Title
Utilization assessment of infectious disease surveillance data to enhance methods for better understanding disease occurrence, trends and gaps in disease reporting in a resource limited setting: Monkeypox in the Democratic Republic of Congo

Permalink
https://escholarship.org/uc/item/51v3n3hx

Author
Hoff, Nicole Amanda

Publication Date
2014

Peer reviewed|Thesis/dissertation
Utilization assessment of infectious disease surveillance data to enhance methods for better understanding disease occurrence, trends and gaps in disease reporting in a resource limited setting:

Monkeypox in the Democratic Republic of Congo

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Epidemiology

by

Nicole Amanda Hoff

2014
ABSTRACT OF THE DISSERTATION

Utilization assessment of infectious disease surveillance data to enhance methods for better understanding disease occurrence, trends and gaps in disease reporting in a resource limited setting:

Monkeypox in the Democratic Republic of Congo

by

Nicole Amanda Hoff

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2014

Professor Anne W. Rimoin, Chair

Background: Monkeypox (MPX) virus is a zoonotic infection found in a variety of mammals, and infects humans with a smallpox-like illness. In the 30 years since the eradication of smallpox, monkeypox has emerged as the most severe orthopox infection occurring in humans. Most cases have been, and continue to be, reported in the Democratic Republic of Congo (DRC) where MPX is a reportable disease to the Integrated Disease Surveillance and Response (IDSR) unit. Despite the inclusion of MPX in the surveillance system, there may still be a number of limitations as to how accurately and how systematically this data has been collected, thus it is necessary to explore available data for trends in disease occurrence and reporting. Methods: IDSR data consists of weekly reports on 15 diseases of epidemic potential or targeted for elimination or eradication. Case counts of all reportable diseases including MPX, acute flaccid paralysis (AFP), measles and tetanus reported via the IDSR unit to the 4th Direction in the
Ministry of Health of the DRC were available from January 1st, 2001 through December 31st, 2013. The country is made up of over 10,000 public health facilities, which are required to report to the IDSR each week. Data available from the reports include: number of suspected cases and deaths, health zone, province, week reported, and numbers disaggregated by age category. A number of statistical methods were used to determine change in incidence, associations and comparisons with other diseases and lab reporting, and time series analysis. Additionally a model was created with parameters to determine the gaps in the system and to quantify the potential underreporting of suspected MPX cases. **Results:** Between 2001 and 2013, three phases of the surveillance system were identified: the “implementation phase” (2001-2003), the “adjustment phase” (2004-2007), and the “stable phase” (2008-2013). Overall, there was an increase in suspected MPX cases reported via the IDSR. In total, 19,437 suspected cases and 336 suspected deaths (1.7% case fatality rate) were reported. During our study period, the mean number of reported MPX cases weekly was 42 (range: 0 -125). There were provincial differences in MPX reporting by week, however no significant trends were identified. Laboratory confirmed polio cases in a health zone had a negative impact on MPX, tetanus and measles reporting, but had a positive impact on AFP reporting. Health zones with confirmed cases of MPX had a positive association with MPX reporting, but a significant negative association with other diseases (AFP, measles and tetanus). We estimated that the possible under-reporting rate was 9.4 (range 5.0 to 15.2), with the majority (56%) of the cases being missed due to under-ascertainment of health services, and 8.3% lost due to inability to pay for services or visiting locations outside of the public health sector. **Discussion:** Based on trends from 2008-2013, the “stable reporting phase”, the increase in MPX is likely to be a true increase. The analyses indicate that while the system should be integrated (disease detection and confirmation) for all reportable diseases, that each
component may only work within the specific diseases. Each missed case of a person with a suspected disease reduces the true incidence of that disease, leading to underestimates of disease burden. We estimate that only about 10% of the actual cases are making it to the national level. This could significantly limit the ability to detect emerging public health problems.
The dissertation of Nicole Amanda Hoff is approved.

Ronald Brookmeyer
Robert J. Kim-Farley
Jamie Lloyd-Smith
Frank J. Sorvillo

Anne W. Rimoin, Committee Chair

University of California, Los Angeles
2014
DEDICATION

I would like to dedicate this work to my family, friends, and mentors, which with their overwhelming support, I was able to succeed and grow in so many ways these past few years. First, to my parents, you have been pillars of support, always there with unwavering encouragement through all of my studies. They have let me grow and explore the world, and take the time necessary to complete this work. To my brother, Bryce, you have always been a source of motivation and has shown me how to be strong when I wanted to give up. To my friends (too many to name, but you know who you are), near and far and from every step in my life path. You have been there for me when I needed a good laugh and a shoulder to lean on. To those many who have read and re-read, and then re-read again this work, always providing invaluable comments and feedback – I am forever indebted to you. To Andrew, thanks for the chair that helped my posture and gave me a small smile while working through my analysis. Finally, to my advisor and mentor, Anne Rimoin, thank you for believing in me and giving me the chance to work with you on so many projects, not only as a student, but also as a colleague, both in Los Angeles and in the Democratic Republic of Congo. The past five years working with you have included many of the most important lessons I have learned during my education, you have always been there to guide, train, support, and encourage me, and for that I am forever grateful.
TABLE OF CONTENTS

LIST OF TABLES ........................................................................................................................................ ix

LIST OF FIGURES ....................................................................................................................................... x

ACKNOWLEDGEMENTS .............................................................................................................................. xi

VITA .............................................................................................................................................................. xiii

Chapter 1: Introduction ............................................................................................................................... 1
  1.1 Infectious disease surveillance ............................................................................................................. 1
  1.2 Types of surveillance systems ........................................................................................................... 3
  1.3 Surveillance Activities in DRC .......................................................................................................... 6
  1.4 Obstacles to disease surveillance in DRC ......................................................................................... 7
  1.5 Emergence and Epidemiology of monkeypox .................................................................................... 8
  1.6 Clinical features/characteristics of human monkeypox ................................................................. 11
  1.7 Diagnostic criteria of human monkeypox ......................................................................................... 12
  1.8 Mortality due to monkeypox ............................................................................................................ 13
  1.9 Burden of monkeypox ....................................................................................................................... 14
  1.10 Burden of monkeypox in DRC ....................................................................................................... 14
  1.11 References ....................................................................................................................................... 15

  2.1 Abstract ............................................................................................................................................. 24
  2.2 Background ....................................................................................................................................... 26
  2.3 Method .............................................................................................................................................. 28
  2.4 Results .............................................................................................................................................. 31
  2.5 Discussion ........................................................................................................................................ 34
  2.6 Reference ......................................................................................................................................... 47
Chapter 3: Integrated Disease Surveillance in the DRC – are we meeting the goals? A comparison of lab surveillance and passive reporting. ................................................................. 50
  3.1 Abstract.......................................................................................................................... 50
  3.2 Background...................................................................................................................... 52
  3.3 Methods .......................................................................................................................... 55
  3.4 Results............................................................................................................................. 59
  3.5 Discussion......................................................................................................................... 61
  3.6 References....................................................................................................................... 75

Chapter 4: A descriptive and quantitative analysis of potential underestimation of human monkeypox cases in the passive surveillance system in the Democratic Republic of Congo 78
  4.1 Abstract............................................................................................................................ 78
  4.2 Background....................................................................................................................... 80
  4.3 Methods .......................................................................................................................... 82
  4.4 Results............................................................................................................................. 87
  4.5 Discussion......................................................................................................................... 89
  4.6 Reference ........................................................................................................................ 97

Chapter 5: Concluding Remarks ........................................................................................... 100
  5.1 Outcomes and Implications ............................................................................................ 100
  5.2 Limitations ..................................................................................................................... 100
  5.3 Conclusion ...................................................................................................................... 102
  5.4 References ...................................................................................................................... 104
# LIST OF TABLES

## CHAPTER 1

| Table 1. IDSR Reportable Diseases in DRC | 6 |

## CHAPTER 2

| Table 1. IDSR Reportable Diseases in DRC | 40 |
| Table 2. Number of health zones reporting suspected monkeypox cases to the 4th Direction, DRC, 2001-2013 | 41 |
| Table 3. Suspected MPX Incidence in DRC (with and without the active surveillance areas), 2001-2013 | 42 |
| Table 4. Suspected MPX Incidence in selected provinces of DRC, 2001-2013 | 43 |
| Table 5. Average percent change in predicted yearly incidence for MPX, Tetanus, AFP (2001-2013, 2001-2007, and 2008-2013) | 44 |

## CHAPTER 3

| Table 1. Confirmed case of monkeypox (same week) and the association with reportable diseases, Incidence Rate Ratio (IRR) of Reported Diseases in the IDSR, 2008-2013. | 72 |
| Table 2. Confirmed case of Polio (same week) and the association with reportable diseases, Incidence Rate Ratio (IRR) of Reported Diseases in the IDSR, 2008-2013. | 73 |
| Table 3. Confirmed case of Polio (3 to 5 weeks after confirmation) and the association with reportable diseases, Incidence Rate Ratio (IRR) of Reported Diseases in the IDSR. | 74 |

## CHAPTER 4

| Table 1. Base and range inputs for model parameters for quantifying gaps in health system - using MPX reporting numbers | 94 |
LIST OF FIGURES

CHAPTER 1

Figure 1. Clinical features of chickenpox, smallpox, and monkeypox 12

CHAPTER 2

Figure 1. Disease reporting to the 4th Direction, 2001-2013 45
Figure 2. The evolution of IDRS System: suspected cases of MPX, AFP, and Tetanus, 2001-2013 46

CHAPTER 3

Figure 1. Democratic Republic of Congo, Health zone map with the Tshuapa district in red 66
Figure 2a) Weekly trend for suspected monkeypox cases reported from from December 30, 2007 to December 31, 2013 in DRC 67
Figure 2b) Smoothed weekly trend and cycle plot with 1 year forecast 67
Figure 2c) Smoothed weekly trend, cycle and seasonal plot without irregularities 67
Figure 3. Country and selected provincial mean weekly counts (2008-2013) for suspected monkeypox cases reported to the IDSR 68
Figure 4a) Weekly trend for AFP cases reported from from December 30, 2007 to December 31, 2013 in the DRC 69
Figure 4b) Smoothed weekly trend, and cycle plot with 1 year forecast 69
Figure 4c) Smoothed weekly trend, cycle and seasonal plot without irregularities 69
Figure 5. Mean weekly AFP Case counts (2008-2013) reported IDSR 70
Figure 6a) Comparison of mean weekly trends for reported MPX and AFP cases over 6-year period for DRC 71
Figure 6b) Comparison of mean weekly trends for reported MPX and AFP cases over 6-year period for Kasai Oriental 71

CHAPTER 4

Figure 1. Typical reporting flow diagram for the Ministry of Health, DRC 93
Figure 2. Model tree for disease reporting flow for IDSR system. 96
ACKNOWLEDGEMENTS

I would like to start by acknowledging my advisor and mentor, Dr. Anne Rimoin – who believed in me and my work and had the confidence to send me to a French speaking African country, DRC, with almost no international experience, to work with her on on-going projects. For my route to DRC, the confidence in my advisor, and the time I needed to gain experience, I would like to acknowledge Russell Faucett, and the Faucett Catalyst Fund, which supported most of my work aboard through the Faucett Catalyst Fund Fellowship (2011-2013). Without this continued support, I may not have had the chance to flourish and grow, and have the chance to work with so many great researchers and public health leaders during my time in the DRC. Additionally, I would like to thank the members of my dissertation committee. First, to Jamie Lloyd-Smith – who provided much thoughtful feedback and commentary over the years as I moved forward in preparing and completing my analysis for this dissertation. To Ronald Brookmeyer, Robert Kim-Farley, and Frank Sorvillo – who all provided invaluable feedback and shared many of their own experiences in this field as I completed my own dissertation. I would also like to acknowledge Philip Eckhoff for his support and many great ideas on how to approach some of the methods when I struggled to see how the data could be used in a meaningful way.

I would like to acknowledge and thank the DRC’s Ministry of Health, specifically the Direction for Disease Control (DLM or 4th Direction as it is most commonly referred to) for the approval and use of their data collected as a part of the Integrated Disease and Surveillance (IDSR) system. I would also like to thank and acknowledge the National Institute for Biomedical Research for the use of their data collected as a part of the IDSR for disease confirmation, and Professor Emile Okitolonda, Professor Jean-Jacques Muyembe, and Dr. Benoit
Kebela Ilunga, who supported my work and provided much guidance as I moved forward to finish my dissertation. Additionally, to all those in the health zones, health facilities, and local communities who I have had a chance to not only meet but also work with, to those who have collected and continue to collect the data try to improve the health of the people – thank you, your work is important.
VITA

Education

May 2007  Bachelor of Arts in Biology and Sociology  
Hood College, Frederick, Maryland

May 2009  Master of Public Health in Epidemiology  
Tulane University, New Orleans, Louisiana

Academic/Professional Appointments

2006-2007  Biological Research Aid, USDA Agricultural Research Services,  
Fort Detrick, MD

2007-2009  Student Researcher, Infectious Disease Epidemiology Section,  
Louisiana Office of Public Health, New Orleans, LA

2009-2011  Student Researcher, Department of Epidemiology, UCLA Fielding  
School of Public Health, Los Angeles, CA

2012-Present  Consultant, Surveillance and Polio Eradication Activities, World  
Health Organization, Kinshasa, Democratic Republic of Congo

2013-2014  Technical Committee Member, Demographic and Health Survey,  
Kinshasa, Democratic Republic of Congo

2014  Instructor, Protestant University of Congo Medical School,  
Kinshasa, Democratic Republic of Congo

2011-Present  Assistant Program Coordinator, UCLA-DRC Research Program /  
UCLA Fielding School of Public Health, Kinshasa, Democratic Republic of Congo

Publications


benzathine penicillin g in low-resource settings: a randomized controlled trial. *Clinical Pediatrics, 50*(6), 535-542.


**Abstracts and Presentations**


**Honors and Awards**

<table>
<thead>
<tr>
<th>Year</th>
<th>Award</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>Tri-Beta Biological Honors Society, Hood College</td>
</tr>
<tr>
<td>2007-2009</td>
<td>Public Health Traineeship Grant, Tulane University</td>
</tr>
<tr>
<td>2009</td>
<td>Delta Omega Public Health Honors society, Tulane University</td>
</tr>
<tr>
<td>2010</td>
<td>Summer Research Fellowship, UCLA Fielding School of Public Health</td>
</tr>
<tr>
<td>2011-2013</td>
<td>Faucett Catalyst Fund Fellowship Award–Dissertation research in developing country: Kinshasa, DRC, UCLA Fielding School of Public Health</td>
</tr>
</tbody>
</table>
Chapter 1: Introduction

1.1 Infectious disease surveillance

Public health surveillance is typically defined as the “ongoing, systematic collection, analysis, interpretation, and dissemination of data regarding a health-related event for use in public health action to reduce morbidity and mortality and to improve health.”

This is the principal instrument used in public health to recognize and manage spread of diseases and the data collected should be used in a timely manner for action, planning and evaluation, and research to improve the health of the population. Due to the broad definition of surveillance systems, they can serve a multitude of purposes for improving health by integrating health data for individuals with statistical methods and visualization methods. A functional surveillance system at the national level is essential for effective disease control.

Disease surveillance systems should be the first step in determining if immediate action is needed based on if the disease is a major public health concern. In addition, properly collected surveillance data can be used to determine the burden of disease (for individual diseases and groups of diseases), monitor changes in disease occurrence (increases during epidemics and decreases with control policies), assess geographic spread and high-risk populations, identify emerging health concerns, and help prioritize allocation of health resources when they are limited.

