Critical Path Analysis
From Detection to Protection
Critical Path Analysis
From Detection to Protection

January 2015
Background

**PIP Framework: The Beginning**

The roots of the discussions that lead to the adoption of the PIP Framework by the 194 Member States of WHO in May 2011 start with the re-emergence of H5N1 in 2003. By 2006, the virus had entrenched itself in the agricultural sector of several south-east Asian countries and there were increasing numbers of sporadic human infections. Manufacturers began to develop appropriate vaccines in 2006 using candidate vaccine viruses developed with viruses provided to the WHO coordinated Global Influenza Surveillance Network (which became the Global Influenza Surveillance and Response System under the PIP Framework). The high cost of these vaccines as well as the anticipated limited supply was cause for great concern by developing countries that queried why they should share viruses with a system that provided nothing in return.

The practices of the WHO coordinated network also came under scrutiny. A consequence of the devastating 1918 pandemic, the surveillance network informally started in the late 1940’s and comprised a few public health laboratories specialized in influenza working together in a collaborative and informal manner. The objective was to gain knowledge about influenza, conduct regular surveillance, and ensure that timely information was shared about emerging viruses. As an informal network, there were no written rules or regulations for the activities conducted by the members. While this informal approach was sufficient for the mid-20th century this was no longer so in the 21st century. Thus, one of the outcomes of the PIP process was the development of terms and conditions to the sharing of viruses – both within the network and with parties outside it.

In January 2007, Indonesia championed the cause of developing countries’ access to vaccines by declaring that it would withhold further sharing of its strains of A(H5N1) viruses with the WHO network until a more fair, equitable and transparent system was developed. Two intergovernmental processes ensued and over four years later, the World Health Assembly unanimously adopted the PIP Framework.

**What is the PIP Framework?**

The Framework is an ambitious and innovative, Member State driven approach to increase global pandemic influenza preparedness and response, including more equitable access to pandemic vaccines. In so doing, it recognizes the role of industry as an important contributor to addressing the challenges of pandemic preparedness and response.¹

Through the Framework, Member States affirmed the fundamental principle that virus sharing and benefit sharing are “equally important parts of collective action of global public health”. As such:

- States should exercise their sovereignty by sharing their influenza viruses with human pandemic potential with WHO’s network - and be made available for use by any interested entity (with appropriate bio-safety/security)
- Users of these materials and information should comply with the benefit sharing mechanisms established in the PIP Framework, notably to conclude benefits sharing agreements with WHO (known as “Standard Material Transfer Agreements 2” or “SMTA 2”) and contribute to the annual Partnership Contribution².

**What is the Partnership Contribution?**

One of the key benefit sharing mechanisms of the Framework, the Partnership Contribution is an innovative approach to improve the world’s readiness for pandemic influenza, and its ability to launch a robust response. The Partnership Contribution is paid to WHO every year by influenza vaccine, diagnostic and pharmaceutical manufacturers that use the WHO GISRS, for example, by receiving virus materials. The total yearly amount that WHO is to receive is US$ 28 million.

---

¹ WHA64.5, PP4
which is based on the estimated costs to run the WHO GISRS\(^3\).

The Director-General decides how the funds should be used, based on advice and consultation with the Advisory Group\(^4\), as well as interaction with industry and civil society\(^5\). The WHO Executive Board also plays a central role, deciding on how much is allocated to preparedness on the one hand, and response on the other\(^6\).

For the period 2012-2016, the Executive Board decided on the following division of PC funds: approximately 70% to preparedness measures and 30% response activities, recognizing the need and usefulness of flexibility in allocating funds\(^7\).

---

\(^3\) See PIP Framework section 6.14.3 Footnote 1 which establishes that the reference index for the Partnership Contribution will be the running costs of GISRS which, in 2010 were estimated to be US$ 56.5 million. The Partnership Contribution was set at 50% of those running costs which may change over time.

\(^4\) The Advisory Group is an independent group of 18 experts that provide advice and recommendations to the Director-General on the implementation of the Framework. See Section 7.2 and Annex 3 of the PIP Framework for more information.


\(^7\) See EB 131/4 http://apps.who.int/gb/ebwha/pdf_files/EB131/B131_4-en.pdf

---

Introduction

What is the CPA?

