biorisk management personnel. Moreover, incidents that lead to so-called "unknown" exposures (where an infection occurs but the pathway out of containment is never identified) may result in an investigation and improvements in procedures within that specific facility, but may not be considered at other facilities that haven't experienced the same outcome. In addition, due to the lack of a specific cause, these types of events cannot be formally considered in an experiential risk assessment, because, lacking a specific cause, the estimated or actual effect of new control measures cannot be determined. All these factors combine in the PV research community to undermine some of the GAPIII requirements that seem unnecessary when one examines only commonly-considered risks in PV laboratories. For example, a quantitative, evidence-based tool could determine that contamination leaving the facility on the body of a worker is a significant driver of the overall risk of a loss of containment incident. This finding could help undergird the GAPIII requirement for a shower and also point the facility to an underappreciated escape pathway for PV that should be mitigated. Likewise, because PV is an enteric, and not a respiratory pathogen [5], PV stakeholders may be undervaluing air handling and respiratory protection as risk mitigation measures (which undermines some confidence on GAPIII requirements). However, because roughly half of respirable particles inhaled end up in the gastrointestinal system, aerosols of PV may pose an infection risk. The degree to which this exposure route drives risk will depend on the number and size of the particles generated (which is itself a function of the physics of the incident), the concentration of active virus particles within each airborne particle and the containment and personal protective equipment present. Only a quantitative tool can incorporate the necessary details within all of these facets when assessing risk. At the same time, the amplification and concentration of PV in the facility results in a potential exposure environment distinct from the "natural" environment in which most human experience with PV has occurred. Though these differences likely drive differences in risk, experience with the "natural" environment influences risk-based decision making even in the lab. A quantitative tool can account for these differences, and provide new estimates of risk developed around a model more closely representing the actual facility. These types of evidence-based understanding available in a quantitative tool are critical for the scientific community to buy in to the GAPIII requirements and support them.

Today's PV RAs are not quantitative and therefore cannot address questions that are key to the sustainability of PV research in the US. For example, soon, a facility that handles less than one infectious dose of PV will face many of the same requirements as a vaccine facility that produces liters of live agent. Clearly, infection risk is a function of the types of procedures conducted, but also depends upon the frequency of those procedures, the volumes of agent manipulated, and the titer of the cultures.. As discussed above (Section 5.2.1), GAPIII currently relies on the facility to make many decisions about poliovirus risk control practices necessary to ensure compliance.

Similarly, quantitative methods are required to meet the spirit of some risk assessment guidance given in GAPIII to meaningfully reduce risk. For example, GAPIII requires that risk assessments

consider the influence on risk of various PPE, human factors, health surveillance practices, new equipment acquisition and decontamination procedures and, as discussed above, only quantitative methods can, consistently and comparably, determine the relative risk mitigation value of all these investments. For example, quantitative methods can model where human errors are likely driving risk and help identify the most cost effective training to conduct. Similarly, quantitative methods can inform protocol development (which decontamination protocol is superior to reduce risk; how long should possibly exposed workers use a chemical toilet) and which purchases to make to most reduce risk.

Given that specific aspects of risk assessment and risk control decisions are left to PEFs, a tool that supports risk assessment and decision making would help ensure PEF compliance with GAPIII. A quantitative tool, in addition, enables the tailoring of risk mitigation measures to the specific risks at each site, improving the quality of decision making. Moreover, facilities are likely to face choices about which control measures to implement, some of which are costlier than others. A quantitative tool that assesses risks in a site-specific way and assesses the risk-reduction afforded by each measures ensures that risks are adequately addressed in a cost-effective way.

The variety of RA methods in use today illustrate that RA is not uniform across the PV community. This lack of uniformity in RA obviously leads to risk mitigation measures that are also not applied uniformly. Given one PV infection outside a facility could threaten eradication, any weak link is unacceptable. Also, lacking a broadly-applicable tool, each facility must invest in devising an RA methodology and executing it, which is an expensive outlay of time and effort. A single tool given to the community could ensure that all labs are equipped to mitigate risk cost-effectively.

5.4.4. Requirements: Scope and Purpose for a Risk Assessment Tool

The requirements identified can be divided into three groups. Those that relate to the scope and purpose of the tool, those that relate to tool inputs and outputs, and those relate to data-sharing. This section describes the requirements of the first group, those of scope and purpose, which are summarized in Table 2.