A surveillance system is typically established as a vertical program with multiple levels of event reporting. All data received at the national level should be analyzed and disseminated to partners, including those reporting at the local level. Feedback loops, which include timely reports with the trends, progress, and control of reported diseases, are essential, and can be a
source of motivation to those collecting data. While this structure allows for a central controlling entity, it can allow for the system to become ineffective and difficult to manage. For example, there is a substantial amount of funding for Acute Flaccid Paralysis (AFP) active disease surveillance, which could create an additional burden for data collection because it represents a departure from the typical scope of passively collected surveillance data for other reportable diseases.

It is necessary to ensure that surveillance targets coincide with disease epidemiology, available infrastructure, and resources. Importance should be placed on collecting data needed for disease control, which differs depending on the disease. A surveillance system can become focused on collecting and sending large amounts of raw data, leaving no time for analysis and dissemination. Implicated health workers at all levels need to be educated on how to carry out duties in a timely manner. As health priorities change, continual opportunities for training in-service staff are needed, and may lead to additional costs.

In June 2007, The World Health Assembly (WHA) released the updated International Health Regulations (IHR). The most recent IHR requires that all World Health Organization (WHO) member states assess their base capacity for surveillance and response. Proposed activities, such as using an integrated system with multiple levels with feedback, were meant to strengthen the ability to detect and report infectious diseases and other potential public health emergencies of international concern (PHEIC) to WHO, and increase implementation of early interventions.

A number of evaluations in developing countries have been completed. The large number of weaknesses and limitations of these surveillance systems suggest their ineffectiveness to deliver appropriate data for public health management. Problems most cited in recent
evaluations include:

1. Poor infrastructure or overly complex data-collection systems;
2. Limited skilled and motivated health workers, laboratories and resources;¹⁶
3. Perception that data users have limited input for data collection;¹⁷
4. Lack of timely, complete and reliable reporting for cases and emergencies;¹⁸–²¹
5. Lack of analysis, dissemination and feedback of collected data.¹⁸,²²

Movement into a digitalized world has created an opportunity to obtain information quickly through informal media sources, such as the Internet, compared to traditional systems of disease reporting. Heymann and colleagues reported that over 65% of initial news on infectious diseases events now comes from these types of informal sources.²³ This could indicate that collected data in the formal system is not disseminated efficiently.

Further, it has been noted that emerging and already controlled or eliminated diseases in more developed nations most often occur in countries which lack basic epidemiological and laboratory capacity for early detection and containment.²³ Lack of resources is most commonly affiliated with infectious disease events and has been associated with the inability to control the disease.²⁴

### 1.2 Types of surveillance systems

There are two main approaches to disease surveillance, active and passive surveillance; these terms alone are not sufficient enough to describe a surveillance method.⁴ Passive surveillance is the most common approach used for gathering disease data. This approach allows health centers to send data without being regularly prompted or reminded, and there is often no feedback. Those reporting may have only limited training on disease reporting requirements. The information included is minimal and generally only includes case counts. Due to lack of
incentives, this system is often incomplete.\textsuperscript{25} The active surveillance approach requires substantially more time and resources compared to the other surveillance systems. However, it is often more complete than passive approaches. This type of surveillance is generally implemented during outbreaks or disease eradication efforts, such as AFP surveillance for polio eradication. Active surveillance may also include community health workers visiting villages to do active case finding to detect sick patients who may not visit the health center.\textsuperscript{25}

**Notifiable Disease Reporting**

Notifiable disease reporting is based on public health laws that require certain diseases to be reported to national authorities in a specified amount of time. Diseases with outbreak potential or those targeted for elimination/eradication are considered notifiable for each country across the world. Within each country there may be additional diseases of importance that require reporting.\textsuperscript{4} This reporting system is frequently based on a passive method, commonly called facility-based routine surveillance.\textsuperscript{26} The system may incorporate an active community-based component, where health team members go directly to the community and seek out cases that are not visiting the health facilities.\textsuperscript{26} This method is often used to enhance the completeness of a passive surveillance system, and it could be useful for emerging diseases if the system is sensitive enough to detect new events.\textsuperscript{26}

**Laboratory-Based Surveillance**

Laboratory-based surveillance relies on diagnostic testing of samples as the platform for diseases surveillance.\textsuperscript{4} This allows for confirmation of identified suspected cases, which often is not available in the aggregate reporting of a passive system for notifiable disease reporting. This system requires the ability to transport, store, and test samples in a timely manner, which may present logistical difficulties in resource-limited settings. Using this method allows for collection
of additional information on cases, including age, sex, location, and some clinical characteristics. Furthermore, feedback of test results to the patients is important, especially when motivation for clinicians collecting samples is limited.

**Sentinel Surveillance**

An alternative method for active surveillance is sentinel surveillance, in which a representative sample of reporting centers is selected for active disease surveillance reporting. Sentinel surveillance requires more time and resources than passive surveillance methods, but allows for collection of more detailed disease data since centers have already agreed to participate. If intensive investigation of each case is needed in a limited geographic region, sentinel surveillance may be the most efficient.⁵

**Syndromic Surveillance**

Syndromic surveillance is often used for early outbreak detection. It is based on collecting data on symptoms in an automated data acquisition program. The main difference in syndromic surveillance compared to other described systems, is the use of disease indicators as opposed to looking for the diseases itself.⁴

**Registries and surveys**

Registries will collect detailed information including laboratory results and risk factor information. These registries can be used for long-term follow-up of cases.⁴ Surveys are conducted on a periodic or on-going basis can provide a method for monitoring a number of factors associated with disease, including behaviors, knowledge, and availability of health services.⁴
1.3 Surveillance Activities in DRC

The surveillance structure of the Ministry of Health (MoH) is based on a vertical system of reporting from health centers included at the local level to the national level. At the national level, surveillance activities are managed through the MoH Direction for Disease Control, commonly called the 4th Direction. They are responsible for coordinating disease surveillance called the Integrated Disease Surveillance and Response (IDSR), outbreak investigation, and conducting epidemiological research. The structure of the program is based on disease surveillance recommendations from the WHO. Weekly reports on 15 diseases of epidemic potential or targeted for eradication or elimination (Table 1) are compiled and published in a weekly bulletin for DRC, similar to the CDC’s MMWR (Morbidity and Mortality Weekly Report).

<table>
<thead>
<tr>
<th>Table 1. IDSR Reportable Diseases in DRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acute flaccid paralysis (AFP)*</td>
</tr>
<tr>
<td>• Bacterial dysentery</td>
</tr>
<tr>
<td>• Cholera</td>
</tr>
<tr>
<td>• Malaria</td>
</tr>
<tr>
<td>• Malaria</td>
</tr>
<tr>
<td>• Measles</td>
</tr>
<tr>
<td>• Meningitis</td>
</tr>
</tbody>
</table>

*Targeted for elimination/eradication  
+Listed officially as Neonatal tetanus, but include adult cases, thus we have considered it as tetanus.

There are 11 provinces in the DRC, each of which has a provincial 4th Direction office which reports to the national level each week. Each week, the provincial 4th Direction, in collaboration with the Provincial Medicine Inspector (PMI) collect reports of cases disease and deaths from each district or health zone. Each province is divided into health districts that are charged with the coordination of health zones. In functional health districts, data is received from
health zones and transmitted to the provincial level on a weekly basis, not all districts are functional.

The country is comprised of 516 health zones, and on average between 10 and 15 health zones make up a district. This is the operational level of the system, and most programs are implemented at this level to be carried out throughout the zone. Nurses are typically the primary care givers and are responsible for activities related to disease prevention (including the expanded program for immunization, well-baby clinics, and nutrition programs), and disease surveillance. Each week, the HZD collects information for the surveillance program and transmits the data to the district or provincial level. The collected information is sent to the higher level by using the Internet, radio communication, cellular telephones, or when no other method is possible, foot. In many areas, transport and communication are difficult, and reports will be delayed or may never reach higher levels.

In each health zone, smaller catchment areas called “health areas” (AS) have health centers and health posts to support local populations without access to the reference hospital. Nurses typically manage the centers and posts, providing primary health care and preventative care. They are also responsible for submission of weekly disease surveillance reports to the HZD. At the most local level, community-based volunteers work in villages that may not have health centers or posts. The community-based volunteer program was implemented in 2002 to strengthen local health centers.

1.4 Obstacles to disease surveillance in DRC

DRC’s passive surveillance system (IDSR) has a number of barriers that limit its ability to function efficiently. The health care system has limited support from the government and has thus become increasingly reliant on support from external donors. Many government employed
health care workers reliant on the limited government support that may be sporadic and non-consistent for extended periods of time, leaving them without a regular source of income. This may reduce motivation to carry out planned activities including disease surveillance. Further, reliable access to transportation and communication are difficult. Motorcycles and bicycles are often not available, or may not be properly maintained and have adequate fuel. The sub-standard road infrastructure throughout most of the county makes surveillance activities very difficult to consistently carry out. Due to these problems and many others, disease surveillance in many areas is considered a low priority, especially for health care workers overburdened with primary health care and general management activities.  

For those reporting diseases, complaints about collection forms being difficult and time consuming have been noted. Limited funds and training for case investigations have led to incomplete forms (when available); as well as limited follow-up of cases. Additionally, specimen collection, transportation and storage ability is hindered due to lack of supplies and cold-chain infrastructure. If specimens are collected, they may be stored for extended periods of time in conditions that threaten sample integrity. Thus, even a smaller fraction of suspected MPX cases with a sample would be confirmed with a laboratory diagnosis under the current system.

### 1.5 Emergence and Epidemiology of monkeypox

Monkeypox virus, first isolated from the lesions of *Cynomolgus* monkeys in 1958, is a zoonotic orthopoxvirus that causes a smallpox-like illness. By the 1971, smallpox had been eliminated in many countries, including DRC, however, a similar illness was still being reported in rural regions of the country. It was during this time that MPX was recognized as a distinct disease in humans. Cases from heavily forested areas of western and central Africa were
confirmed positive for MPX from samples collected between 1970 and 1979 during mass vaccination campaigns for smallpox.\textsuperscript{32}

In 1980, the WHO Advisory Committee on Orthopoxviruses declared smallpox eradicated and recommended that vaccination cease. During this time most children had been vaccinated against smallpox, however, the majority of monkeypox cases identified were in unvaccinated children, suggesting that the smallpox vaccine conferred a degree of immunity to monkeypox.\textsuperscript{31,33-37} However, the cost and complexity of sustaining a special vaccination program for monkeypox, at that time a comparatively rare disease, was considered unwarranted. Models from surveillance data predicted the reproductive number (\(R_0\)) to be less than 1 and determined that human-to-human transmission would not pose a significant public health threat.\textsuperscript{31,38,39}

In 1981-1986 WHO supported active surveillance in select health zones in DRC to determine whether monkeypox could fill the niche created when smallpox was eradicated and vaccination campaigns were halted.\textsuperscript{40} At the time of the 1980s surveillance, only a very small percentage of persons would not have been vaccinated. Today, people have not been vaccinated for over 30 years, creating a highly susceptible population. Long-term protectiveness of the vaccinia vaccine used for protection against smallpox has been observed; Rimoin and colleagues noted that 25 years after cessation of vaccination, individuals might still have immunity to orthopox viruses.\textsuperscript{33} It is unknown if persons with prolonged exposure to monkeypox virus would continue to confer complete immunity.\textsuperscript{33}

In a 1986 report, Jezek and associates described MPX infection in 338 patients, among those, 93 cases were thought to be from human-to-human transmission, with one chain of
transmission lasting for three cycles, or four generations.\textsuperscript{41,42} Typically, human-to-human transmission was usually observed only in family members and close contacts, indicating that MPX was less transmissible than smallpox. Cases were typically identified in remote villages with low population density, and this may have contributed to disease containment.\textsuperscript{42,43}

From 1986 until 1995 only 13 cases of human monkeypox were reported.\textsuperscript{44} However, between 1996 and 1997, a large outbreak in the Kasai Oriental Province was reported, initially identifying 92 suspect cases with 419 additional suspect cases found after intensive investigation.\textsuperscript{45,46} The MPX case definition used for identification, which included fever and vesiculopustular rash, may have been non-specific enough to include varicella infections as well.

Until 2001, smaller outbreaks were reported in DRC. Meyer and colleagues\textsuperscript{47} used viral isolation and amplification by polymerase chain reaction (PCR) to differentiate between MPX virus (MPXV) and varicella virus. The inclusion of varicella cases could distort the actual number of monkeypox cases observed. This discrepancy could exaggerate rates of reported secondary transmission while decreasing case-fatality rates.\textsuperscript{47,48}

Monkeypox is routinely reported in rural villages located either in or near heavily forested areas, and does not have a reported variation based on seasonality.\textsuperscript{49,50} It is hypothesized that humans can become infected by direct interaction with an infected animal’s body fluids or lesions.\textsuperscript{38,51-54} Further, deforestation and increased hunting of reservoir species for economic reasons may contribute to increased human contact with MPXV.\textsuperscript{33} Limited investigations of human-to-human transmission have been completed; but based on the available data, it is thought decreased immunity to smallpox could allow for increased and sustained transmission of monkeypox.\textsuperscript{35,38,42,55,56}
In May 2003, the only known outbreak outside of Africa was reported in the Midwest United States. The Centers for Disease Control and Prevention (CDC) documented 80 cases, both laboratory-confirmed and probable.\textsuperscript{54, 57-66} During this outbreak, no case fatalities or secondary transmission were reported. After intensive investigations, the outbreak was connected to prairie dogs which had contact with sick rope squirrels and giant pouched rats imported from Ghana.\textsuperscript{59} Data collected during these investigations have been important in updating the case definition, and recording clinical characteristics, information that was previously difficult to obtain in the typical environment MPXV has most commonly been found.

1.6 Clinical features/characteristics of human monkeypox

The clinical characteristics of human monkeypox virus infection closely resemble smallpox, though transmissibility between humans and case-fatality rates are lower.\textsuperscript{67, 68} Most clinical data on human monkeypox is limited to information obtained during surveillance activities from 1981-1986, small outbreaks in the DRC, and the 2003 outbreak in the US.\textsuperscript{41}

Typically the incubation period is between 10 to 14 days (range, 1 to 31 days), after which the patient experiences febrile prodromal illness including fever, malaise, and enlarged lymph nodes (lymphadenopathy), after which a maculopapular rash develops.\textsuperscript{41, 67, 69} Lymphadenopathy, occurring in 90% of unvaccinated MPX patients, is a key symptom differentiating monkeypox from smallpox and chickenpox infection, since it rarely occurs in the latter diseases.\textsuperscript{70} Additional signs and symptoms include chills, sweats, headache, backache, sore throat, cough, and shortness of breath.