This Critical Path Analysis provides a high level overview of the complex, multi-sectoral ‘path’ that starts at the time of the detection of a new influenza virus and culminates with the protection of the global community. The CPA aims to succinctly and clearly:

- Show the extent of the work to be undertaken to strengthen global capacities from detection to protection,
- Highlight areas that are weakest and need strengthening
- Validate and provide the context and rationale for the specific interventions chosen by WHO (including costs) for the period 2013-2016;
- Provide the expected impact of the funds in improving global preparedness.

The CPA will serve as the roadmap for current and next phases of work, enabling all stakeholders to:

- Share a common understanding on the process steps;
- Highlight priorities for intervention;
- Engage in strategic discussions and long-term planning with a view to better preparing the world for the next pandemic influenza.
- Ensure that, in time, all elements of the path are addressed.

---

Note:
This document will be shared with Member States and posted on the PIP web page.

This document is a companion piece to Gap Analyses and Partnership Contribution Implementation Plan (2013-2016), both published in January 2014, and which identify gaps and needs to improve global pandemic readiness and identify priority areas of work (AOW) for 2013-2016.
The Four Steps of the Critical Path: From Detection to Protection

The Path has 4 steps which each have several elements within them. The remainder of this document provides details on each of these steps. Each step is accompanied by an illustration. Within those illustrations, where possible and relevant, references have been provided to specific elements of work in the PIP PC Implementation Plan 2013-2016. With respect to each illustration, the following applies:

- Boxes in bold colours reflect activities that have been selected as priorities in the PIP PC Implementation Plan 2013-2016.
- Below each bold box, there is a code (e.g. L&S O1K1) which refers to the following in the PIP PC Implementation Plan 2013-2016:
  - The first 3 capitalized letters refer to the Area of Work as follows:
    - L&S: Laboratory & Surveillance;
    - BOD: Burden of Disease;
    - REG: Regulatory Capacity building;
    - DEP: Planning for Deployment
  - The next letter and number (e.g. O1) refer to the Output in that Area of Work and the last letter and number refer to the Key Deliverable (e.g. K1) in that Output.

Further information on the activities being implemented, as well as financial details, are found in the PIP PC Implementation Portal. (To access the Portal click on the following link: https://extranet.who.int/pip-pc-implementation/).

- Boxes with dotted outlines are elements of the Critical Path which are in need of strengthening but were not selected as priorities for the first phase of PIP PC implementation (2013 – 2016). Subject to their continued relevance and the availability of funds, they could be addressed in the next phase(s) of implementation (2017 and beyond).
PANDEMIC INFLUENZA PREPAREDNESS (PIP) FRAMEWORK - Critical Path Analysis - From Detection to Protection | 7
**Step 1 – Pandemic Risk Assessment**

**Objective – Why this step is important**

Pandemic influenza begins with the emergence of a new influenza virus for which the public health and economic impact is unknown. When a new virus is detected through effective surveillance systems, further work is done in laboratories to understand its characteristics, the disease it causes, and its potential impact on the population and the health system. Virological data and disease information, as well as other kinds of data (worker absenteeism, economic impact, impact on travel and trade) are integrated to contribute to an overall risk assessment that can inform public health decisions that, in turn, become the basis of appropriate response measures. Comparison of data to previous influenza pandemics and seasonal epidemics is key to tailoring an appropriate response.

While pandemic influenza necessarily starts with one case, the virus quickly spreads in communities and across borders producing disease in many areas and countries. Thus, although National response strategies are fundamental, the rapid and extensive spread of the disease always requires a global, coordinated response. This challenges systems to work together to share information and materials in a rapid, systematic and timely manner.

**Key Results - What the step provides/produces**

Development of a comprehensive assessment of the risk posed by the new virus requires the following three types of information and, where relevant, appropriate materials, that should be widely shared:
- Information about the virus (e.g. virulence, diagnostic features, antiviral susceptibility information, etc.)
- Information on the disease and existing immunity among populations (e.g. seriousness, risk factors, risk groups, speed of spread, etc.)
- Materials such as diagnostic reagents, vaccine viruses and potency reagents

To be useful and accurate, a global risk assessment must compile information from many different geographical areas and critically compare and assess findings against previous events of seasonal influenza outbreaks, making use of existing disease burden information.