Table 2. Scope and Purpose Tool Requirements

Tool Requirement	Rationale/Description
Allow the assessment of all incident/scenarios contemplated in GAPIII	Stakeholders feel all incidents/scenarios in GAPIII were important to consider
Enable the assessment of both biosafety and biosecurity risks	Stakeholders feel both biosafety and biosecurity were important
Allow the assessment of risks related to potentially-infectious materials (PIM)	Certain facilities handle PIM much more frequently than confirmed PV
Enable the tool to supplement existing risk management practices	Stakeholders desire a tool to supplement existing practices, and typically not to replace them
Ensure the tool fosters standardization across laboratories	Stakeholders felt that the potential standardization offered by a tool is one of the tool's strongest benefits especially in PV facilities worldwide

PV stakeholders agreed that a tool should **allow the assessment of risk for all incidents/scenarios contemplated in GAPIII** plus others that the tool reveals as risky. These scenarios include[9]:

- Everyday procedures:
  - Handling of infectious poliovirus materials
  - Animal handling
  - Centrifugation
  - Control of needles and sharps
  - Use of vacuum pumps
  - Culture, purification and storage techniques
  - Minimization/containment of aerosols
  - Pipetting
  - Sonication and other mechanical forms of cell/tissue disruption
  - The use of BSCs
  - The use of disinfectants, including spill controls, routing decontamination, hand washing, and showering
- Emergency scenarios:
  - an infected/potentially infected worker or other contact (e.g. family member, emergency responder or community member)
  - a major spillage/aerosol release
  - physical facility and equipment failure, including a control system failure of the disinfection regime
  - An emergency within the laboratory, such as accident or illness to a worker within the containment area and need for evacuation
  - Fire---this is important (from electrical issues within the lab)—full body Tyvek suits
  - Flood (from pipes bursting)
  - Explosion
  - Utility failures including electricity, gas, steam and water supplies
  - Unanticipated experimental results, such as unexpected virulence (unknown biological agents or biological agents expected to be avirulent)
- Biosecurity Incidents, including:

[9] Grouping of scenarios into broad general types was done by the study team to simplify that presented in GAPIII.

- breach of security
- the potential loss of poliovirus through theft or any other reason

Consistent with this view, PV stakeholders confirmed that **the tool should enable the assessment of both biosafety and biosecurity risks**. We note that very little data are available (and even less could be entered into a tool that is disseminated publicly) on the capabilities and interests of those wishing to exploit biosecurity vulnerabilities, so a tool probably cannot directly compare biosecurity risks and mitigation measures with biosafety risks and mitigation measures, nor could a biosecurity tool be evidence-based and purely quantitative. However, a tool could provide some support for biosecurity risk-based decision making, for example by evaluating mitigation measures that are typically implemented against a set of generic threat categories. In addition, a tool could foster understanding of the consequences of a biosecurity incident, given that the consequences depend largely on the agent.

PV stakeholders, voicing concerns and confusion regarding the GAPIII requirements related to Potentially Infectious Material (PIM), expressed a requirement that **the tool must assess risk related to PIM** of various types. Some research laboratories and public health facilities we talked to handle PIM much more frequently than they handle purified PV or samples known to contain PV, and many critical activities in these labs have nothing to do with PV research. These PIM include recent fecal samples from areas where wild-type PV is circulating, recent samples from areas where oral PV vaccine is still used and decades-old clinical samples from the US and Europe. Given the frequency with which these samples may be used for ongoing research, researchers are keen to understand risk mitigation measures that are not unduly burdensome and aligned with the risk these samples actually pose.

PV facilities were mostly satisfied with the RA systems they had in place, and thought that an **RA tool would supplement, not replace their existing RAs**. As described above, every facility interviewed has a RA system in place, albeit some were much less extensive and robust than others; some considered scientific and technical data while others used professional experience and judgement about risk. All RAs were qualitative. In some cases, the RA tool would simply fill in gaps in their existing practices, while in other cases the RA tool would replace some of the more burdensome steps in the RA.

The interviews with PV stakeholders revealed remarkable consistency in what they sought a PV RA tool to do. Nearly unanimously, PV researches cited the desire of a single tool to **standardize the RA process across PV laboratories and vaccine facilities**. This standardization would address the concern in the community that laboratories with sparse RA processes also may have fragile mitigation measures in place (in other words, a robust RA process is generally a necessary precedent for a robust risk mitigation process). A RA tool distributed to PV facilities and incorporated into their RA process could help ensure that all laboratories are considering AT LEAST the same baseline risk elements, release scenarios, release pathways and possible mitigation measures. PV stakeholders stated that the standardization afforded by a RA tool is especially necessary because they felt that some PV facilities may be using less robust RA methodologies and an outbreak anywhere in the world threatens eradication. Moreover, some PV stakeholders commented on the unnecessary expenditure of effort currently required by each PV facility to develop and improve their own RA methodologies; a standard RA tool could save resources across the research community.