The rash, usually appearing first on the face, spreads in a centrifugal distribution to the palms and soles of the feet, another distinguishing factor from varicella infection (Figure 1). As in smallpox, monkeypox lesions develop and progress together through the stages of macules,
papules, vesicles, pustules and umbilation, then scab and desquamation, this entire process usually lasts 2-4 weeks, this is distinguished from chickenpox which often has a much faster progression of febrile prodrome and evolution of rash.\textsuperscript{70, 71} During the first week of the rash, patients are considered to be infectious, and cases without rash have been described in the literature.\textsuperscript{69, 72}

\textbf{Figure 1}. Clinical features of chickenpox, smallpox, and monkeypox

Clinical differences have been noted between patients in the US outbreak and those in Central Africa, who typically present with more severe illness.\textsuperscript{66, 69, 73, 74} Differences in severity are attributed to differences in disease virulence. Sequencing of genetically distinct clades of monkeypox viruses identified two distinct groups: West African isolates and the Congo basin isolates.\textsuperscript{73} In non-human primates, the Congo basin isolates have demonstrated increased virulence and more destructive clinical characteristics, and based on epidemiologic analysis of genetic sequence data are thought to be more virulent in humans as well.\textsuperscript{75-80} Genetic analysis showed that the strain responsible for the outbreak in the US was from the West African isolate.\textsuperscript{77}

\textbf{1.7 Diagnostic criteria of human monkeypox}

\textbf{Clinical}: Clinical symptoms can be used for classifying suspected cases using a definition provided by WHO, and for confirmation, laboratory testing of a sample is required.
Additionally, the CDC updated their case definition in January 2004 after the US outbreak which provides more detail on laboratory, epidemiologic, and exclusion criteria. The WHO uses the following definition:

“Any person who presents with a sudden high fever (≥ 99.3°F /≥ 37.5°C if a thermometer is available, otherwise by guardian or patient self report), followed after a few days with a rash (macular, papular, vesicular, or pustular; generalized or localized; discrete or confluent) predominantly concentrated on the face, the palms of the hands, and/or the soles of the feet or the presence of at least five smallpox like scars.”

**Laboratory:** If a case of MPX is suspected, samples should be taken and be reported immediately. Samples should include blood, crust specimens from at least two lesions and vesicle tissue. There are currently a number of laboratory diagnostic methods that can be used to identify MPX virus for confirmation. These include polymerase chain reaction (PCR), electron microscopy (EM), virus culture (VC), immunohistochemistry (IHC), and IgG and IgM-capture enzyme-linked immunosorbent assay (ELISA). PCR testing is sensitive enough to differentiate between Congo Basin and West African monkeypox strains.

### 1.8 Mortality due to monkeypox

Limited data is available for mortality due to monkeypox infection, however, data from outbreaks in central Africa, predict that case fatality ranges between 1.5 – 17%. Jezek et al. reported a case fatality rate of 11% in unvaccinated individuals, while vaccinated persons had a much lower rate indicating a potentially protective effect after infection of the vaccinia virus vaccination. When death was the outcome, it typically occurred during the second week of infection. However, due to an interval before a sick person realized they are infected, the time may actually be longer. There were no fatal cases in the US outbreak.
1.9 Burden of monkeypox

During the end-stages of smallpox eradication and initial surveillance activities in the 1970’s, 47 cases of human MPX were laboratory confirmed in Sub-Saharan Africa; the majority (38 of 47) of the cases were reported in DRC, the remainder were reported in Cameroon, the Central African Republic (CAR), Gabon, Ivory Coast, Liberia, Nigeria and Sierra Leone.\textsuperscript{32,40}

Limited publications in the literature are available describing the ongoing occurrence of human MPX since termination of the WHO surveillance program in 1986. Recent investigations in the Republic of Congo (RoC) documented six generations of person-to-person transmission in a hospital setting. Previously, four generations was the longest reported chain of transmission, and after, the inter-human virus circulation died out; they concluded from the study that the virus had a very low potential for epidemic spread in humans.\textsuperscript{42,56} Human-to-human transmission across generations can help gage a virus’s ability to have a persistent infection in humans. The potential for the MPX virus to evolve and infect humans without re-introduction by a zoonotic host, posses a major public health concern. MPX virus is now considered to be the most important orthopoxvirus infection in humans since the eradication of smallpox.\textsuperscript{40}

1.10 Burden of monkeypox in DRC

The true burden of MPX infection in DRC remains largely unknown, with no reliable countrywide estimates. Cases often occur in remote and difficult to access locations. Years of civil war throughout the country and the inability to confirm diagnosis in the field have made research on the ecology, epidemiology, natural history, and pathogenesis of the infection difficult.
1.11 References


86. CDC. Updated interim CDC guidance for use of smallpox vaccine, cidofovir, and vaccinia immune globin (VIG) for prevention and treatment in the setting of an outbreak of monkeypox infections. . 2005.


2.1 ABSTRACT

BACKGROUND

In the Democratic Republic of Congo (DRC), human monkeypox (MPX) is one of the 15 reportable diseases compiled in the country’s passive surveillance system: the Integrated Disease Surveillance and Response (IDSR). To date, this system has not been explored in depth for any single disease. We used IDSR data from 2001 to 2013 to describe how MPX reporting has evolved in DRC, and how changes in the system could affect trends in reporting disease occurrence.

METHODS

Data on suspected MPX cases are reported to the national level, and categorized by health zone and epidemiologic week. We performed an in-depth qualitative and quantitative analysis assessing phases of the surveillance system, yearly trends in reporting and estimated incidence for MPX. Additional analyses exploring trends of tetanus and acute flaccid paralysis (AFP) were completed as a comparison to MPX reporting.

RESULTS

Between 2001 and 2013, three phases of the surveillance system were identified: the “implementation phase” (2001-2003), the “adjustment phase” (2004-2007), and the “stable phase” (2008-2013). Overall, there was an increase in suspected MPX cases reported via the IDSR. In total 19,437 suspected cases and 336 suspected deaths (1.7% case fatality rate) were reported. When restricting the analysis to the “stable phase,” overall country incidence increased
from 2.13 per 100,000 in 2008 to 2.84 per 100,000 in 2013. No significant changes in trends of tetanus or acute flaccid paralysis reporting were identified during the same time period, 2008-2013.

DISCUSSION

Based on trends from 2008-2013, the “stable reporting phase,” the increase in MPX is likely to be a true increase. MPX was the only disease showing a significant increase in incidence compared to the other reportable diseases. Further analyses should examine trends using additional sources of data, which will provide critical information for improved prevention and control strategies and highlight areas of improvement for future data collection efforts.
2.2 BACKGROUND

In 1998, the Integrated Disease Surveillance and Response (IDSR) unit was established in response to a strategy presented by the World Health Organization’s Regional Office for Africa (WHO/AFRO), to strengthen public health surveillance and response in a number of African countries.\textsuperscript{1-3} In the Democratic Republic of Congo (DRC), the IDSR was created under the Ministry of Health (MoH) Direction for Disease Control (DLM, commonly referred to as the 4\textsuperscript{th} Direction). This system was implemented to integrate existing surveillance and response systems, including laboratory surveillance data. The 4\textsuperscript{th} Direction was charged with assessing and responding to emerging threats and outbreaks identified through the IDSR, as well as conducting epidemiologic research. Weekly reports on 15 diseases, 13 of epidemic potential, and 2 targeted for elimination or eradication (Table 1), are compiled and published in a bulletin for DRC similar to the Morbidity and Mortality Weekly Report (MMWR) published by the Centers for Disease Control and Prevention (CDC).\textsuperscript{4}

DRC is currently comprised of 516 health zones in 11 Provinces, with over 10,000 health centers required to send weekly passively collected surveillance reports. These reports are compiled at the health zone and transmitted through intermediate levels to the national 4\textsuperscript{th} Direction. Additionally, for some diseases, individual samples with patients names are sent to the National Institute of Biomedical Research (INRB) for laboratory confirmation, but these systems are not officially linked.\textsuperscript{4}

During the past three decades the overall health care system in DRC has deteriorated to a poorly functioning system.\textsuperscript{5, 6} Hence, it is difficult to implement an effective and fully functional surveillance system. The country continues to recover from a multi-year civil conflict which left many areas without roads and limited transportation, as well as over a million refugees and
internally displaced persons. These obstacles make consistent communication with many of the local health centers extremely difficult, especially during the rainy season. Additionally, much of the country’s terrain is heavily forested which is considered even less accessible; these areas have been identified as key locations for emergence of viral diseases, including human monkeypox (MPX).

MPX virus is a zoonotic infection found in a variety of mammals, including humans. Humans infected with MPX develop a smallpox-like illness. A large majority of cases are reported in DRC where the disease is endemic in forest animals with frequent spillover into human populations. With no reliable countrywide estimates, the true burden of MPX infection in DRC remains unknown. MPX cases often occur in remote and difficult to access locations, with limited ability to confirm diagnosis in the field, making research on ecology, epidemiology, natural history, and pathogenesis of the infection challenging.

MPX officially became reportable to the IDSR in 2000. Before its inclusion in the system, MPX cases were only sporadically reported. The first human case was identified in DRC in 1970, and additional cases continued to be confirmed through the end stages of the smallpox eradication campaign when all persons with rash-like illness were tested to confirm absence of smallpox. After the eradication of smallpox, the World Health Organization (WHO) conducted an active surveillance program in select areas from 1981 to 1986. From 1986 to 1995 only 13 cases of MPX were reported. Then between 1996 and 1997, there was a large outbreak in the Kasai Oriental Province. During the initial investigation of this outbreak, 92 suspect cases were identified with 419 additional suspect cases identified through an intensive case search. The MPX case definition used for identification has a low specificity, which can also include varicella infections, and after laboratory testing, many of the identified cases in this outbreak
were considered misclassified. Between 1997 and 2000, smaller outbreaks continued to be reported in DRC. Between 2005 and 2007, active MPX disease surveillance was conducted in a small district in central DRC to assess the current burden of infection. Investigators noted a 20-fold increase in MPX incidence since the 1980s, rising from 7.2 to 144.2 cases per 100,000 persons.

Understanding and improving the state of the disease surveillance system is essential to help prioritize allocation of health resources when they are limited. Properly collected surveillance data can be used to determine the burden of disease, monitor changes in disease occurrence, assess geographic spread, identify high-risk populations, as well as emerging health concerns. Despite the challenges in DRC as a resource limited setting, data is available on suspected MPX cases and the surveillance system used to collect it. To date, the system has not been explored in depth for any single disease. We used IDSR surveillance data from 2001-2013 to qualitatively and quantitatively describe how the MPX surveillance system has evolved in DRC using two other reportable disease as controls, acute flaccid paralysis (AFP) and tetanus, and how it can be better utilized as an important tool for future disease surveillance.

2.3 METHODS

The case counts of all diseases reported to the 4th Direction from January 1st, 2001 through December 31st, 2013, were made available courtesy of the DRC MoH. We compiled all IDSR datasets for MPX, AFP, and tetanus for each year into a Microsoft Access® database. Our variables included Province, district (composed of about 5-10 health zones), health zone, epidemiological week (Monday to Sunday), case counts and death counts disaggregated by age group (0-11 months, 12-59 months, and 5 years +), weekly case fatality, and population estimates (by health zone, district, Province, and country). AFP and tetanus were used as a
comparison to suspected MPX cases to assess changes in disease reporting over time. AFP was chosen based on a yearly-expected baseline rate of paralysis (2 per 100,000 population), and is the key characteristic for identifying clinical polio cases.\textsuperscript{22} Tetanus was selected as it was expected that rates would stay the same or decrease (with increasing vaccination rates) over time.

The case definition used for identification of suspected MPX cases has remained almost unchanged since 2001: any person appearing with a sudden onset of high fever, followed a few days after by a vesicular-pustule eruption presenting predominantly on the face, palms of the hands and soles of the feet or the presence of at least 5 smallpox type scabs.\textsuperscript{4}

Countrywide population estimates were approximated using data from the 2013 Country Plan for the Expanded Program for Immunization (EPI), which estimates the number of children who need to be vaccinated against many different diseases in each health zone based on the total population expected, using a mix of official projections, local estimates and growth rates from large-scale surveys including the Demographic and Health Survey (DHS).\textsuperscript{23} The 2013 population was back extrapolated to account for 3\% growth (the official population growth factor used since the last census conducted in 1984) each year to 2001.\textsuperscript{23} As a comparison, we used the 1984 census which is widely regarded as the standard, and extrapolated forward 3\% every year.\textsuperscript{24-26} However, this population estimate was only used as a comparison as it was not available for individual health zones. We updated health zone names, which were not consistently spelled during the 13-year time period in order to create a standard set of names. We removed duplicates or multiple entries with the same health zone name and epidemiological week, likely created by delays in reporting: for example, a report entered first as 0 cases, and then later changed as cases were reported. Each health zone could only have one report for each epidemiologic week.
All analyses were completed using SAS v9.4.\textsuperscript{27} Crude case fatality rates and the proportion of health zones reporting MPX cases compared to health zones reporting at least one case of any reportable disease each year were calculated. Estimated incidence rates and 95% confidence intervals were calculated at the national and provincial levels. Generalized linear models (GLM) were used to explore trends of yearly-predicted percent change in incidence for suspected MPX, AFP, and tetanus during the 13 years. Significance was based on the probability that the calculated chi-square test statistic is as extreme or more extreme than what was observed under the null hypothesis; we accepted a p-value \( \leq 0.05 \) to reject the null hypothesis of no difference between the variables.

The outcome variable was disease case counts (MPX, AFP or tetanus), and the independent variable was either year or province. We used a negative binomial distribution to account for over-dispersion of cases, and the logarithm of the yearly population based on EPI estimates used as an offset variable in order to obtain estimates of the incidence rates based on case count outcomes. Based on historical events, personal interviews, and changes in reporting or health system, we divided the data into 3 time periods or phases: 1) 2001-2003; 2) 2004-2007; and 3) 2008-2013. A categorical variable for the time periods was created and tested in pairwise fashion. Using the t-test for comparison for MPX reporting, period 1 and 2 were not significantly different from each other (p=0.54), but were both significantly different from phase 3 (p<0.05), and thus were combined to look at the incidence change from 2001-2007 using the same GLM procedure described above. Analyses with and without two locations where active surveillance has been implemented were completed as these areas could skew the overall results for the country. These areas had increased training of health care workers and knowledge of the disease
- Tshuapa and Sankuru districts (24 health zones). Maps exploring changes in reporting from 2001-2013 were created using Health Mapper 4.3.28

This study was reviewed and approved by the Ethics Committee of the Kinshasa School of Public Health, Kinshasa, DRC and by the Institutional Review Board of Human Research Ethics at the University of California, Los Angeles.

2.4 RESULTS

Overall MPX Trends

During 2001 to 2013, 19,646 suspected MPX cases were reported with 336 suspected deaths among them (Table 2). The mean number of suspected cases reported over the 13 years was 1,511 per year, in 2012, 2,629 suspected cases were reported (Incidence: 3.11 per 100,000, 95% CI: 0.44, 22.10), the most in any given year (Table 3). The crude case fatality rates ranged from 0.8% to 4.2%, with a mean case fatality rate of 1.7% over the 13 years (Table 2).

Suspected cases of MPX were most commonly reported in the northern and central portion of the country (Figure 1). The Equateur province had the highest incidence of suspected MPX cases, followed by Kasai Oriental province, and Maniema province (Table 4). Many of the other provinces had health zones which regularly reported no suspected cases. The number of health zones reporting MPX each year increased from 31 to 136 (Table 2) between 2001 and 2013. Of the 514 health zones reporting any diseases to the IDSR during the 13-year period, 52% reported at least one suspected case of MPX.

Phases of the IDSR

We identified three distinct phases of disease reporting during the course of the 13-year time period for the IDSR based on trends, reporting habits, changes to the system, and other events in the DRC (Figure 2). For MPX, there was a significant increase overall in incidence of
cases reported (2001 to 2013, p<0.001). This trend remained the same even after removal of the 2 districts which had implemented active surveillance programs (Table 5).