**Key Capacities – What capacities are necessary to undertake the step**

Issuing an informative and accurate risk assessment for the use of stakeholders across all sectors (e.g. governments, international institutions, private and public health) requires the following capacities:

- Capacity at the national level to detect new viruses and investigate the transmission patterns through rapid investigation and response teams.
- Capacity to monitor the disease as it spreads. The monitoring system must integrate laboratory and epidemiological surveillance information.
- Capacity to collect and share information and materials nationally (within a country) and globally (with GISRS) in a timely manner.
- Capacity to use influenza disease burden data to make public health decisions and prioritize health resources.
- Capacity to use benchmarks from other similar events (e.g. previous pandemic, comparison with seasonal outbreaks) to understand the unfolding of event

**Key Factors of Success: Identifying critical issues and challenges**

A robust and effective response requires solid foundations which include:
- Well-functioning surveillance systems that monitor the spread of the disease and assess disease burden and impact
- Well-functioning laboratories capable of carrying out virus identification and characterization
- Capacity to integrate laboratory analyses with epidemiological information and sharing results broadly
- Timely sharing of materials and information
- Accurate risk assessment

Effective, efficient, accurate and successful completion of this step requires well-trained, informed staff that have the necessary equipment and technical tools to work collaboratively with relevant partners and counter-parts.

With guidance from the Advisory Group, WHO considered and, as appropriate and relevant, applied the criteria listed below to prioritize countries that should receive support to strengthen their laboratory and surveillance capacities or efforts to conduct disease burden studies for the period 2013-2016:

- Country needs for influenza epidemiological and laboratory surveillance
- H5N1 vulnerability
- Country development status
- IHR core capacities
- Political situation of a country, notably whether it is in a complex emergency
- On-going donor funding and investments in a country
- Absorptive capacity of a country
- Country population size
- Geographical location of a country in the region/sub-region (notably for island states)
- Interest of a country/Ministry of Health to work in influenza
- Ability of countries to build on existing capacities to produce influenza surveillance data that can be shared with neighbouring countries.

The Advisory Group also noted the importance of providing Partnership Contribution resources to countries that need basic capacities as well as to countries that have existing capacities but where additional support can serve as a regional resource to other countries.

On the basis of the foregoing, for the period 2013-2016, up to 50 developing countries that meet some or all of the criteria above have been prioritized to receive Partnership Contribution resources to strengthen laboratory and surveillance capacities or to carry out disease burden studies.
Step 1: Pandemic risk assessment

**Influenza virus**

- Sample collection
  - EQAP
  - Preliminary lab diagnosis in NIC

**Cluster investigation**

- National level
  - National risk assessment
    - Lab diagnostic reagent development
      - Lab diagnostic reagents
        - Materials to start development of vaccine

**Shipping fund project**

- Shipping viruses
  - Virus characterization
    - WHO/ECDC/ERL
  - Vaccine virus selection
    - WHO/ECDC/ERL
  - Vaccine virus & vaccine reagent development

**Viruses & Special studies (e.g. animal models)**

- Animal surveillance & Special studies (e.g. animal models)

**Virus characterization**

- Virus characterization
  - WHO/ECDC/ERL
  - Vaccine virus & vaccine reagent development

**Vaccine viruses & potency reagents**

- Vaccine viruses & potency reagents

**Special studies at beginning of a pandemic**

- Special studies at beginning of a pandemic
  - WHO/ECDC/ERL

**GLOBAL INFLUENZA RISK ASSESSMENT & MONITORING**

- Severity assessment
  - Seriousness, spread, impact, immunity
  - Benchmark

**Burden of disease assessment**

- Burden of disease assessment
  - WHO/ECDC/ERL

**Burden of disease of influenza**

**Information for action**

**Communication on pandemic severity**

**PANDEMIC RISK ASSESSMENT**
Step 2 – Medical Supplies Development and Production

Key objective of the step – why this step is important
The aim of this step is to manufacture products that will assist in the prevention, treatment and control of the disease. During pandemic response, the interplay between pharmaceutical and non-pharmaceutical interventions will be critical. This step is part of the global pharmaceutical response that will contribute to reducing morbidity and mortality. It addresses the production and registration/licensing of critical products such as vaccine, antiviral medicine and diagnostics that will be used to ensure robust and successful response interventions.