When considering the use of the tool in the context of meeting GAPIII requirements, PV stakeholders agreed that the tool could be **used to boost confidence in the importance of the most controversial GAPIII requirements by showing their value at reducing risk.** In contrast, PV stakeholders disagreed if the tool should be used to refute GAPIII requirements that are burdensome but may be shown to have little real value in risk reduction. While some felt that there is still an opportunity to tweak the GAPIII requirements to better suit the needs of the PV research community, others felt that any notion that the requirements may be flawed may undermine the entire regime. The most controversial requirements included showering out, the decontamination of effluent (which is most problematic if shower water must be decontaminated) and the inability to use rtPCR to show that PIM contains no PV[10] (or at least has a minimal risk of containing PV).

Similarly, some stakeholders expressed a desire to use the tool to help reduce the stringency of GAPIII requirements on laboratories that can demonstrate their PV work constitutes low risk whereas others thought that lacking a uniform global standard would sow confusion. For example, some stakeholders felt that the tool could demonstrate that laboratories served by sophisticated, closed sewer systems have a *de minimis* risk of loss of containment via wastewater and so should not be required to treat effluent, while laboratories served by rudimentary, open sewer systems should still meet that requirement. Likewise, given the fact various types of PIM have different probabilities of carrying active PV (compare fecal samples from areas where polio was endemic to respiratory samples from areas where OPV was used), risk mitigation measures COULD be tuned to the type of PIM manipulated in a facility, but once again, this tuning would break the uniformity of GAPIII, and could create multiple, inconsistent global standards (beyond the types of PIM already described in GAPIII). Moreover, the capacity of local public health to identify the first infections with PV and contain an outbreak with rapid patient isolation and vaccination could affect the consequences of an outbreak , and therefore facility risk mitigation could be scaled accordingly, with the same disadvantage of promulgating multiple standards.

5.4.5. Requirements: Outputs and Inputs for a Risk Assessment Tool

This section describes the requirements for the inputs and outputs of a potential tool, which are summarized in Table 3.

Table 3. Summary of Requirements for Tool Outputs and Inputs

Tool Requirement	Rationale/Description
Enable the identification of previously unidentified elements of risk	Stakeholders felt that their RA processes may miss unexpected pathways for loss of containment (LOC).
Enable the identification of mitigation measures that require minimal capital investment	Laboratories are often short on funding and, critically, space to implement changes to their capital equipment
Enable the tool to inform specific aspects of SOPs	Facilities face specific data gaps when developing SOPs that tool could inform

[10] While the prohibition against using rtPCR to determine presence or absence of poliovirus in PIM is not explicit in GAPIII, the guidance for non-poliovirus facilities (April 2018), states, in bold type no less, "[b]ecause no diagnostic test is 100% sensitive and available tests may differ widely in their sensitivity and degree of validation, it is impossible to exclude the presence of PV in a given sample. (p.6)"

Tool Requirement	Rationale/Description
Ensure the tool is quantitative	Several aspects of risk are facility- and experiment-dependent, which stakeholders feel only a quantitative tool can thoroughly capture and model
Enable the comparison of risks of local infection to other risks to eradication	Stakeholders feel comparing laboratory risk to other risks would ensure risk mitigation measures were not excessive

PV stakeholders commented that a tool would be useful to **identify previously unidentified elements of risk**. As described above, because the risk landscape is changing as eradication nears, a quantitative RA tool could account for changes in probability or consequence of various loss of containment incidents as population immunity wanes, and thereby identify new pathways and mitigation measures to address them. Also, a PV tool can identify elements of risk that simply have not been problematic in the experience of the PV stakeholders but certainly could contribute to risk. For example, a long-established PV laboratory we visited had a robust RA and risk mitigation process which led to SOPs to mitigate the risk of accidents in many procedures conducted in their laboratory. However, they lacked an SOP for an accident that involved the vortexer—such as the cap improperly secured. Given that human error could easily cause the cap on a tube to be improperly placed (such that it leaks or comes off when agitated), this accident should most certainly be considered. An RA tool that incorporates human error into its loss of containment pathways would clearly identify vortexing as a procedure that could drive risk and recommend that SOPs be developed to respond to vortexing accidents. Similarly, since all PV stakeholders recognize that PV is not a respiratory pathogen, most stakeholders discounted mitigation measures on aerosol hazards, but this belief is based largely on intuition, not evidence. A PV tool could determine how important aerosols are for loss of containment of PV (via swallowing of some airborne particles) and support risk mitigation measures that are commensurate with risk.