**Phase 1: Surveillance System Implementation Phase**

We considered the years 2001-2003 the “surveillance system implementation phase,” as the IDSR was newly implemented and MPX had been introduced as a reportable disease in 2000 (AFP and tetanus had already been integrated into the system). During this phase, age group and population data were not collected, however, health zones submitting reports, reported zero cases for each disease with no cases as opposed to leaving this information blank as we observed in later phases. During this phase, a total of 2,024 suspected MPX cases were reported with 43 deaths (case fatality rate: 2.14%) (Table 2). The Kasai Occidental and Bandundu Provinces had the highest incidence (2.70 per 100,000 persons and 2.20 per 100,000 persons, respectively). During this time there was high variation in AFP and tetanus incidence (Figure 2).

**Phase 2: Adjustment Phase**

The second phase between 2004 and 2007 was considered the “adjustment phase.” By 2004, most health zones were only reporting on the disease if they had one or more case of a specific disease, leaving the rest of the case counts blank, or entered as missing. If they reported case counts for at least one disease during the epidemiologic week, they were assumed to have zero cases for the other diseases, even if there was no reports for the other disease case counts. Additionally, in 2004, the IDSR integrated additional variables including age categories, case fatality, and population for the health zone. This time also marks the end of widespread civil unrest. From 2005 to 2007 an *active* surveillance program for MPX was implemented in the Sankuru District of Kasai Oriental Province.
Between 2005 and 2006, there was a sharp increase, then decrease in the suspected MPX incidence for the country (2.48 per 100,000 persons to 1.11 per 100,000 persons) (Table 3). Both Kasai Oriental and Equateur province had similar trends; in 2005 Kasai Oriental had an incidence of 11.26 per 100,000 compared to 2006, 3.66 per 100,000 persons. Tetanus reporting remained relatively stable, while there was a continued fluctuation of AFP reporting, based on predictions in percent change per year, neither none had significant changes (2001-2007: p=0.586 (tetanus) and p=0.182 (AFP)) (Table 5).

**Phase 3: Stable Reporting Phase**

We consider 2008-2013, the “stable reporting phase.” By 2008, there were 515 health zones, with 502 of those reporting at least one case of any reportable disease during the year compared to 464 the year before; the 516th health zone was created in 2012. Zero cases were still assumed when health zones sent information on at least one disease during the week, but no other information. The number of health zones reporting any disease stayed fairly stable and there were no changes to case definitions of the 15 reportable diseases. Since 2008, there has been an on-going second active surveillance system in the Tshuapa District (12 health zones) of the Equateur province; increased case reporting to the IDSR for suspected MPX was observed in this area.

MPX incidence between 2008 and 2013 (2.13 to 2.84 per 100,000, respectively) increased significantly with a predicted estimated change per year of 6.2% (p=0.002). Equateur and Kasai Oriental had the highest provincial incidences for 2013 (12.83 and 5.78 per 100,000, persons respectively). However, the predicted trend in percent change per year remained significant after removal of the Sankuru and Tshuapa Districts (p<0.001). While the number of health zones reporting any disease increased by 12, there were 17 additional health zones (after
excluding the Tshuapa District) reporting at least 1 case of suspected MPX. The predicted change in incidence for AFP, indicated a slight decrease in yearly reporting, but was not significant (p=0.297). The same was seen for Tetanus, which showed a slight, but non-significant decrease during 2008 to 2013 (p=0.756) (Table 5). Overall, during the “stable phase” of the IDSR system, we only observed an increase in reported cases of MPX.

2.5 DISCUSSION

Over the past 13 years, we observed an increasing trend in incidence of suspected MPX cases and the number of health zones reporting cases to the national level through the passive (IDSR) system. Between 2001 and 2013, there was an almost 4-fold increase in estimated incidence of suspected MPX and a 14.2% increase in the number of zones reporting suspected MPX compared to reporting any disease for the country. From 2008 to 2013, there was a 45% increase in the incidence of suspected MPX cases reported.

In order to determine if these trends were the result of improvements in disease surveillance, we compared the incidence of MPX to other reportable diseases (AFP and tetanus), and for the country with and without sites where active case searching programs had been implemented. During the stable phase of reporting, AFP and tetanus reporting was stable as expected; only MPX had a significant increase in incidence, suggesting the possibility of a true increase. Additionally, when looking at the incidence of MPX with and without Sankuru and Tshuapa districts, a significant predicted increase was still observed, this was found countrywide as well as in provinces each district was located in.

Given the comparison with AFP and tetanus, as well as the comparison with and without active surveillance programs, we are able to exclude factors related to improved surveillance in favor of other factors that may contribute to the increased incidence of MPX observed in our study. These
MPX specific factors could include: (1) increased vaccinia-naïve populations, and decreased immunity in previously vaccinated persons; (2) increased dependence on bush meat as a regular source of economic and nutritional sustenance; (3) over-reporting of other rash-illness diseases as suspected cases of MPX reported to the IDSR; (4) large-scale migration due to civil unrest; and (5) an increase in susceptibility to MPX in persons who are immunocompromised due to HIV/AIDS. The first three factors listed are expected to have the biggest impact on our study population as much of the civil unrest is in less densely forested areas and the HIV/AIDS prevalence is considered low, and has remained fairly stable.\textsuperscript{7,29} If there was increased over-reporting of other rash-illness diseases, it would lead to an artificial increase in incidence, as opposed to a true increase in MPX disease occurrence as we propose. The possibility of an increase in non-MPX rash-illness could be further explored using samples which are received at the National Institute for Biomedical Research (INRB), to determine if there has also been a change in confirmation of samples compared to negative samples.

During the stable phase, 17 additional health zones (2.8\% increase from 2008 to 2013) reported at least one case of MPX, indicating that not only has the incidence of suspected cases increased, but the geographic distribution may also be expanding. Recent publications based on ecological niche modeling, support these findings by predicting that the overall distribution of human MPX cases could extend to most of the DRC, especially in primary forested areas of the country.\textsuperscript{12,11}

Our study is subject to a number of limitations. The use of aggregated data limits the ability to make causal inferences on individual risk of disease. There may also be underreporting of cases due to the fact that health areas, health zones, and sometimes provinces do not have 100\% completeness of reporting, and may miss sending in their report entirely. Thus if a week
was missing for a health zone, it was not included in the overall data, it was considered missing for all reportable diseases. However, as we were interested in change in incidence, it is unknown if there is additionally a change in the degree of under-reporting during this time period, and would be hard to ascertain this information. Also, this type of data did not allow us to control for confounders, may have had misclassification within the groups, and may suffer from temporal ambiguity.³⁰

Additionally, there is not a consistent source of population data used to calculate incidence for the country. There has been large-scale population movement during the past two decades. Over one million people are considered either refugees or an internally displaced citizen, and a large percent of rural populations considered transient who either live in the forest or are seasonal fishers, and thus do not have a stable residence. We used the EPI population data, which is available at the provincial, health zone and health area level, due to the fact that the standard population data, the 1984 census, is only available at the national level.²⁵ ¹³, ²⁶, ³¹ The estimated population in 2013 used by the EPI is 87.1 million, while the most recent Demographic and Health Survey (DHS), estimates the population to be 77.8 million.²³, ²⁹ The population estimates may lead to underestimates of MPX incidence, as there may be some inflation of the population to ensure enough doses of vaccine are received for mass vaccination campaigns.

Case counts are likely to be significantly underreported based on the use of a passive surveillance system, which relies on the health center to report all cases consistently. Furthermore, due to a non-specific case definition for MPX it is likely that there may be misclassification, as several diseases meet the criteria. It is unclear what impact this could have on the overall reporting and disease trends. Additional sources of data, including laboratory data,
could provide insight into whether or not a bias towards the over-reporting of suspected cases of MPX exists. Although the INRB collects samples for laboratory analysis from health zones with suspected MPX cases, linkage to the IDSR system remains incomplete. The INRB collects data on samples including patient names, but the IDSR only collects aggregate data with no names. In addition, only a small percentage of suspected MPX cases reported in the IDSR will have samples taken, and samples collected can be laboratory confirmed from health zones not consistently reporting cases via the IDSR.

WHO’s active surveillance program, conducted from 1981-1986, suggested that the observed increase in MPX case numbers were a result of strengthened surveillance. Thirty years later our data indicates the possibility of a true increase in disease occurrence, even when areas with intensified active surveillance are removed from the analysis. This is in agreement with active surveillance program which took place between 2005 and 2007 in the Sankuru District which found a significant increase in incidence compared to the 1980’s surveillance. Between 2005 and 2006, there was an unexpected sharp increase then decrease in cases reported to the IDSR. However, based on the active surveillance system in the Sankuru District, there was an increase in 2006, in the number of samples collected and confirmed at the national laboratory. This may indicate that the focus on disease detection was targeted though sample collection rather than reporting in 2006.

Our calculated incidence was lower than estimates calculated during the Sankuru District active surveillance program. The largest contributing factor is the difference in detection between active and passive surveillance methods, with active searching identifying many more cases. An additional factor is the variation between population estimates, as the adjusted population used for the active surveillance was based on a local census, and found the standard
population in the area was significantly over-estimated. However, when we used the estimated population from the active surveillance project and the passive case counts in the same area during the same time (Sankuru District, 2005-2007), the mean incidence increased from an the mean of 7.0 per 100,000 to 59 per 10,000 (range: 26.0 - 85.8 per 100,000 per year). The increase in incidence based on the denominator changing suggests the need for improved accuracy of the available population data.

The DRC health care system has limited support from the government, and remains heavily reliant on support from external donors, who often have specific agendas related to their own health care priorities. Given the limited resources available, extensive data analyses utilizing the surveillance data are rarely accomplished. But despite these structural and reporting limitations, we still observed a significant increase in suspect disease occurrence and geographic distribution of cases for MPX. However, population estimates must be updated to provide accurate estimates of disease incidence in DRC.

Based on provincial trends in our analysis, additional programs to examine changes in disease risk should be implemented in Equateur, Kasai Oriental, Orientale, and Maniema provinces, as these provinces had the highest reported incidences. Small-scale programs have already been implemented in specific districts of these provinces, which target active surveillance to look at clinical characteristics and individual risk factors to MPX. However, more research is needed to understand other factors contributing to the observed increase in MPX incidence. In our study, areas with the highest incidence were areas with already implemented MPX-based programs, including active surveillance and education programs. Yet many areas that have not had any type of MPX intervention programs also had a significant increase in incidence. These areas should be targeted to determine if they would also benefit
from an active surveillance system, sentinel surveillance sites, or increased education on case detection and reporting.

There is an increased need for additional investment in the operational level of the system to strengthen passive reporting. This should include more streamlined reporting methods, clearly defined “0 reporting,” confirmation that no duplicates exist (arising from delayed reporting, or additional case reporting after the target week), and increased feedback from the national level to the health zone. Finally, there needs to be improved linkage between the passive (clinical based) reporting and the laboratory (confirmation) reporting of MPX. Currently, only a small percentage of samples are taken compared to the total number of cases passively reported, and those cases cannot be directly linked to the laboratory system.

We have demonstrated that the increase in suspected MPX cases cannot be explained by improved collection and reporting in the surveillance system. Not only has the number of MPX cases continued to increase over time while other diseases stayed stable, but the increase remained significant even after areas with active case searching programs were removed. Targeting multiple areas in both the active and passive surveillance methods used to collect information on MPX could have a major impact on improving our overall understanding of MPX disease, distribution, and changes in occurrence. These improvements could have a broader impact on the surveillance system as a whole for reporting of other emerging diseases and diseases targeted for eradication.
Table 1. IDSR Reportable Diseases in DRC

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Acute flaccid paralysis (AFP)*</td>
</tr>
<tr>
<td>2.</td>
<td>Bacterial dysentery</td>
</tr>
<tr>
<td>3.</td>
<td>Cholera</td>
</tr>
<tr>
<td>4.</td>
<td>Malaria</td>
</tr>
<tr>
<td>5.</td>
<td>Measles</td>
</tr>
<tr>
<td>6.</td>
<td>Meningitis</td>
</tr>
<tr>
<td>7.</td>
<td><strong>Monkeypox (MPX)</strong></td>
</tr>
<tr>
<td>8.</td>
<td>Tetanus*</td>
</tr>
<tr>
<td>9.</td>
<td>Plague</td>
</tr>
<tr>
<td>10.</td>
<td>Rabies</td>
</tr>
<tr>
<td>11.</td>
<td>Typhus</td>
</tr>
<tr>
<td>12.</td>
<td>Upper respiratory infection (URI)</td>
</tr>
<tr>
<td>13.</td>
<td>Viral hemorrhagic fevers (VHF)</td>
</tr>
<tr>
<td>14.</td>
<td>Whooping cough (Pertussis)</td>
</tr>
<tr>
<td>15.</td>
<td>Yellow fever (YF)</td>
</tr>
</tbody>
</table>

* Targeted for elimination or eradication
Table 2. Number of health zones reporting suspected monkeypox cases to the 4th Direction, DRC, 2001-2013

<table>
<thead>
<tr>
<th>YEAR</th>
<th># Suspected cases</th>
<th># Suspected deaths</th>
<th>Case Fatality (%)</th>
<th># HZ Reporting 1 or more MPX</th>
<th># HZ reporting any disease</th>
<th>% Reporting MPX</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>388</td>
<td>13</td>
<td>3.4%</td>
<td>31</td>
<td>253</td>
<td>12.3%</td>
</tr>
<tr>
<td>2002</td>
<td>881</td>
<td>14</td>
<td>1.6%</td>
<td>50</td>
<td>292</td>
<td>17.1%</td>
</tr>
<tr>
<td>2003</td>
<td>755</td>
<td>16</td>
<td>2.1%</td>
<td>44</td>
<td>295</td>
<td>14.9%</td>
</tr>
<tr>
<td>2004</td>
<td>1024</td>
<td>29</td>
<td>2.8%</td>
<td>77</td>
<td>374</td>
<td>20.6%</td>
</tr>
<tr>
<td>2005</td>
<td>1708</td>
<td>25</td>
<td>1.5%</td>
<td>83</td>
<td>454</td>
<td>18.3%</td>
</tr>
<tr>
<td>2006</td>
<td>783</td>
<td>20</td>
<td>2.6%</td>
<td>76</td>
<td>464</td>
<td>16.4%</td>
</tr>
<tr>
<td>2007</td>
<td>970</td>
<td>11</td>
<td>1.1%</td>
<td>90</td>
<td>464</td>
<td>19.4%</td>
</tr>
<tr>
<td>2008</td>
<td>1599</td>
<td>67</td>
<td>4.2%</td>
<td>119</td>
<td>502</td>
<td>23.7%</td>
</tr>
<tr>
<td>2009</td>
<td>1919</td>
<td>26</td>
<td>1.4%</td>
<td>108</td>
<td>502</td>
<td>21.5%</td>
</tr>
<tr>
<td>2010</td>
<td>2322</td>
<td>26</td>
<td>1.1%</td>
<td>107</td>
<td>504</td>
<td>21.2%</td>
</tr>
<tr>
<td>2011</td>
<td>2208</td>
<td>18</td>
<td>0.8%</td>
<td>123</td>
<td>507</td>
<td>24.3%</td>
</tr>
<tr>
<td>2012</td>
<td>2629</td>
<td>35</td>
<td>1.3%</td>
<td>133</td>
<td>508</td>
<td>26.2%</td>
</tr>
<tr>
<td>2013</td>
<td>2460</td>
<td>36</td>
<td>1.5%</td>
<td>136</td>
<td>514</td>
<td>26.5%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>19646</td>
<td>336</td>
<td>1.7%</td>
<td>264</td>
<td>514*</td>
<td>52.5%</td>
</tr>
</tbody>
</table>