The timely use of vaccine and antivirals reduces morbidity and mortality in affected populations. Preventing influenza, through use of vaccines, also helps reduce transmission. Diagnostic products are also important at certain times in a pandemic to verify the presence of the pandemic virus and monitor its spread in populations.

Key Results - What the step provides/produces
This step will produce vaccines, antiviral medicines, and diagnostic products that meet the highest standards of quality and safety.

Key Capacities – What capacities are necessary to undertake the step
Two critical and intimately linked capacities come into play in this step:
• Capacity to manufacture products under good manufacturing practices and meeting the WHO pre-qualification standards.
• Functioning regulatory authorities that have established processes to expedite review, registration and market authorization for specific products.

Key Factors of Success: Identifying critical issues and challenges
Successful implementation of this step is essential for an effective, timely and high-impact pandemic response. The challenges to success, however, are significant and may include addressing some of the following issues, depending on the characteristics of the emerging pandemic:
• Overlap with seasonal vaccine production: the timing of when a pandemic virus emerges in relation to northern or southern hemisphere seasonal vaccine production cycles, will be extremely important in deciding when to switch from seasonal to pandemic vaccine production;
• Regulatory issues related to product approval, registration, licensing and/or market authorization will affect the timing of availability in different markets;
• Results of clinical trials for vaccines or new antiviral medicines as appropriate; and
• Communications on the safety and efficacy of these products, and the process that will be established to make them available in a structured, predictable, fair and equitable manner to countries and communities.

Activities to support successful implementation will include:
• Refining the WHO Regulatory Systems Strengthening (RSS) tools to assess regulatory needs for influenza products including vaccines, antivirals and diagnostics;
• Addressing regulatory capacity building needs and providing technical support as per the Institutional Development Plan (IDP) for select countries in each WHO region;
• Developing tools to monitor and evaluate progress to address gaps identified in the IDP; and
• Developing and operationalizing post-marketing surveillance systems to ensure that product specific adverse events are recorded, assessed by national regulatory authorities and, where appropriate, corrective measures are taken.
Step 2: Medical supplies development and production

- Prepare & submit regulatory dossier
- Formulation
- Clinical trials
- Prepare clinical materials
- Produce working seed

- Functional NRA
  - REG O1K1&2, REG O2K1&2, REG O3K3
- Common regulatory approach
  - REG O3K1

- Product registration application & review *
- In non-vaccine producing countries

- Market authorisation granted
- Import licence

- Filling
- Packaging

Communication on vaccine or medicine safety & characteristics
Step 3 – Deployment

Key objective of the step – why this step is important
Products such as antiviral medicines, vaccines and diagnostics, play a critical role in the control and treatment of pandemic influenza. During a pandemic, not all countries will have access to life saving products. It is therefore of paramount importance, in line with the spirit of the PIP Framework, to facilitate access by the largest number of countries in need, to pharmaceutical interventions.

During a pandemic there will a many different products to deploy to a large number of countries at different times, and by different manufacturers or partners. Deployment\(^{6}\) needs to be carefully orchestrated to ensure that products are sent in a timely manner, to the places where they are most needed and where they can be used efficiently and expeditiously. The efficient distribution of scarce resources will be a barometer of success of global pandemic response.

Deployment of pandemic influenza response products brings together numerous stakeholders – public, private and non-governmental. This requires effective coordination in a significant number of areas including logistics, supply management, and regulatory affairs. Ensuring coordinated actions among stakeholders is critical to ensure timely, equitable, safe and effective interventions. The following are essential functions of government:
• To ensure the rapid registration, review and market authorization of pandemic response products so that they may be distributed in country and used as rapidly as possible once they are available from manufacturers and/or donors;
• To develop, maintain, test and update as necessary, plans to distribute/administer vaccines, antivirals, laboratory diagnostics, and other ancillary pandemic response products; and

Key Results - What the step provides/produces
The key result of this step is the efficient and effective deployment of essential pandemic response products to countries in need. This assumes the development of appropriate tools to manage deployment operations. Activities to achieve this include:
• Developing a common approach to manage deployment operations and sharing it with stakeholders and deployment partners;
• Develop a logistics tool to simulate potential distribution options based on known variables, including costs;
• Develop generic simulation exercises to test the tool; and
• Revise, update and simplify country deployment readiness plans, including model agreements between WHO and country recipients.