PV stakeholders unanimously voiced a desire for the tool **to identify risk mitigation measures that require minimal capital investments**. A tool that pointed only to new physical systems or engineering controls as mitigation measures (beyond those already specified in GAPIII) would be of minimal use because many PV laboratories (especially in the developing world) have modest resources and, critically, are highly space-constrained so that new equipment may be difficult to site. In contrast, many effective risk mitigation measures can be implemented without the purchase of any capital equipment. In meeting this requirement, the tool should identify where SOPs are needed to address risky accidents, non-conforming events and exposed workers. The RA tool should also identify where changes in a protocol could reduce risk (such as the implementation of directional movement of material to ensure that all PV-contaminated material cannot be carried to an area that is otherwise virus-free) and minor equipment and laboratory workflow modifications (such as the placement of small vortexers or centrifuges in a BSC , secondary liquid waste containment or the segregation of centrifuge tubes to workstations near the appropriate centrifuge). Lastly, the tool should identify where training is necessary to address critical elements of human error (for example, if contamination of the hands after glove removal is shown to be a significant risk driver, extra focus on the safe removal of gloves and thorough handwashing could be valuable).

Similarly, various PV stakeholders noted that the tool could be used to **inform specific aspects of SOPs.** For example, data on the shedding of PV by those infected in the facility could be used to

inform SOPs for isolation. Specifically, the tool could be used to determine how infection risk changes over time for unvaccinated children in the same household as someone infected in the facility or how risk changes over time from PV shed into the sewer versus a chemical toilet. As another example, stakeholders have doubts about the efficacy of current destruction/decontamination/ deactivation protocols. The tool could be used to determine how various protocols affect infection risk of those in contact with previously contaminated materials.

PV stakeholders recognized that, in order to accurately capture risks specific to each PV facility and vaccine development site, **the tool must be quantitative**. This requirement is based on the fact that probability of infection is driven by the amount of active virus in the exposure inoculum, which, in turn, is a function of the culture titer and volume. Frequency of exposure events is a function of the frequency of accidents, which is, in turn, a function of the number of opportunities for failures, a number directly proportional to how frequently various experimental manipulations are conducted. A quantitative tool would recognize the differences in loss of containment risk of a facility that infrequently works with very small cultures of live virus versus a facility that produces liters of virus on a daily basis, and would enable the tuning of risk mitigation measures to those differences in risk. Without the ability to tune risk mitigation measures to the manipulations conducted in any particular facility, risk mitigation measures suggested by the tool would be mismatched, likely either too permissive to reduce risk adequately or too extensive and therefore cumbersome and not cost-effective. Moreover, accounting for site-specific practices in the facility would build confidence in both the tool and evidence-based risk assessment broadly, by ensuring that the measures are indeed relevant to the activities in each facility.

Given that any work with infectious agents carries some risk of infection and loss of containment, PV stakeholders noted that **the tool should allow the comparison of risks of local infections to other risks that threaten eradication** (from continued vaccination with OPV, long term shedders, unidentified PIM or the intentional *de novo* synthesis of PV by a malicious actor). This comparative approach could help ensure that laboratories are not forced to adopt excessive risk mitigation measures in an attempt to reduce risk to zero. Although PV stakeholders asked for the tool to enable this comparative assessment, data on some of these risks (such as the likelihood of malicious actors synthesizing PV) would be unavailable, so not all risks can be modeled. Consistent with the theme of comparative risk, one facility suggested that the risk that public health, medical and scientific data could be lost (and the health consequences of that loss) should be compared to risk of loss of containment accidents given that some facilities are facing a choice of shutting down or destroying valuable PIM if they are forced to meet GAPIII standards.

5.4.6. Requirements: Data Sharing in the Context of an Risk Assessment Tool

This section describes the requirements for how a potential tool could foster data sharing, which are summarized in Table 4.