*There are 516 identified health zones, but 2, in North Kivu are not considered functional, and do not send surveillance reports.
Table 3. Suspected MPX Incidence in DRC (with and without the active surveillance areas), 2001-2013

<table>
<thead>
<tr>
<th>YEAR</th>
<th>Incidence, per 100,000, 95% CI</th>
<th>Incidence per 100,000 (without active surveillance areas), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>0.64 (0.09, 4.50)</td>
<td>0.61 (0.09, 4.30)</td>
</tr>
<tr>
<td>2002</td>
<td>1.4 (0.20, 9.90)</td>
<td>0.94 (0.13, 6.70)</td>
</tr>
<tr>
<td>2003</td>
<td>1.16 (0.16, 8.30)</td>
<td>0.72 (0.10, 5.10)</td>
</tr>
<tr>
<td>2004</td>
<td>1.53 (0.22, 10.90)</td>
<td>0.82 (0.12, 5.80)</td>
</tr>
<tr>
<td>2005</td>
<td>2.48 (0.35, 17.60)</td>
<td>0.96 (0.13, 6.80)</td>
</tr>
<tr>
<td>2006</td>
<td>1.11 (0.16, 7.80)</td>
<td>0.67 (0.09, 4.80)</td>
</tr>
<tr>
<td>2007</td>
<td>1.33 (0.19, 9.40)</td>
<td>0.60 (0.08, 4.20)</td>
</tr>
<tr>
<td>2008</td>
<td>2.13 (0.30, 15.10)</td>
<td>1.00 (0.15, 7.40)</td>
</tr>
<tr>
<td>2009</td>
<td>2.48 (0.35, 17.60)</td>
<td>1.20 (0.17, 8.80)</td>
</tr>
<tr>
<td>2010</td>
<td>2.91 (0.42, 20.70)</td>
<td>1.40 (0.19, 9.60)</td>
</tr>
<tr>
<td>2011</td>
<td>2.69 (0.38, 19.10)</td>
<td>1.60 (0.23, 11.60)</td>
</tr>
<tr>
<td>2012</td>
<td>3.11 (0.44, 22.10)</td>
<td>2.00 (0.28, 14.40)</td>
</tr>
<tr>
<td>2013</td>
<td>2.82 (0.40, 20.10)</td>
<td>1.50 (0.22, 10.90)</td>
</tr>
</tbody>
</table>
Table 4. Suspected MPX Incidence in selected provinces of DRC, 2001-2013

<table>
<thead>
<tr>
<th>YEAR</th>
<th>Equateur Incidence per 100,000</th>
<th>Kasai Oriental Incidence per 100,000</th>
<th>Maniema Incidence per 100,000</th>
<th>Bandundu Incidence per 100,000</th>
<th>Orientale Incidence per 100,000</th>
<th>Kasai Occidental Incidence per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>0.53</td>
<td>0.83</td>
<td>0.06</td>
<td>2.20</td>
<td>0.07</td>
<td>2.70</td>
</tr>
<tr>
<td>2002</td>
<td>6.58</td>
<td>3.84</td>
<td>0.06</td>
<td>0.88</td>
<td>0.26</td>
<td>0.49</td>
</tr>
<tr>
<td>2003</td>
<td>4.60</td>
<td>0.16</td>
<td>0.48</td>
<td>1.66</td>
<td>3.23</td>
<td>0.34</td>
</tr>
<tr>
<td>2004</td>
<td>3.40</td>
<td>4.94</td>
<td>0.17</td>
<td>1.59</td>
<td>1.74</td>
<td>1.08</td>
</tr>
<tr>
<td>2005</td>
<td>8.29</td>
<td>11.26</td>
<td>1.01</td>
<td>0.20</td>
<td>0.82</td>
<td>0.52</td>
</tr>
<tr>
<td>2006</td>
<td>2.48</td>
<td>3.66</td>
<td>0.82</td>
<td>1.23</td>
<td>2.07</td>
<td>0.06</td>
</tr>
<tr>
<td>2007</td>
<td>2.03</td>
<td>6.20</td>
<td>0.48</td>
<td>1.49</td>
<td>0.83</td>
<td>1.45</td>
</tr>
<tr>
<td>2008</td>
<td>9.66</td>
<td>4.82</td>
<td>0.41</td>
<td>1.71</td>
<td>0.79</td>
<td>1.86</td>
</tr>
<tr>
<td>2009</td>
<td>10.71</td>
<td>5.96</td>
<td>3.55</td>
<td>3.32</td>
<td>0.54</td>
<td>0.65</td>
</tr>
<tr>
<td>2010</td>
<td>12.19</td>
<td>7.91</td>
<td>7.39</td>
<td>3.22</td>
<td>0.34</td>
<td>0.36</td>
</tr>
<tr>
<td>2011</td>
<td>10.98</td>
<td>4.43</td>
<td>6.98</td>
<td>3.14</td>
<td>2.64</td>
<td>0.75</td>
</tr>
<tr>
<td>2012</td>
<td>11.02</td>
<td>6.88</td>
<td>5.96</td>
<td>2.78</td>
<td>2.19</td>
<td>3.67</td>
</tr>
<tr>
<td>2013</td>
<td>12.83</td>
<td>5.78</td>
<td>2.67</td>
<td>1.52</td>
<td>1.90</td>
<td>2.25</td>
</tr>
<tr>
<td>TOTAL</td>
<td><strong>7.69</strong></td>
<td><strong>5.25</strong></td>
<td><strong>2.53</strong></td>
<td><strong>1.91</strong></td>
<td><strong>1.37</strong></td>
<td><strong>1.28</strong></td>
</tr>
</tbody>
</table>

1. Tshuapa District located in this Province
2. Sankuru District located in this Province
Table 5. Average percent change in predicted yearly incidence for MPX, Tetanus, AFP (2001-2013, 2001-2007, and 2008-2013)

<table>
<thead>
<tr>
<th>Disease reported</th>
<th>All Years (2001-2013)</th>
<th>Phase 1+2 (Years 2001-2007)</th>
<th>Phase 3 (Years 2008-2013)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% change</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>MPX (whole country)</td>
<td>10.5</td>
<td>(6.2, 15.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MPX (without active surveillance areas)</td>
<td>8.3</td>
<td>(5.1, 11.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AFP</td>
<td>3.0</td>
<td>(-2.0, 8.3)</td>
<td>0.236</td>
</tr>
<tr>
<td>Tetanus</td>
<td>-3.9</td>
<td>(-6.8, -1.0)</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Figure 1. Disease reporting to the 4\textsuperscript{th} Direction, 2001-2013

Legend:
- Health Zone not reporting
- Health zone with any disease reporting
- Health zone reporting at least one suspected case of MPX
Figure 2. The evolution of IDSR System: suspected cases of MPX, AFP, and Tetanus, 2001-2013 reintroduction

- 2004: Change in health zone structure and age groups added to IDSR

Adjustment Phase (2004-2007)
- 2005: Reintroduction of polio
- 2005-2007: Intensified active surveillance in the Maban District, Eastern Sudan

Stable Reporting Phase (2008-Present)
- 2008: Present: Intensified active surveillance in the Wau District, Equatoria
- Dec. 2013: Last confirmed case of polio in DRC

Legend:
- Red: MPX Cases
- Blue: AFP Cases
- Green: Tetanus Cases

Number of reported cases reported to the IDSR
2.6 REFERENCES


Chapter 3: Integrated Disease Surveillance in the DRC – are we meeting the goals? A comparison of lab surveillance and passive reporting.

3.1 ABSTRACT

BACKGROUND

Classic disease surveillance programs have generally focused on a single disease or group of symptoms. More recently, national programs and organizations have worked to develop integrated platforms where information on multiple diseases and symptoms are collected in parallel to improve the quality of data, especially in limited resource areas. In the Democratic Republic of Congo (DRC), the Integrated Disease Surveillance and Response (IDSR) unit has been implemented to collect information on multiple diseases. Using human monkeypox (MPX) and acute flaccid paralysis (AFP) as a case study, we studied existing passive surveillance and laboratory test confirmation data to explore how increases in effort for one disease, through laboratory confirmation affect surveillance for other diseases reported to the passive surveillance system.

METHODS

We used available case counts from the IDSR and lab data from the National Institute of Biomedical Research (INRB) from 2008 to 2013 to explore factors which could be associated with disease reporting. We performed a time series analysis to determine if there are trends in reporting for MPX and AFP, and assessed the association of confirmed polio cases and confirmed MPX cases with passively reported cases of MPX, AFP, measles and tetanus.
RESULTS

During our study period, while MPX incidence significantly increased, there were no significant temporal trends within each year identified for individual disease occurrence or reporting similarities between the two diseases. For the country, the mean number of reported MPX cases weekly was 42 (range: 0 -125) and the mean number of AFP cases was 24.3 (range: 14.2-33.8). There were provincial differences in MPX and AFP reporting by week. Confirmed polio cases in a health zone had a negative association with MPX, measles and tetanus reporting, but had a positive association with AFP reporting. Health zones with confirmed cases of MPX had a positive association with MPX reporting, but a negative association with other diseases: AFP, measles and tetanus.

CONCLUSION

The IDSR was implemented to integrate disease identification and confirmation, and improve the overall detection of all reportable diseases. The analyses indicate that the specific individual disease components may only work to strengthen individual disease detection and may divert attention from the system as a whole. Further research should be done to learn how the system could be better integrated for improved utilization of already limited resources.
3.2 BACKGROUND

Public health surveillance can be used to monitor changes in disease occurrence and is typically defined as the “ongoing, systematic collection, analysis, interpretation, and dissemination of data regarding a health-related event for use in public health action to reduce morbidity and mortality and to improve health.”1-5 Two main strategies are used to collect surveillance data for disease detection: passive and active collection of data. Passive surveillance is a strategy whereby problems are identified using data generated through routine collection at a local level. This system relies heavily on the participation of those collecting the data at the local level, since they must send it with minimal intervention from higher levels, including the provincial and national levels for data analysis and feedback.6 The active surveillance approach requires substantially more time and resources as it requires those from higher levels in the system to actively look for cases of disease. Together, these strategies can have a greater impact enabling quicker detection of changes in disease occurrence, and more efficient disease control efforts.

Classically, surveillance systems have focused on a single disease or group of symptoms. This type of system is often found in low resource settings and is usually donor driven, based on objectives from external funders.7,8 More recently, national programs and organizations have worked to create integrated platforms where information on many diseases collected through multiple sources can simultaneously be gathered in one system. This strategy conserves resources by avoiding unnecessary duplication of efforts and should help improve the quality of data collected, especially in resource limited areas.7

An integrated system can be impacted by systemic components, which are human driven and external components, which are environmentally driven. Systemic components include the
efficacy, thoroughness, timeliness, sensitivity and completeness of data collection, sample collection and laboratory confirmation, active case-based searching, and sentinel surveillance at selected sites for disease detection. Environmental components include seasonal variation such as precipitation, humidity, and temperature. These variations can affect both actual disease occurrence and disease reporting, especially in areas where roads and communication are limited because these areas may become inaccessible during certain times of the year due to seasonal changes.

Surveillance in the Democratic Republic of Congo (DRC) is made up of both single and integrated disease reporting systems. Passive disease reporting occurs through the Integrated Disease Surveillance and Response (IDSR) unit, which was mandated by the World Health Organization’s African Regional Office (WHO/AFRO). The DRC’s IDSR was established in 1998 to strengthen public health surveillance and response.\(^9\)\(^-\)\(^11\) In DRC, the IDSR targets 13 diseases of epidemic potential and two diseases targeted for elimination and eradication.\(^12\) The IDSR collects aggregate data without any personal identifying information in a vertical reporting system beginning at the local level and ending at the national level, where the data is compiled and published in a weekly bulletin.\(^12\) Cases of disease reported through the IDSR are considered suspect cases, and in order to be confirmed, a lab sample must be tested\(^1\). The laboratory samples with a corresponding reporting form are sent directly from the health zone to the National Institute of Biomedical Research (INRB) and WHO, containing personal identifying information. The system was implemented to integrate existing surveillance activities, including the laboratory surveillance data; however differences in data collection and reporting make linkages of the two systems difficult to implement.

\(^1\) Unless there is no confirmatory test such as for tetanus.
We selected two different diseases to measure the integration of the surveillance system, composed of multiple parts, including passive reporting and laboratory confirmation. Human monkeypox (MPX) is considered a disease of epidemic potential, while polio is targeted for eradication. Both diseases selected have integrated laboratory components, and to-date, have no identified seasonal variation in occurrence in DRC.\textsuperscript{13-15}

Monkeypox virus is a zoonotic infection found in a variety of mammals that can infect humans with a smallpox-like illness.\textsuperscript{16} While MPX is considered a rare disease with limited geographic distribution, in the 30 years since the eradication of smallpox, the disease has emerged as the most severe human orthopoxvirus infection.\textsuperscript{17} A majority of the cases are reported in the DRC, where it is routinely found in rural settings in or near heavily forested areas.\textsuperscript{16, 18} Due to the inaccessibility of many regions where the disease is found and limited active MPX surveillance, little is known about the seasonality of this disease or other factors influencing reporting. While there has been no identifiable pattern of seasonal changes in disease occurrence to-date, the 1980’s WHO Active Surveillance in the Tshuapa and Sankuru districts found increased numbers of cases reported between the summer months of June and August.\textsuperscript{13, 16, 14, 19} Cases of MPX reported through the IDSR are considered only suspect cases, and in order to be confirmed, a lab sample must be collected and tested.

Poliomyelitis is caused by an enterovirus, with the sole identifying symptom being rapid onset of paralysis. Only about 1 in 200 cases of polio will lead to acute flaccid paralysis, suggesting that one case of polio-induced paralysis could be the result of wide virus circulation.\textsuperscript{20} In temperate climates, the peak season for infection is the summer months, but a seasonal pattern in tropical climates has not been identified.\textsuperscript{15} This disease is in the final stages of eradication, and as of October 22, 2014, there were 247 cases confirmed for 2014 world-wide.\textsuperscript{21} The last
identified case of polio in DRC was on December 20, 2011, however, active surveillance of AFP is ongoing.22 Because several other enteroviruses also share the paralysis symptom, the majority of samples collected test negative for polio. Due to the scarce number of cases worldwide, the discovery of a single polio case leads to massive efforts to scale up surveillance in the infected area.

Using MPX and AFP as models, we utilized existing passive surveillance data from the IDSR in DRC to explore the association of two components of the integrated system: seasonality of reporting (environmental) and laboratory confirmation (system based). Our aim was to determine if these factors were associated with disease reporting trends during the period 2008 to 2013. As an additional comparison we looked at the effect on two other reportable diseases: suspected measles and tetanus cases. Measles was selected as it is considered linked to the AFP surveillance reporting, and tetanus was selected as it should have constant reporting throughout the year and does not require laboratory confirmation.