Key Capacities – What capacities are necessary to undertake the step
The following actions have been identified to ensure optimum deployment during a pandemic:
• Development of appropriate national plans to anticipate needs at the time of distribution of pandemic supplies (material, technical, financial);
• Development of appropriate regulatory mechanisms to rapidly, efficiently and safely approve and make available necessary response products (e.g. antivirals, vaccines);
• Global coordination of partners/donors/manufacturers to monitor and distribute in real-time the products to countries in need; and
• Efficient shipment of different products from different sources to diverse recipients.

Key Factors of Success: Identifying critical issues and challenges
• Coordination: Global coordination and transparency on the timing of availability of products will increase communication and foster timely distribution, maximizing their usefulness (e.g. vaccine distributed after the epidemic peak).
• National Preparedness: National preparedness including adequate distribution plans will improve approval for accessing donations.
• Planning and Forecasting: Improved forecasting of needs, especially for ancillary products, will reduce delays in the use of vaccine.
• Communication: Improved risk communications may enhance vaccine uptake and reduce perceptions of unfairness in the deployment process.
• Management: Efficient management of global stocks will reduce loss of products.
• Shipping: Effective organisation and quality of virus shipments will reduce costs and delays in risk assessment.

\(^{6}\) For purposes of the PIP Implementation Plan and the CPA, “deployment” is meant to cover access to, and shipment and transport of pandemic response supplies and materials to the first point of entry into a recipient country. It does not cover in-country distribution.
Step 3: Deployment

Manufacturers

WHO

Prioritize country recipients

Plan initial demand

Activate SMTA2s & Country Recipient Agreements

Activate national preparedness plans

Prepare master allocation & logistics table with all stakeholders

Regular review of demand & stocks

Operationalize national plan

Package / prepare / approve shipments

Ship products

Communication on vaccine & medicine availability

National level

PANDEMIC INFLUENZA PREPAREDNESS (PIP) FRAMEWORK - Critical Path Analysis - From Detection to Protection | 13
Step 4 – Response Operations

Key objective of the step – why this step is important
The last step of the process is the implementation of response and control measures at the national level. Countries must ensure receipt and distribution of response products to their populations. Micro-planning for implementation of pharmaceutical interventions will ensure efficient and effective allocation of scarce resources.

Key Results - What the step provides/produces
The ultimate goal is to ensure that populations are protected and receive vaccine and adequate treatments in a timely manner. The capacities necessary to undertake the step are:

- Adequate facilities to receive, store and distribute products;
- Capacity to implement or operationalize response measures as set out in national plans;
- Micro-planning for the distribution and use of products at national level;
- Management of emergency vaccination campaigns (cold chain, waste management, financial and human resources, logistics, security);
- Systems to monitor interventions and impact (e.g. monitoring of adverse effects of vaccine or treatment, population coverage, impact on epidemiological trends and mortality); and
- Communications on risk management.

Key Factors of Success: Identifying critical issues and challenges
Lessons learned from the 2009-2010 pandemic have been gleaned and analysed. Anticipating issues such as those outlined below, and preventively putting in place mitigation measures should ensure that the same errors are not repeated.

- Logistics issues:
  - Vaccine stuck at the airport - delay in customs clearance
  - Waste of products due to bad distribution processes
  - Inadequate implementation of vaccine campaigns or treatment protocols;
- Pharmaco-vigilance: Establish systems to monitor and report adverse effects, and rapidly intervene in case of unexpected AEFI (Adverse Events Following Immunization)
- Real-time response intervention monitoring will allow timely corrections;
- Communication: Real-time, targeted, accurate information and communications on the safety and usefulness of products will increase their impact on the spread of the disease and its mortality.
Step 4: **Response operations**

**National preparedness plan & vaccination strategy**

- **Macro/Micro planning**
  - Logistics
  - Cold chain
  - Human & financial resources
  - Social mobilization plan
  - Supervision
  - Training of health workers

- **Implementation of vaccination campaign**

- **Waste management**

- **Monitoring & evaluation**
  - Coverage
  - Adverse events following immunization

- **Regulatory authorisation for use**

- **Reception of medical supplies**

- **Customs: importation**

- **Distribution of product to vaccination centres**

**Communication on vaccine safety & delivery**

**National level**

**PANDEMIC INFLUENZA PREPAREDNESS (PIP) FRAMEWORK - Critical Path Analysis - From Detection to Protection | 15**
Risk Communications – Cross-cutting priority area of work

Risk communications capacity building for pandemic preparedness is aimed at ensuring that countries have staff, structures, policies, procedures, skills and other core elements in place for communicating accurately, effectively and in a timely manner to national and international audiences during public health emergencies of international concern, such as an influenza pandemic. The ultimate aim is for the public and key stakeholders to take key health-protective actions that minimise death, illness and economic and societal impact.