Table 4. Scope and Purpose Tool Requirements

Tool Requirement	Rationale/Description
Ensure shared data remain anonymous	Stakeholders feel their data must remain anonymous
Enable a mechanism for expert feedback, potentially via data aggregation	Stakeholders feel receiving feedback from NACs and WHO would be valuable, subject to data-sharing anonymity constraints.

Tool Requirement	Rationale/Description
Enable the identification of best practices	A tool that aggregates data for analysis could identify practices that most reduce risk and then share those practices with the community, fostering broader uptake
Enable the identification of critical control points	A tool that identifies the riskiest pathways could focus mitigation efforts

An RA tool can benefit biorisk management in several ways. As discussed above, the tool could be used by facility personnel to improve biorisk management in that facility. A tool could also be used to share data with the National Authority for Containment (NAC) to facilitate auditing (to direct auditors to the riskiest elements within the facility or to provide pre-audit advice on further mitigation measures that should be developed). Lastly, if the tool enables data sharing across the entire community, each facility could benefit from the data and analysis of all laboratories. For this reason, PV stakeholders were asked about their requirements and limitations on data sharing.

PV stakeholders agreed that **data sharing is desirable but must be anonymous** (both within the community, internationally and with their NAC). This requirement for anonymity precludes the use of a RA tool to guide audits of particular laboratories, but does not preclude the use of the tool by auditors to identify, for the type of facility about to be visited, which equipment and practices should be most scrutinized because they have the most potential to reduce risk in similar laboratories.

PV stakeholders expressed a desire to get **feedback and advice from nationally recognized experts, the NAC and WHO**. While the desire for anonymity prohibits direct interaction via the tool between the facility and outsiders, the desire for anonymity permits several types of data to be shared, which were named by PV stakeholders. In short, the **tool could collect anonymized data and aggregate it for analysis**. This aggregation and analysis would enable the creation of a list of Frequently Asked Questions that could be answered by nationally recognized experts, the NACs or WHO (the answers could be informed by the tool used by these groups). The outputs of the tool could identify specific practices implemented by one (or more) unidentified site(s) that reduce risk for particular manipulations more than those implemented by the rest of the community, thereby **identifying best practices**. The tool could also identify the manipulations or release pathways that contribute most to risk and the measures that most reduce risk, **identifying critical control points**, which should be the focus of training, inspections and perhaps, the subject of innovation.

Some PV stakeholders were uncomfortable sharing data on identified deficiencies or the insufficiency of long held practices in well-established laboratories. These stakeholders felt that the benefit of addressing these deficiencies publicly was not worth the risk of broadcasting that PV research may not be safely conducted. Notably, however, these same stakeholders thought that a primary use of the tool should be to identify these deficiencies and insufficient practices privately, within the facility, for improved risk mitigation.

6. CONCLUSIONS

1. Eradicating poliovirus is a critical public health effort, and the world is well on its way toward accomplishing that goal.

2. GAPIII provides global consensus recommendations on how to minimize the risk of a poliovirus research facility re-introducing poliovirus into a community post-eradication, and efforts are ongoing in the US and elsewhere to comply with GAPIII requirements and guidelines.

3. As presented in Section 5.4, however, GAPIII relies heavily on facilities to make their own decisions, and additional critical information may be required to accomplish risk management.

4. Little poliovirus-specific information (such as data to front-load best practices for decontamination, worker surveillance, incident reporting and investigation) is provided by GAPIII, GAPIII-derived guidance, or included in literature. Consistent and available data sources, at a minimum, might improve facility-specific decisions, even if risk assessment methods differ.

    a. Of particular note, many statements about risk, including pathways and prioritization, rely on data derived from vaccine production facilities. In considering risk assessment and risk management for all PEFs, it cannot be assumed, without more research, that a research laboratory, for example, is a scaled-down production facility.

5. A more robust approach to risk assessment and risk-based decision-making is needed to ensure that the least capable PV facility is performing an adequate risk assessment

    a. Given that risk assessment practices vary widely and the minimum requirements for risk assessment are rather limited and vague, a facility could easily comply with RA standards and still not recognize all critical elements of risk or the most cost effective risk mitigation measures. The consequences of one loss of containment event are the imperiling of global eradication.