3.3 METHODS

Data Sources

IDSR Data: Case counts of MPX, AFP, measles and tetanus reported from December 31, 2007 through December 31st, 2013 to the IDSR unit under the 4th Direction, an office under DRC’s Ministry of Health (MoH) were used.23 The public health care system of DRC is made up of over 10,000 health facilities required to send passive surveillance reports each week to 516 health zones in 11 provinces. Data available for reported cases include: health zone, province, week reported, and age category (0-11 months, 12 to 59 months, or 5 years and older).

MPX Laboratory Data: Collected biological specimens for MPX confirmation are sent directly from the health zone to the INRB.24 Between 2008 and 2013, there were 149 confirmed
cases of MPX. Sample information includes date of onset of illness, the date of sample collection, and the date of sample processing, as well as sample type (crust, vesicle, blood, etc.). Village, age, and sex were also reported. We aggregated the samples received and confirmed by health zone and week. Additionally, we created a binary variable of confirmed cases of MPX, 1 if there was a case confirmed in the health zone and epidemiologic week, and 0 if no case was confirmed.

AFP Laboratory Data: All cases of AFP are investigated and samples are collected and sent directly from the health zone to the INRB for laboratory confirmation. Between 2008 and 2013, there were 201 confirmed cases of polio in 152 individual health zones and epidemiologic weeks. After confirmation of one case, increased surveillance activities should take place within the health zone. AFP data, based on health zone and the week of case investigation, was incorporated into the dataset. We created a binary variable of confirmed cases of polio, 1 if there was a case confirmed in the health zone and epidemiologic week, and 0 if no case was confirmed. Health zone notification occurs between 3 to 5 weeks after the case investigation, as testing and confirmation can take up to 21 days based on the testing algorithm. Thus we created four additional variables to represent the lag time after confirmation of a polio case. A binary variable was used, 1 if there was a confirmed case of polio 3 to 5 weeks before based on the date of investigation and 0 otherwise. Thus if there was a case of polio in the first epidemiologic week, it would also be indicated on the variable for week 3, 4, and 5 after investigation. We combined this variable to look at the entire time period between 3 to 5 weeks after initial investigation of a confirmed polio case, as this was our assumed range necessary for confirmation, feedback, and deployment of recourses to the health zone.
**Statistical Analysis**

All data sources were combined into one dataset and data management was performed using Microsoft Access®. We assumed that health zones sending reports with at least one disease listed having cases in that week but not all, had zero cases for the other diseases not specifically reported. We removed the Tshuapa District, Province Equateur from our models which used MPX lab data, since an active surveillance program is on-going (Figure 1)<sup>2</sup>.<sup>19</sup> All analyses were completed using SAS v9.4.<sup>25</sup>

We examined seasonality and time trends (using weekly case counts) for MPX and AFP cases reported to the IDSR. First and 2<sup>nd</sup> degree autocorrelation using linear regression models for MPX and AFP was observed at the country and provincial levels, thus we explored alternate methods. We modeled weekly trends using the unobservable components model (UCM) for determining if trends in seasonality or cycles could be identified, as well as predicting future case reporting for the next 52 weeks.<sup>26</sup>

We used hierarchical multi-level models (generalized linear mixed models) for count data to model the association between laboratory confirmation and incidence of suspected cases. The predictor variables were laboratory confirmed cases of either monkeypox or polio. Outcome variables were suspected diseases reported in the passive IDSR system: incidence of suspected MPX, AFP, measles and tetanus cases. The dataset had three levels of clustering: health zones in districts in provinces. We assumed that cases would be more geographically clustered within health zones, districts, and provinces and normally distributed. Geographic clustering was

---

<sup>2</sup> This represents 12 health zones with on-going active case research conducted by Centers for Disease Control and Prevention (CDC) in Atlanta, CA, USA.
considered a random effect in the mixed models with a random intercept. We explored the possibility of clustering at the health zone, health zone in the district, and health zone in the district in the province. We initially tested each model with either the a negative binomial distribution to account for over-dispersion or the Poisson distribution assuming that accounting for clustering was adequate for correcting variance around the mean. The estimated over-dispersion factor (Pearson Chi-Square/degrees of freedom) calculated for each model; one was considered the optimal value for the goodness of fit test. For incidence of MPX, AFP, and tetanus, we found the optimal model should account for health zone clustering with Poisson distribution, and for measles, the optimal model should account for clustering at all levels (health zone, district, and province) with a negative binomial distribution. However, we noted that all models explored exhibited similar outcome results in the same direction for all diseases. We calculated incidence rate ratios (IRR) and corresponding 95% confidence intervals (CI) for all individual outcomes. The population offset used was the health zone population extrapolated from the 2013 Expanded Program for Vaccination (EPI) Microplan as this data was available for each health zone.27

We used the two different variables (same epidemiologic week, and 3 to 5 weeks after confirmation) for a confirmed case of polio in a given health zone and the association with the passive reporting system for AFP, MPX, tetanus, and measles. We also explored the association between confirmed cases of MPX with reportable diseases: suspected MPX cases, PFA, tetanus, and measles. We expected that health zones reporting suspected cases of MPX would be associated with confirmed positive samples tested at the INRB. A lag variable was not created.

---

3 We also believed that time could also act as a random effect, but the models were too large to be completed using the selected program, SAS v9.4
for laboratory confirmed MPX cases, as there is limited feedback to the health zone if there is a positive case, and no active searching if a case is identified.

**Ethical Review**

This study was reviewed and approved by the Ethics Committee of the Kinshasa School of Public Health, Kinshasa, DRC and by the Institutional Review Board of Human Research Ethics at the University of California, Los Angeles.

### 3.4 RESULTS

**Seasonality**

Suspected MPX cases: For the country, the reporting remained fairly stable throughout the years with no identified trends in seasonality identified for the country (Figure 2a) or the provinces of Equateur, Kasai Oriental, and Bandundu. Prediction models for the subsequent year (2014) resulted in wide intervals, with a constant trend (Figure 2b), and without irregularities, wide intervals, with random fluctuation (Figure 2c). When collapsing the data for the 6 years, we found weeks 4 to 11 (February) and 34 to 37 (September) had the highest overall number of reported MPX cases, while weeks 27 to 28 (July) and 51 to 52 (December) were the lowest (Figure 3). Equateur and Bandundu province had similar distributions of reported cases to the country. Kasai Oriental only had one peak period, weeks 29 to 40 (August-October), and week 51-52 (December) had the lowest number of cases (Figure 3).

AFP cases: We found similar results looking at AFP case reporting, there were no significant trends found by country or province (looking at the same provinces we explored for MPX) (Figure 4a). When looking at prediction models for the subsequent year, there were wide intervals and a constant trend (Figure 4b) and when the irregularities were removed, random fluctuation with wide intervals (Figure 4c), similar to what we observed for MPX predictions.
After collapsing the yearly reporting to represent a 52 week time period, there was a peak period for the average number of cases reported during weeks 25 to 29 (July), and a shorter peak during week 47 (November), while weeks 1 and 52 (first and last week of the year), and week 41, had the lowest number of reported cases (Figure 5). The mean number of AFP cases reported per week was 24.3, and remained fairly stable throughout the year. Equateur, Bandundu, and Kasai Oriental had some similarities in case distribution throughout the year, but did not have the same peak or low periods as MPX case reporting (not shown).

The occurrence of cases was different for MPX and AFP, except for the last weeks of the year, which was the lowest reporting time for each disease. Neither had any significant trends or seasonality detected, or overlapping trends in disease reporting for the country (Figure 6a) or selected provinces (Kasai Oriental)(Figure 6b).

**Laboratory confirmation of MPX and Polio and passive reporting diseases**

MPX Confirmation: The presence of a laboratory confirmed MPX case in a health zone during a specific week compared to those without a laboratory confirmation were significantly associated with an increase in suspected MPX incidence in the same health zone and week (Incidence Rate Ratio (IRR)=1.83, 95% CI: 1.53, 2.18) (Table 1). Incidence of other suspected cases reported were associated with a confirmed MPX case in the same health zone and week, by a stable, non-significant trend (tetanus) or decreasing, significant trend (AFP, measles).

Polio confirmation with no time lag: We also found a significant increase in AFP incidence and confirmed cases of polio in the same week and same health zone compared to those without a confirmed case (IRR: 4.55 (95% CI: 3.86, 5.37) (Table 2). For measles, tetanus, and suspected MPX, we found a consistent decrease in incidence for all three diseases with an
estimated IRR of less than 0.35 (range: 0.038 to 0.99) when there was a case of polio confirmed in the same health zone and week.

Polio confirmation with a 3-5 week lag: Three to 5 weeks after the initial investigation and sample collection for a case of polio in a health zone, we found a significant increase in the incidence of reported AFP cases compared to those without a confirmed case (IRR: 2.97, 95% C.I.: 2.53, 3.47) (Table 3). However, for all other reported diseases explored using the same type of model (MPX, tetanus, and measles), there was a significant decrease in the incidence 3 to 5 weeks after the investigation of a confirmed positive polio case. The presence of a confirmed polio case in a health zone compared to those without a confirmed case were associated with a decrease in incidence of suspected MPX (IRR: 0.80, 95% CI: 0.57, 1.01). The results were similar when each lag between 3 to 5 weeks was explored individually (results not shown).

3.5 DISCUSSION

The results of the factors we explored indicate that there are disease specific impacts for increased surveillance and reporting of suspected cases through the IDSR when there is lab confirmation of the same diseases. This could indicate that disease specific impacts are present in the integrated system as opposed to overall impacts in the disease reporting.

In a passive surveillance system, data collection may be inexpensive; however, its reliance on lower levels to regularly report accurate and complete data may result in significant underestimation of cases of disease occurrence. This could result in delayed identification of outbreaks. When coupled with other sources of data, such as an active surveillance or laboratory-based component, the data may be more useful in detecting, confirming and controlling outbreaks earlier on. An integrated system can be useful in identifying areas of weakness—such as only receiving passive data, with no samples for confirmation or vice-versa.
While seasonal patterns were not specifically identified for MPX, active surveillance in DRC has indicated that an increase in cases has historically occurred during the dry season (June to August) with 35% of the total reported cases occurring between those same months.\textsuperscript{13,28} The previous reports of seasonality for both diseases, not shown any distinct patterns in tropical climates, were similar to our results. We found the weekly suspected MPX cases reported to the IDSR during our 6-year study period fluctuated, but identified two possible peak periods, one earlier in the year (February) and the other later in the year (September), with the lowest incidence occurring in July and December. The exception for this was Kasai Oriental, which only had one main peak period between August and November. Based on the fact that the fewest cases were reported in the last weeks of the year, this may be partly explained by reduced reporting during the holiday season, as we found a similar trend for AFP reporting. When assessing seasonal trends in AFP reporting, the trends were not the same as MPX, but instead over the course of the collapsed 52-week time period, we identified a peak period in July, while the overall trend was fairly constant. The standard deviations and predicted trend for both diseases showed wide variation, indicating that the “noise” or irregularities in the reporting may also impact the ability to decipher if actual seasonal changes in disease occurrence or reporting exist.

In a recent publication regarding monkeypox detection in active surveillance areas, researchers found that after formal training for case identification, there was a significant increase in the number of cases reported, but the percent of cases laboratory confirmed did not significantly increase.\textsuperscript{19} In our analysis, there was a positive association with health zones reporting MPX cases to the IDSR and having a confirmed case. Each year between 20% and 70% of the samples submitted to the INRB test negative for MPX. Suspected cases of MPX
reported may represent true MPX cases as well as other rash-illnesses (e.g. chickenpox) as the case definition is not very specific which could result in misclassification bias. Use of laboratory confirmation in locations where MPX is thought to be circulating can help determine if there are changes in distribution as well as give more thorough information on individual cases. Areas reporting suspected cases of MPX, without any laboratory confirmed sample should be targeted for training to better identify, and collect samples from suspected cases of MPX for confirmation. This can be used to reduce the possibility of an organized response effort if the disease is not truly present in the area.

We explored the association between a confirmed polio case in a health zone with a number of IDSR reportable diseases. The program for disease surveillance is based on an integrative approach, meaning increases in one sector of the program should have a positive effect on the entire system. The DRC’s IDSR guidelines outline an integrated approach whereby the resources used to monitor one disease should also be used to increase the monitoring other reportable diseases, for example active surveillance for AFP, should increase the monitoring ability for other diseases. While they are already searching for AFP cases, they should also collect information on other diseases such as measles, tetanus, and other unusual reportable events. The active case identification system for polio is designed to identify additional cases through intensified case searching if even one case is confirmed. During intensified case searching for polio cases, it should provide health officials the opportunity to visit more difficult to reach areas and allow for additional reporting of other diseases that typically may not be reported. However, as the money is based on tracking polio cases, this type of integration may seldom be followed.
We found a positive association between reporting of AFP cases and a laboratory confirmed polio case, and a negative association with other diseases, including MPX. Financing for eradication activities typically comes from international funders, and is significantly increased in areas where there has been a confirmed case. This funding may result in increased health care worker training or staff reinforcement for AFP case searching. Recent studies have shown the Global Health Investments (GHI) which include the polio eradication efforts can influence health systems, but this interaction has not been well documented. The increased investment in targeted health services, including AFP case detection may divert focus of the system away from other diseases, especially in areas where the systems may be carried out in parallel reporting structures, when the health system is fragile, including understaffing of health facilities, all major factors in DRC. Since there has not been a confirmed polio case in almost three years, there is no impact on reporting from 2012 and 2013. Mass vaccination and regular active surveillance activities are still ongoing, and these could continue to impact reporting for AFP. However, while these activities should also positively impact the integrated system and increase reporting for other diseases, our evidence indicates that it may also have additional negative impacts on reporting for other diseases by diverting attention from the overall system.

There are a number of limitations to our analyses. The data may have significant time delays and some health zones do not regularly send data, therefore some weeks could be the representation of multiple weeks of data. This may inflate the case counts for certain weeks, and reduce counts in other weeks, and may account for some of the fluctuations in our data. There may be discrepancies within the definition of an epidemiologic week by location, due to the structure in the surveillance system. This is especially true in difficult to reach areas, which public health facilities in the system may not be able to regularly send weekly surveillance
reports to the higher level, or may not have been trained in surveillance activities to ensure consistency at all sites. The epidemiologic week defined by the IDSR Surveillance manual, begins each Monday.\textsuperscript{12}

Our methodology could provide a platform for data analysis for use with other reportable diseases that may have components which make reporting less complete. Properly collected surveillance data should be used to monitor changes in disease occurrence (increases during epidemics and decreases with control policies), and assess geographic spread.\textsuperscript{5} To-date, there have been limited analyses with surveillance data to discuss the trends and associations with the reporting structure when there are additional parallel structures for data collection. Basic trends for the suspected cases of disease reported via the IDSR and laboratory confirmed data are often analyzed separately, as opposed to an integrated approach. Comparisons could be made at the health zone level to better understand reporting habits, and to determine if there are zones which have seasonal trends either in disease reporting or disease occurrence. Expanded integration of data collected from multiple diseases at the same time can help guide the creation of clear recommendations for improvements for understanding trends, and reporting habits from specific geographic locations collected. The results of this study indicate that the goals of surveillance integration are not being attained in the current system in DRC, but instead funding for individual disease activities, including diseases eradication efforts, may be disrupting the overall system.
Figure 1. Democratic Republic of Congo, Health zone map with the Tshuapa district in red
Figure 2. a) Weekly trend for suspected monkeypox cases reported from December 30, 2007 to December 31, 2013 in DRC. b) Smoothed weekly trend and cycle plot with 1 year forecast. c) Smoothed weekly trend, cycle and seasonal plot without irregularities
Figure 3. Country and selected provincial mean weekly counts (2008-2013) for suspected monkeypox cases reported to the IDSR
Figure 4. a) Weekly trend for AFP cases reported from December 30, 2007 to December 31, 2013 in DRC. b) Smoothed weekly trend, and cycle plot with 1 year forecast. c) Smoothed weekly trend, cycle and seasonal plot without irregularities.
Figure 5. Mean weekly AFP Case counts (2008-2013) reported IDSR
Figure 6. a) Comparison of mean weekly trends for reported MPX and AFP cases over 6-year period for DRC. b) Comparison of mean weekly trends for reported MPX and AFP cases over 6-year period for Kasai Oriental.
Table 1. Confirmed case of monkeypox (same week) in a health zone and the association with reportable diseases, Incidence Rate Ratio (IRR) of Reported Diseases in the IDSR, 2008-2013. Model 1: Accounted for clustering at health zone level with Poisson distribution. Model 2: Accounted for clustering in health zone in district with a negative binomial distribution. Model 3: Accounted for clustering in health zone in district in province with a negative binomial distribution.