Communication is necessary during each of the 4 steps to avoid and address rumours and increase the confidence of populations in public health interventions – both pharmaceutical and non-pharmaceutical. During the 2009 pandemic, some of the communications challenges identified were:

- **During step 1**: Adequately communicating the severity of the pandemic
- **During step 2**: Effectively communicating about the safety and usefulness of the vaccine
- **During step 3**: Responding to questions about the fair distribution of pandemic response products
- **During step 4**: Addressing issues at country level in relation to implementation of response measures, notably vaccination campaigns, and in particular the low acceptance of vaccination by populations in some countries.

In 2010, following the 2009 pandemic, the Review Committee on the Functioning of the International Health Regulations recommended that WHO develop an organisation-wide communications policy and an approach to improve routine and emergency communications. The Review Committee specified that due consideration should be given to ensuring that this policy matched the content, form and style of media communications.
The International Health Regulations (2005) Checklist and Indicators for Monitoring Progress in the Development of IHR Core Capacities in States Parties (2011) * specifies that countries must develop risk communications capacities in the following nine areas of work, and maintain these essential capacities for use during Public Health Emergencies (PHE), such as pandemics:

1. Identify risk communications partners and stakeholders
2. Develop Risk Communication Plans (RCP)
3. Test RCP through simulation exercises
4. Develop policies, Standard Operating Procedures (SOPs) or guidelines on the clearance and release of information during a PHE
5. Develop an information source that will be accessible and regularly updated with relevant for the media and the public are available
6. Develop relevant and accessible Information, Education and Communication (IEC) materials tailored to the need so of the public
7. Provide info on PHE to public and partners within 24 hours of confirmation of such an emergency
8. After a PHE, evaluate the communications for timeliness, transparency and appropriateness
9. Share the results of the evaluation with the global community

The Review Committee noted that many countries lacked many of these core capacities and were not on a path to compete their plans and infrastructure improvements by the 2012 deadline.

In 2012, IHR self-reporting by Member States showed the following information on risk communications capacities:
- 16% of countries met all 9 requirements, 2% met none of the requirements and 27% provided no reporting
- 55% of countries reported they were at different stages in meeting the 9 requirements above.
  - While this number reportedly increased to 75% in 2014, many countries still lack the ability to provide real-time, transparent risk communications and engagement of the public, using styles and language that are understandable and respect people’s beliefs and fears, including those related to a potential pandemic.
- While most countries report significant progress on the implementation of the IHR, over 80 governments admit that not all capacity requirements have been met, and have requested a further extension of two years to meet requirements.

The PIP PC Implementation Plan 2013-2016 provides details on activities to be undertaken to build Risk Communications capacities.

* See http://www.who.int/ihr/IHR_Monitoring_Framework_Checklist_and_Indicators.pdf
In closing

Ensuring that the right capacities are strengthened

Lessons learned from the 2009 (A)H1N1 pandemic revealed many critical gaps in global and national preparedness. The Critical Path Analysis illustrates and explains the steps from emergence of a new virus to the protection of populations. The CPA will facilitate identifying the critical steps and gaps in the process so that targeted capacity building and strengthening efforts may be designed. In this manner, the lessons of 2009 will be addressed and when the next pandemic virus emerges, the world will be better able to respond effectively, efficiently, transparently, and equitably.

The work to operationalize the Path in full will require several years – well beyond 2016 – and collaboration across many sectors. The work set out as priorities in the 2013-2016 Implementation Plan should be considered the beginning of WHO’s work.

In time, with the support of partners, it is anticipated that the Path will be fully operational: at that time, the world will be prepared and a robust, effective, equitable and efficient global response to pandemic influenza will be possible.