6. As described in Section 5.5, the proposed risk assessment tool could improve and assist risk management in two major areas. First, the tool could address the GAPIII information gap by incorporating the missing information into the tool and providing it to users during the risk management process. Second, the requirements data gathered in this study clearly show that an RA tool could address many critical gaps in PV biosafety that may threaten global eradication:

    a. The tool could help standardize RA globally, improving practices in unsophisticated facilities and reducing the burden of conducting good RAs in the community.

    b. The tool could address known weaknesses in experience-based RA, including the inability to account for a shifting risk environment and an inability to accurately account for risk of very rare but catastrophic events.

    c. The proposed quantitative nature of the tool could enable the consideration of how experimental frequency and culture volumes and titers affect risk, both enabling the tool to be tailored to each lab, and enabling the tool to point to specific measures that may most reduce risk.

d. The tool could help provide a strong evidence basis for the necessity of various risk mitigation measures, thereby strengthening the culture of containment in the PV community.

7. In addition, PV stakeholders stated several requirements necessary for the tool to best meet their needs, namely:

    a. The tool should enable the assessment of all scenarios/incidents illustrated in GAPIII, including both biosecurity and biosafety incidents.

    b. The tool should be able to integrate into existing risk assessment and management practices.

    c. Because risk can never be completely eliminated in active disease research laboratories, the tool should be comparative, considering risks from vaccination, long term shedders and unrecognized PIM.

    d. The tool should allow the anonymous sharing of data in the PV and regulatory community. The aggregated data could be analyzed to identify Frequently Asked Questions (allowing an avenue of feedback from national experts, NACs and WHO), the sharing of best practices and the identification of critical control points that contribute most to risk.

In sum, while the ongoing efforts to ensure global containment and GAPIII compliance are laudable, much could be done to improve poliovirus knowledge and risk management, which would support GAPIII compliance and help ensure the world remains poliovirus-free after eradication. Given the conclusions above, **we recommend that data to better inform critical risk-based decision-making be gathered and refined, and that the tool proposed in this report be developed**.

6.1. Recommendations

6.1.1. Recommendation 1. Improve Quality of and Access to Poliovirus Data

Regardless of whether tool development is undertaken, improving quality of and access to data to inform facility-specific risk-based decision-making will benefit poliovirus containment efforts. Options include, but are not limited to:

- Development of "crowd-sourced[11]" data on properties of poliovirus sources and manipulations that can be used in facility-specific risk assessments and also could inform tool development
    - For example, the Pathogen Safety Data Sheet format (or similar) included as Appendix B could be available for web-based and monitored editing, allowing poliovirus stakeholders to update information that might be critical to poliovirus risk control, but not necessarily publishable.
- Refinement of the catalog of practices, or similar, begun in Table 2 for use as a starting point for risk assessment and risk-based mitigation selection. This document could provide helpful information and common vocabulary for both the facilities and the national authorities.

[11] For example, a wiki-like platform

- Collection and evaluation of poliovirus-specific practices to then develop best practice guidance on critical control measures
    - Examples include:
        - Medical surveillance of workers, either routinely or after a potential exposure incident
        - Incident definition, reporting, response, and investigation protocol guidance to provide increased diligence towards scenarios with potential to contaminated or expose workers
        - A suite of suggested disinfection, decontamination, and destruction methods, along with suggested protocols for facility-specific validation.
        - The potential contribution of aerosols or fomites to poliovirus ingestion risk

6.1.2. Recommendation 2: Develop the Tool

Given the strong stakeholder consensus for tool requirements, utility and development, were a tool to be developed, tool development should be completed in three major phases: data collection, model & user interface development (development of both can occur concurrently), and piloting. Below, we describe each phase in more detail.

6.1.2.1. Step I: Data Collection

As described in Section 3.2, building a quantitative model requires a significant amount of accurate data on facility containment features and their risk reduction properties, types of experiments conducted, and epidemiological data on the infection dose-dependence and transmission of poliovirus. For example, modeling just the first stages of a spill incident would require knowing the type of flasks used in poliovirus research, their failure rates when dropped, and the volumes likely to be spilled. Although this example is specific to a particular type of tissue culture system, the model will consider the variety of manipulations conducted across the PEFs (including microtiter plates) and the variety of experiments conducted (including neutralization assays, sequencing, mouse work, etc). Computing the consequences of that event just for potential hand-to-mouth transfer would requiring knowing, for example, glove failure rates, glove doffing failure rates (to determine how much virus may transfer to the body), and hand washing effectiveness for polio. Computing the risk of ingested droplets that may be created as a result of the spill would require an additional set of data. Given the importance of these data, prior to building a model, a data collection effort to gather all relevant data must first be undertaken. The vast majority of these data would be collected by the research team (for data underpinning risk factors common to all PEFs) whereas the PEFs themselves would input only data specific to their facility (such as experimental type and frequency). In this way, the tool can be loaded with the best available data, enable the modeling of various types of experimental manipulations and environments for polio research, and yet calculate risk specific to each facility.