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR (95% CI)</td>
<td>IRR (95% CI)</td>
<td>IRR (95% CI)</td>
</tr>
<tr>
<td>Suspect MPX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.83 (1.53, 2.18)</td>
<td>2.40 (1.39, 4.17)</td>
<td>3.42 (2.17, 5.43)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Suspect AFP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.38 (0.18, 0.80)</td>
<td>0.43 (0.20, 0.95)</td>
<td>0.41 (0.19, 0.89)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Suspect Tetanus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.65 (0.37, 1.15)</td>
<td>0.49 (0.27, 0.89)</td>
<td>0.57 (0.31, 1.02)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Suspect Measles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.039 (0.025, 0.062)</td>
<td>0.032 (0.02, 0.06)</td>
<td>0.047 (0.024, 0.091)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>
Table 2. Confirmed case of Polio (same week) in a health zone and the association with reportable diseases, Incidence Rate Ratio (IRR) of Reported Diseases in the IDSR, 2008-2013. Model 1: Accounted for clustering at health zone level with Poisson distribution. Model 2: Accounted for clustering in health zone in district with a negative binomial distribution. Model 3: Accounted for clustering in health zone in district in province with a negative binomial distribution.

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR (95% CI)</td>
<td>IRR (95% CI)</td>
<td>IRR (95% CI)</td>
</tr>
<tr>
<td>Suspect MPX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.33 (0.082, 0.99)</td>
<td>0.05 (0.011, 0.22)</td>
<td>0.15 (0.037, 0.60)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Suspect AFP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4.55 (3.86, 5.37)</td>
<td>4.99 (3.94, 6.32)</td>
<td>5.31 (4.2, 5.31)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Suspect Tetanus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.12 (0.038, 0.37)</td>
<td>0.12 (0.039, 0.38)</td>
<td>0.12 (0.037, 0.36)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Suspect Measles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.32 (0.28, 0.35)</td>
<td>0.18 (0.12, 0.27)</td>
<td>0.26 (0.18, 0.38)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>
Table 3. Confirmed case of Polio (3 to 5 weeks after confirmation) in a health zone and the association with reportable diseases, Incidence Rate Ratio (IRR) of Reported Diseases in the IDSR, 2008-2013. Model 1: Accounted for clustering at health zone level with Poisson distribution. Model 2: Accounted for clustering in health zone in district with a negative binomial distribution. Model 3: Accounted for clustering in health zone in district in province with a negative binomial.

<table>
<thead>
<tr>
<th>Suspect Disease</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR (95% CI)</td>
<td>IRR (95% CI)</td>
<td>IRR (95% CI)</td>
</tr>
<tr>
<td><strong>Suspect MPX</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.80 (0.57, 1.01)</td>
<td>0.18 (0.086, 0.37)</td>
<td>0.48 (0.23, 0.99)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td><strong>Suspect AFP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.97 (2.53, 3.47)</td>
<td>3.29 (2.68, 4.04)</td>
<td>3.44 (2.81, 4.20)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td><strong>Suspect Tetanus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.59 (0.39, 0.90)</td>
<td>0.58 (0.37, 0.89)</td>
<td>0.56 (0.36, 0.86)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td><strong>Suspect Measles</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.70 (0.66, 0.74)</td>
<td>0.54 (0.40, 0.73)</td>
<td>0.69 (0.52, 0.93)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>
3.6 REFERENCES


Chapter 4: A descriptive and quantitative analysis of potential underestimation of human monkeypox cases in the passive surveillance system in the Democratic Republic of Congo

4.1 ABSTRACT

BACKGROUND

A major objective of disease surveillance systems is to provide critical information on burden of disease that will inform prevention and control policy and focus of public health efforts. In settings, such as the Democratic Republic of Congo (DRC), where resources for adequate surveillance are limited and often rely on under trained health care workers with limited resources, reporting of disease may only represent a fraction of the total cases. We present a novel computational method using a scenario tree to model the gaps in DRC’s disease reporting system, using monkeypox (MPX) as an example.

METHODS

Case counts of MPX reported from January 1st, 2013 to December 31st, 2013 to the Direction of Disease Control in the Ministry of Health (MoH) were used. Using a scenario tree model, we estimated the proportion of suspected cases lost in the reporting stream in health zones not considered silent. An extensive flow diagram was created to identify all disease-reporting schemes (and non-reporting) in the IDSR system.

RESULTS

In 2013, a total of 2,460 cases of suspected human MPX virus were reported to the IDSR, in the simulated model, the actual number of cases could be 5.0 and 15.2 (mean 9.4) times higher than what was observed in the IDSR at the national level. According to our estimates the true number of suspected cases would have ranged from 12,380 to 37,600 (average=23,280) suggesting a far more severe picture of human MPX in DRC than the passive surveillance system indicates.
CONCLUSION

To our knowledge, this is the first model of this type created for disease reporting in DRC, which documents every place a case could be missed in the passive reporting system. Our model found that most of the cases are lost in the 1st level when 60% of the total cases may not seek any treatment. This number is even higher in the least accessible areas; overall, only about 10% of possible cases may be reported to the national level. Policy implications and determination of cost-effectiveness for filling in the gaps within the system may be difficult and inaccurate to estimate, implementing programs to better involve community workers in disease surveillance should be a priority.
4.2 BACKGROUND

Disease surveillance systems are the first step in determining the relative importance of a disease and its potential as a threat to public health. Properly collected surveillance data can be used to determine the burden of disease, monitor changes in disease occurrence, assess geographic spread, identify high-risk populations and emerging health concerns, and help prioritize allocation of health resources.¹

A surveillance program is typically established with a vertical reporting structure, starting with the collection of reported cases at the most local level or health facility, and moving to higher levels in the system, ultimately reaching the national level.² The passive disease surveillance structure in the Democratic Republic of Congo (DRC) is housed in the Direction for Disease Control (4th Direction) of the Ministry of Health (MoH), and is based on the vertical structure (Figure 1). To be detected in the system, an individual must visit a health facility and be diagnosed with one of the 15 reportable diseases and then it must be reported in the Integrated Disease Surveillance and Response (IDSR) system. Once a report is initiated, it must still be transmitted through multiple levels before reaching the national level. At the national level, the 4th Direction is responsible for coordinating the disease surveillance activities through the IDSR system on a weekly basis.³ At each level, there is a risk that the report may not be transmitted to the next level. Each location with data missing creates gaps in the system, which could significantly underestimate the true burden of disease occurrence.

Over the past few decades, the health care system in the DRC has deteriorated to a poorly functioning one, and by some standards, it is considered a collapsed system.⁴ In 2013, DRC was ranked 2nd on the list of failed states.⁴,⁵ In a country where health facilities often do not have the medications needed to treat the most basic health problems, resources for disease surveillance are
severely limited. In addition, there are significant problems with transportation and communication in remote areas. This affects estimates of the true burden of disease in DRC as well as other estimates related to disease severity, geographic changes over time, and transmissibility, which are especially important for diseases considered emerging and with epidemic potential.6

Monkeypox (MPX) is one of 15 diseases included in the IDSR, and is considered a disease of epidemic potential.3,7 Therefore, regular monitoring of suspected cases is critical to ensure that, if there is an outbreak, a response can be implemented quickly and efficiently for disease control. MPX is an orthopox virus and a zoonotic infection infecting humans with a smallpox-like illness.8,9 MPX is routinely reported in rural villages located either in or near heavily forested areas which are typically difficult to access.10,11

The first case of human MPX was identified in 1970, during intensified active surveillance activities for the smallpox eradication program.12 Vaccinia vaccine was found to be cross-protective against orthopox viruses including MPX.8 However, 35 years after eradication of smallpox and subsequent cessation of vaccination, most of the community does not have immunity against orthopox viruses.13,14

Over the past 13 years, there has been a significant increase in MPX incidence in DRC, based on data collected through the passive IDSR system, (2000 to 2013: 0.64 per 100,000 vs. 2.82 per 100,000).15 This increase is even more pronounced when comparing data from active surveillance programs established by the World Health Organization (WHO) in the 1980s to more recent active programs established between 2005 and 2007 (7.2 to 144.2 cases per 100,000, respectively).8,16 When the most recent active surveillance data is compared to the passive surveillance data over the same years in the same health zones, there is increased reporting in the
active sites. While MPX incidence and reporting has increased since the implementation of the passive IDSR system, disease incidence estimates are likely to be underestimated, with a majority of cases not reported due to constraints in the system at each level.

Research has shown that several other rare or emerging diseases may be underestimated through passive disease reporting systems. For measles, considered a rare disease, the World Health Organization (WHO) has suggested that only 10% to 20% of cases are reported in the health system, even in this case-based reporting system that attempts to include every infected individual.\textsuperscript{17} There have been additional reports from other countries, estimating that only between 15%-20% of the cases in a reportable system are actually reported, indicating many diseases may have a much higher burden than expected.\textsuperscript{18-20} In a recent report looking at trends of human brucellosis in Italy, they found on average an underreporting rate of 12.5 (range 2 to 21), and that the actual number of cases could be much higher than reported.\textsuperscript{21}

Here we present a novel computational method using a scenario tree to model the potential gaps in DRC’s MPX disease reporting system. A descriptive analysis will be used to help quantify the missing pieces within the disease reporting system.

4.3 METHODS

Program Structure: The DRC health system is comprised of 516 health zones, which are considered the “operational level” of the health system, and the level at which most health programs are implemented. There are an average of 10 to 15 health zones in a district (which may or may not be operational depending on the area). Health zones are responsible for entering data on a weekly basis received from health facilities: hospitals, health centers, health posts, and other included health facilities. The data with information on the reportable diseases is then transmitted to the district or province level. The data can be sent via internet, high-frequency radio, and
cellular telephones, and when no other method is possible; it is transmitted by other means, including vehicle, motorcycle, bicycle and on foot. In many areas, both transportation and communication are difficult, causing reports to be delayed, and some may never reach the next level.

**Monkeypox Surveillance data, 4th Direction:** Case counts of Monkeypox reported to the 4th Direction are available from January 1st, 2001 through December 31, 2013, courtesy of the DRC MoH. All reported cases are suspected cases based on aggregate reporting, thus no names are reported and cannot be linked to laboratory results. For the purpose of setting up the model, one year of data was considered, January 1st, 2013 to December 31st, 2013.

**Description of model and parameters (Table 1):** Using a scenario tree model, we estimated the proportion of suspected cases lost in the reporting stream. An extensive parameter table was created to identify all disease-reporting (and non-reporting) schemes in the IDSR system. Estimates of probability were obtained from a number of different sources of data including the 2013 DHS, personal interviews (at various levels of the system), expert opinion, vaccination program yearly plans, the National Laboratory (INRB) and the 4th Direction. The table includes the reporting parameter and range for each possible scenario which could lead to reporting to the next level, however, as all base parameters totaled to 100%; we did not include the non-reported parameter as this was assumed to equal 1-reporting parameter. During the simulations, each branch could not be more than 100% or less than 0% (negative cases) based on the reporting parameters.

The model is composed of Surveillance Systems Components (SSC), whereby each element is represented as a “set of events with specified probabilities,” conditional on previous events, as well as an overall probability relating to the sensitivity of detecting a positive event.
given that they are truly infected.\textsuperscript{25-26} The identified ranges were found to be non-normally distributed and we considered the triangle distribution for most parameters, but not all were symmetric as the ranges were typically lower than the mean, with a longer tail towards the higher percentages; we also used lognormal distributions truncated at 0 in cases that the range was skewed extremely far in one direction. We also wanted to ensure that the ranges would not lead to negative values during the simulated runs, thus we truncated the value in the first level of the model for those not seeking health care services, so that the predicted value could not be less than 0. Each simulation was allowed to have independent draws from the ranges, thus we did not account for differences in geographic regions. There were five identified levels in the DRC’s system for passive surveillance reporting, and an additional 6\textsuperscript{th} level identified for samples received and confirmed positive at the INRB.

**Level 1:** Where the person first seeks treatment, data was obtained from a health care utilization survey (DHS) to determine where people most often sought care when they became ill with a variety of diseases including malaria, other fevers and diarrhea. Additionally, to obtain ranges, we met with health zone doctors in different locations, to discuss their populations’ preferences for health care services. The majority of persons do not visit health facilities when they become ill with a number of symptoms, this is based on the severity of the presumed diseases, with more severely affected patients being more likely to visit a health facility. MPX severity ranges from mild to very severe, with most people only having a few mild symptoms including fever, light rash, and enlarged lymph nodes.

**Level 2:** Once a person sought care, percentages were obtained from various health facilities (health posts, health centers, and the general hospitals), and through personal interviews on how cases were then reported to the next level in the system. This level also includes the
percentage of cases that do nothing, are seen at the informal health care providers, or private clinics, and get reported into the system. For example, we interviewed nurses at health facilities to determine what percent of cases they turned away due to inability to pay for services, in their health structure in some health zones, they could be penalized for treating patients and recording them without receiving payment. So patients will be either referred to another clinic, treated and reported, treated and not reported, or not treated and not referred. This can happen at the health post, health center, and general hospital for the health zone. We additionally checked health facility records for suspected MPX cases listed, and then compared the results to what was reported at the health zone level to gauge reporting parameters at more local levels. For reporting from traditional healers and private clinics, we estimated this based on the number of facilities integrated into the system and expert opinion as there is no official data on this integration and reporting parameter, which will have geographical differences. For the word of mouth reporting, we interviewed health zone doctors and those in charge of the weekly surveillance reports. This type of reporting was very minimal, and rarely occurred.

**Level 3:** Reporting from the health zone office to the district level. We compared the number of cases reported at the health zone to the district for the range.

**Level 4:** Reporting from the district level to the province level. We compared the number of cases reported at the district to the province for the range.

**Level 5:** Reporting from the province level to the national level. We compared the number of cases reported at the province to the national for the range.

For the parameter and ranges for levels 3 to 5, we contacted health zone offices and asked how many suspected cases of MPX they recorded in 2013, and then compared the results to the number of cases reported at the district level, then to provincial level, and finally to the national
level. For example, in Lomela Health Zone in the Kasai Oriental Province, a health zone considered rural, with limited accessibility, we found that they had recorded 290 cases of MPX at the health zone level, 87 cases at the district level (30%), 64 cases at the provincial level (73%), and 52 cases at the national level (81%), overall 17.9% of the cases made it from the health zone to the national level. While in an urban health zone with high accessibility, Gombe Health Zone, Kinshasa Province, we found the health zone had 1 reported cases at the health zone, 1 reported case at the district (100%), 1 reported cases at the province (100%), and 1 reported cases at the national level (100%), overall 100% reporting.