Gathering these data would require a data collection effort composed of literature searches and stakeholder re-engagement. Notably, much of the poliovirus-specific data have been gathered in the literature searches already conducted by the study team. In addition, much of the pathogen-independent data (for example, glove failures) have already been gathered by the study team on prior efforts, significantly reducing the required effort. However, some data, both poliovirus-specific and poliovirus-independent, remain to be collected and thus would require a new effort. These data were not yet collected because the need for these data will be driven by the functions and pathways

embedded in the risk assessment tool, which will be defined early in the next phase. Importantly, some data, particularly the specifics about which experiments are conducted (for example, when centrifugation is done in a BSC or not), are available only via direct interaction with stakeholders, and so would require re-engaging them via phone or, ideally, a small number of in-person interviews. Adding interviewees from outside the U.S. will be vital to assure global relevance for the tool.

In some cases, quantitative data may not be available for all model features. In prior similar efforts, the study team has undertaken multiple approaches to overcome this challenge. In certain cases, limited experiments can be conducted to estimate the missing data—for example, our staff can experimentally drop culture flasks to estimate their failure rates, as we have done for other efforts. In other cases, analogous data from other scenarios or industries can be used as an estimate in the life sciences laboratory. For example, human reliability data in life science laboratories is severely lacking, and in prior efforts, the study team used data on categories of errors (motor mistakes, misreading instructions) studied in other industries (such as aerospace or nuclear power) to create analogous error rates in the laboratory. In all cases where data are estimated, the model underlying the tool could perform a sensitivity analysis to determine how finely risk estimates depend on the specific value of the estimated parameter, to provide insights into the uncertainty of the computed risk.

Because the underlying data are in some cases lacking, the tool itself has one critical limitation: the tool will be unable to produce absolute risk estimates (number of infections per year due to accident, for example) and instead will produce only relative risk information (for example, that tissue culture experiments are more risky than sequencing experiments or that training on proper doffing of gloves may reduce risk more than additional respiratory protection of workers). Relative risk information is feasible for the tool to provide because the uncertainty associated with limited data affects calculations for many risk pathways and to the same degree, so any error is compensated by the comparison.

6.1.2.2. Step IIA: Model Development

Once data have been gathered, these data can be incorporated into the statistical model that computes the probability and consequences of loss of containment events. Like our prior work gathering data, the research team has previously built statistical biosafety models to support similar prior efforts, and the underlying model frameworks could be re-used for poliovirus. Prior efforts have used a combination of stochastic fault tree models inside the laboratory, to model the probability and consequences of each step along a release pathway (for example, how well a researcher removes their gloves is a single step), and a branching process model to incorporate local differences in public health capacity, vaccination rates, etc., to simulate local spread of infection in a specific community. Both components of the model are necessary because the risk that a loss of containment incident turns into a local, or potentially global, outbreak is a function of how the incident occurred. For example, incidents where exposures of facility personnel (or the public) are known are likely to be of lower risk because health surveillance measures and social distancing measures will be enacted. However, incidents that are not noticed (such as a worker leaving a facility with contamination on his/her hands—due to improper removal of gloves and handwashing—and infecting his/her family members) may pose a greater risk of a larger local (and global) outbreak.

The team will develop a single model for various types of release scenarios, facility types and risks (such as worker infection and infection outside of the laboratory). Behind the model dashboard will be a series of fault tree models that explore the probabilities of failure and consequences of failure of

a series of cascading events initiated by an incident that could lead to an infection. The probabilities and consequences at the end of each branch of the tree is compared across all incident types to understand the relative risk of all incidents modeled. In this way, this single tool can use data input by each PEF to understand the variety of risks associated with their specific facility. Although the amount of parameters included by the development team will be quite extensive (likely more than 100), the PEFs will need to put in just the data that describes their specific experiments and facility (such as numerical entries for frequency of experiments and volumes and selection of various containment equipment from a pulldown menu).

6.1.2.3. Step IIB: Development of User Interface

At the same time the model underpinning the tool is being developed, the interface of the tool can also be developed. The interface would provide a visual display of the outputs of the model in an easy to understand and easy to manipulate way. Developing the model and the tool simultaneously ensures that the two components "talk to each other" appropriately, and avoids having to re-work the model to be compatible with the interface. As stakeholders will be the final users of the tool, during tool development we envision that design mockups and early versions of the tool interface would be shared with stakeholders to gather feedback on ease of use and available features, to ensure the final product is most usable and best meets stakeholder needs.

6.1.2.4. Step III: Piloting

After the Steps I and II are complete, the research team will have a prototype risk assessment tool. To ensure that the tool is most useful to the research and regulatory community and produces results that are easy to understand, interpret and implement, we suggest that the tool be piloted before it is finalized and widely distributed. This pilot phase can involve several steps. Training sessions could be provided for user groups or stakeholders could be simply given a user guide. The first users could use the tool under the observation of the development team or they could use the tool and report back on its utility and clarity. The outcomes of users that were trained in person could be compared to those who just received the user guide, and both results could be analyzed to determine if the tool itself needs changing (if issues were found by both the instructed users and those who read the user guide only) or if the user guide needs editing (if issues were only encountered by those who were not trained in person). The data from the pilot would be used to further tweak the tool, potentially including new release pathways, altering input or output fields, or changing how results are visualized or communicated. Moreover, since the tool is envisioned to be a platform of sharing biosafety information throughout the community, the look and feel of this tool aspect could be modified.

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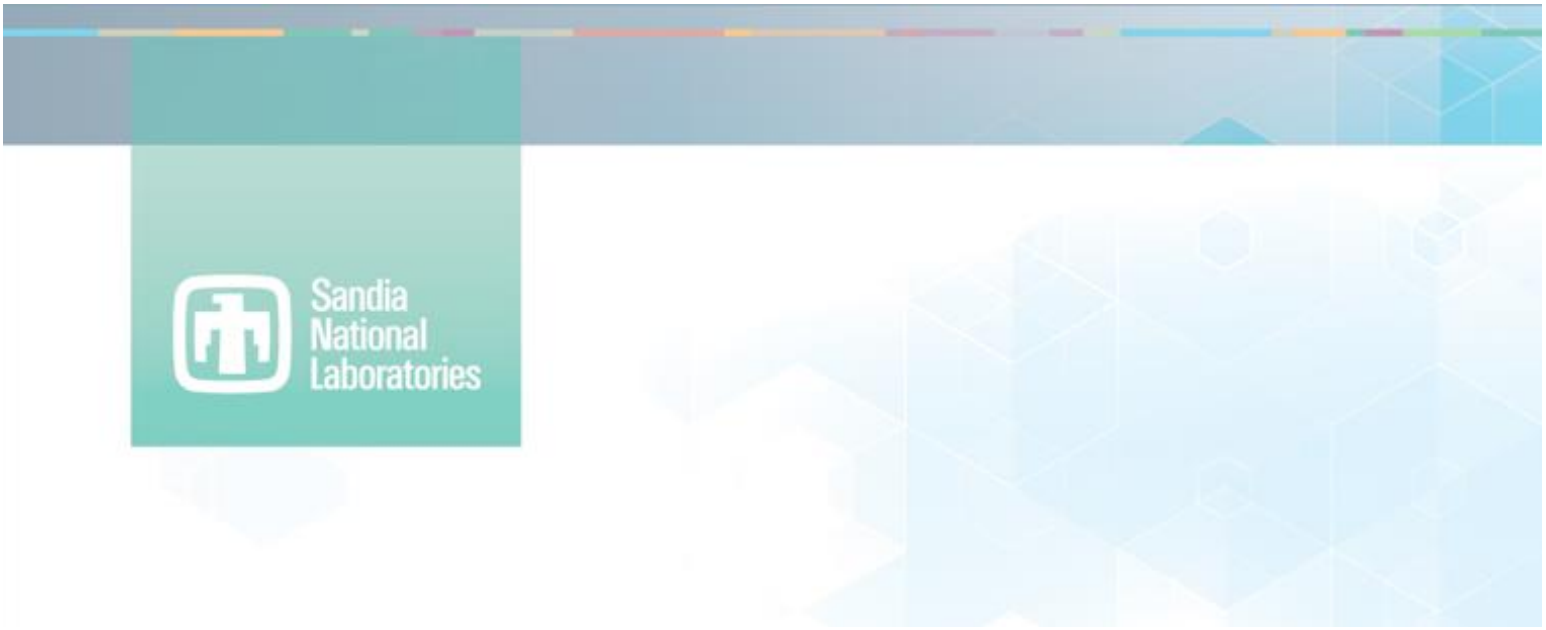
LIST OF APPENDICES



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