**Analysis:** It was assumed reporting was heterogeneous throughout the country, thus will not take into account the significant variability in the accuracy of reporting, and certain geographic locations having a greater burden of MPX disease compared to others. Data analysis was completed using Microsoft Excel and an add-on program, @Risk version 6.

The model was created using input parameters and ranges in a vertical scenario tree, starting with once a person becoming ill and propagated through each level to the final outcome of the total number of cases at the national level, which was the 2013 passive reporting total. Cases either went to the next level or were not reported, and thus did not move to the next level. At the health zone level, the total of all intermediates moving to the next level (health zone), were added together. It was assumed that once a case was reported to the health zone, there was only one pathway to be reported to the district, province, and national levels. In order to obtain this result, the model was run forward using a range of possible total case counts, in order to obtain the range required to obtain the reported number at the national level. Each time the number of actual cases was changed, a simulation was run to obtain the outcome of cases reported to the national level (10,000 iterations per simulation). From these forward simulations,
an estimate and range of potential number of actual cases occurring was obtained. This model does not take into account silent zones which do not report any disease, as it was difficult to receive information from these locations and it was assumed their entire health structure would be significantly different from those reporting. A sensitivity analysis was completed to identify the gaps which may have the greatest impact for data quality improvement.

**Ethical Review:** This study was reviewed and approved by the Ethics Committee of the Kinshasa School of Public Health, Kinshasa, and DRC and by the Institutional Review Board of Human Research Ethics at the University of California, Los Angeles.

### 4.4 RESULTS

In 2013, a total of 2,460 suspected MPX cases were reported to the IDSR. The incidence for the country was estimated to be 2.82 per 100,000 (95%CI: 0.40, 20.16). When we excluded the district with ongoing active surveillance activities (Tshuapa district, Equateur province) there were 1817 suspected cases reported to the IDSR.

The qualitative assessment of the disease surveillance system for reporting cases of MPX to the national level demonstrates the complexity of the system to be reported even as a suspect case (Figure 2 – tree model). Based on health care utilization surveys, after people were sick, 60% of cases did not seek any care, and thus most would be unreported due to underascertainment of health services.\(^{24}\) While this percentage is not specific for MPX, not seeking any care rates were similar for a number of symptoms and diseases, including malaria, fever, and diarrhea, and disease severity is believed to have an impact on utilization. The most utilized health facility was the health center, with variation based on if it was an urban or rural location.

The ability to pay for services once a sick individual visited a health facility led to a variation in reporting rates. When they were unable to pay for services, there were higher referral
rates to other health facilities in the reporting system and lower reporting rates, as these would have to be logged in the facility registry as a case treated, which could be audited by the health zone, to ensure all patients were charged for services. At the health center level, the most used public facility, it is estimated that if a patient is able to pay for services, there is a 73% chance they will be reported to the health zone versus 16.6% if they are unable to pay (includes referrals to other centers) (Figure 2). Thus at the health center level, 83.4% of the cases unable to pay may be lost in the system. Additionally, based on the defined parameters and simulations, that people who are unable to pay for services at any level (2,613, 11.2%), or those visiting health facilities outside of the public sector not included in the surveillance system (2,086, 9%) make up a large proportion of the unreported cases when compared to the total estimated number of cases (Figure 2).

Cases identified at the lowest health level, the health post, have the additional burden of needing to be reported to the health center before the health zone in some cases. For those visiting the informal health providers (IHP) and the private clinics, we assumed that a percentage of all clinics would be incorporated into the system based on individual relations with the health zone doctor and zone financing. Health zones with these groups of facilities incorporated, identified through health service distribution information in DRC, have higher percentages of cases reported to the health zone. In the simulated model, we estimated that only 20% of cases visiting these types of facilities outside of the public system will be reported to the health zone.

We found for the country that the estimated rate could be 5.0 to 15.2 times greater (average 9.4) than what is seen at the national level. According to the estimates, the number of suspected cases occurring was 23,280 (range: 12,380 - 37,600) compared to the 2,460 notified at the national level. When looking at specific provinces of Kasai Oriental and Equateur, which
have the highest reported number of suspected MPX cases, and confirmed samples, we expect that there could be even higher rates of under-reporting. These provinces are less accessible and have overall less complete reporting compared to the whole country (in 2013, Equateur province did not submit 4 weekly reports), yet have the highest number of reported suspected MPX cases at the national level.

4.5 DISCUSSION

To our knowledge, this is the first model using this method created for DRC’s passive surveillance system. We have examined and quantified the possibility of missing cases at every level of the system in order to understand what the true burden of the disease could be. We identified as an input, that most of the cases are lost in the first level due to under-ascertainment of health services when sick people do not seek care. Sixty percent of the total cases may not seek any treatment, which is expected to be even higher in the least accessible areas, where health centers may be located very far from the villages and often have less supplies for supportive care and management of suspected MPX cases. Lastly, when looking at specific provinces, we observed the possibility of even higher under reporting.

A recent publication on reviewing methods for measuring under-reporting and under-ascertainment of diseases, indicate that the most accurate measures derived are when the models are disease, country, age, and sex specific.\textsuperscript{19} For this study using passive data in DRC for suspected MPX cases reported, we were unable to explore age and sex. Other methods to explore individual risk factors for not being reported include using hospital records, retrospective population based studies which include serologic testing in specific locations, and cross-sectional studies to estimate the incidence and prevalence of certain time periods compared to the passively reported data commonly available.\textsuperscript{18, 20, 27} Studies of these types typically identified
high under-reporting rates in the passively collected data. This would be a necessary next step for a more comprehensive understanding of this model.

The overall probability of a case being reported to the national level in the IDSR once the individual become ill was calculated. Due to unknown variables, including external factors not included in the model at each level, there was a significant amount of uncertainty in the overall estimate. The higher probabilities of being unreported earlier in the scenario tree have a larger downstream effect, but do not affect the conditional probabilities.²⁸

External factors may influence reporting decisions in specific geographic regions such as varying seasonal, cultural, and behavioral factors, however, good parameter estimates may be difficult to find, as data is limited. Additional factors would include active disease surveillance and community targeted education programs, which have occurred and are ongoing in a number of locations throughout the country.¹⁶,²⁹ These areas may have more sensitized health care workers, and thus be more likely to report suspected cases of monkeypox; however, they also tend to be in more inaccessible locations making the work more difficult than in urban settings.

The scenario tree was based on overall outcome of case detection within a single year. We did not account for delay in reporting throughout the year, which can vary by location – especially in more inaccessible areas were reports from multiple weeks may be sent at one time. While this should not significantly impact results, we will not be able to report on the incomplete reporting or if a report wasn’t sent at all for a specific week, due to some constraint, including forgetting to send, rain making roads inaccessible, or the communication network not functioning. Several health zones are considered silent for reporting, and thus never send reports, while others miss the majority of weeks, thus leading to even higher underreporting rates. As the system is passive, there are no sanctions for health zones not regularly reporting or reporting at
DRC’s current surveillance system (IDSР) has a number of barriers that limit its ability to function efficiently. The health care system has limited support from the government and is heavily reliant on support from external donors; in 2012, DRC was the 8th largest recipient of official humanitarian aid.\textsuperscript{4,30,31} The sub-standard road infrastructure throughout most of the county makes surveillance activities very difficult to consistently carry out.\textsuperscript{31} Due to these problems, disease surveillance in many areas is considered a low priority, especially for health care workers already overburdened with primary health care and general management activities.\textsuperscript{32}

Additional problems which are observed at the local level include: the inability to record cases when there is no paper or other basic supplies available, the inability to send reports when the person charged with surveillance is sick or away and they have not delegated the task to others. There is also a lack of training to discern between diseases with similar characteristics (e.g. monkeypox and chickenpox), lack of motivation for reporting, collecting samples, and lack of feedback when these activities do take place.\textsuperscript{31}

This method to examine the system as a whole could provide a platform for exploring other diseases, especially those in the passive system, which may have components that make reporting less complete. For example, polio eradication is in the final stages, and it is crucial that every case of AFP be reported. Thus, knowledge of gaps within the system and recommendations for how to reduce the gaps may be highly beneficial in a resource limited setting. Since there is a lack of specific information for MPX disease individually, we used estimates of general care seeking behaviors, especially at the most local level by using health care utilization surveys.
The results of this study underscore the need for increasing access to and utilization of health services at the local level, and better strategies for implicating community workers involved in disease detection to better report the cases that are missed when individuals fail to visit a health facility. Furthermore, additional work needs to be done in the health zone to better incorporate private clinics and informal health practitioners, who are seeing a large number of cases, but are not participating in the reporting system. The third target area is to make health care accessible even for those unable to pay for services. Some organizations have implemented programs which help pregnant women and those infected with HIV to cover the cost of care. However, in many of these areas where a cash society is replaced by a trading economy and people are unable to seek services at a formal facility, they may still be more likely to turn to traditional methods or do nothing. Additionally, with the aid of these models, ground-truthing and other methods for verifying the underreporting rates and adjusting the calculated ranges can be completed. Based on a more comprehensive understanding of the situation at the local level for MPX occurrence, resources can be better programmed to have optimal impact on disease detection, control, and prevention.
Figure 1. Typical reporting flow diagram for the surveillance system of the Ministry of Health, DRC
Table 1. Base and range inputs for model parameters for quantifying gaps in health system - using MPX reporting numbers

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Base (range)</th>
<th>Distribution</th>
<th>Data source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 1. Where does the person 1st seek treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. They do not seek treatment</td>
<td>60% (20% - 70%)</td>
<td>Triangle</td>
<td>DHS 2013</td>
</tr>
<tr>
<td>B. They visit a traditional healer (IHP)</td>
<td>1.6% (1% - 25%)</td>
<td>Log normal</td>
<td>DHS 2013</td>
</tr>
<tr>
<td>C. They visit a private clinics/non-governmental organization (NGO)</td>
<td>9.9% (2.5%-25%)</td>
<td>Triangle</td>
<td>DHS 2013</td>
</tr>
<tr>
<td>D. They visit a health post (HP)</td>
<td>4.7% (2%-25%)</td>
<td>Log normal</td>
<td>DHS 2013</td>
</tr>
<tr>
<td>E. They visit a health center (HC)</td>
<td>16.4% (10%-25%)</td>
<td>Triangle</td>
<td>DHS 2013</td>
</tr>
<tr>
<td>F. They visit at hospital general (HGR)</td>
<td>7.4% (5%-70%)</td>
<td>Triangle</td>
<td>DHS 2013</td>
</tr>
<tr>
<td><strong>Level 2. What happens once they seek treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Do not seek, reported word of mouth (WoM) to Health Zone (HZ)</td>
<td>5% (2.5%-10%)</td>
<td>Triangle</td>
<td>HZ data</td>
</tr>
<tr>
<td>B. Visit IHP, integrated into system, reported to HZ</td>
<td>20% (10%-30%)</td>
<td>Triangle</td>
<td>HZ data, 4th Direction</td>
</tr>
<tr>
<td>C. Visit private clinic, integrated into system, reported to HZ</td>
<td>20% (10%-30%)</td>
<td>Triangle</td>
<td>Based on MSF reporting data</td>
</tr>
<tr>
<td>D. Visit HP, able to pay for services</td>
<td>50% (25%-75%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>D. Visit HP, if pay and reported to HC (Di)</td>
<td>60% (20%-100%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>D. Visit HP, if pay, not reported to HC, but referred (Di)</td>
<td>20% (10-30%)</td>
<td>Triangle</td>
<td></td>
</tr>
<tr>
<td>D. Visit HP, don't pay and reported to HC (Di)</td>
<td>10% (5%-20%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>D. Visit HP, don’t pay, not reported to HC, but referred (Di)</td>
<td>45% (30%-60%)</td>
<td>Triangle</td>
<td></td>
</tr>
<tr>
<td>Di. Visit HP, paid, not reported at HP, visit another health facility (HF), reported to HZ</td>
<td>40% (30%-50%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>Di. Visit HP, paid, not reported at HP, visited another HF, reported to HZ WoM</td>
<td>2.5% (1%-5%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>Di. Visit HP, not paid, not reported, visited another HF, reported to HZ WoM</td>
<td>5% (2.5%-10%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>Di. Visit HP, not paid, not reported, visited another HF, reported to HZ</td>
<td>1% (0%-2%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>Diii. Of those reported in HP to HC, those being reported to HZ</td>
<td>50 (25% - 75%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>E. Visit HC, able to pay for services</td>
<td>50% (25%-75%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>E. Visit HC, pay and reported to HZ</td>
<td>70% (50%-100%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>E. Visit HC, if pay, not reported to HZ, but referred (Ei.)</td>
<td>20% (10%-30%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>E. Visit HC, don't pay and reported to HZ</td>
<td>15% (5%-25%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>E. Visit HC, don’t pay, not reported to HZ, but referred (Ei.)</td>
<td>25% (20%-30%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>Ei. Visit HC, paid, not reported, visit another HF, reported to HZ</td>
<td>15% (5%-30%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>Ei. Visit HC, paid, not reported, visited another HF, reported to HZ WoM</td>
<td>2.5% (1%-5%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>Eii. Visit HC, not paid, not reported, visited another HF, reported to HZ</td>
<td>5% (3%-10%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>Eii. Visit HC, not paid, not reported, visited another HF, reported to HZ WoM</td>
<td>1% (0%-2%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>F. Visit HGR, able to pay for services</td>
<td>60% (35%-85%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>F. Visit HGR, pay and reported to HZ</td>
<td>70% (50%-100%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>F. Visit HGR, if pay, not reported to HZ, but referred (Fi)</td>
<td>20% (10%, 30%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>F. Visit HGR, don't pay and reported to HZ</td>
<td>15% (5%-30%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>Parameters</td>
<td>Base (range)</td>
<td>Distribution</td>
<td>Data source</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>-----------------------</td>
<td>--------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>F. Visit HGR, don’t pay, not reported to HZ, but referred (Fii)</td>
<td>20% (15%-25%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>Fi. Visit HGR, paid, not reported, visit another HF, reported to HZ</td>
<td>15% (5%-30%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>Fi. Visit HGR, paid, not reported, visited another HF, reported to HZ WoM</td>
<td>5% (2.5%-10%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>Fii. Visit HGR, not paid, not reported, visit another HF, reported to HZ</td>
<td>5% (2.5%-10%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
<tr>
<td>Fii. Visit HGR, not paid, not reported, visited another HF, reported to HZ</td>
<td>1% (0%-2%)</td>
<td>Triangle</td>
<td>Selection of HZ</td>
</tr>
</tbody>
</table>

**Level 3. What happens once the case arrives at HZ**

The case is reported to the District | 75% (30%-100%) - | Triangle | 4th Bureau (Province) |

**Level 4. What happens once the case arrive at District**

The case is reported to the Province | 85% (70%-100%) | Triangle | 4th Bureau (Province) |

**Level 5. What happens once the case arrives at Province**

The case is reported to the National level (4th Dir.) | 90% (80%-100%) | Triangle | 4th Direction |
Figure 2. Model tree for disease reporting flow for IDSR system. We identified 5 levels in the reporting system. Green boxes indicate reporting to health zone, red boxes indicated not reported, orange boxes indicate the cases could or could not pay for services and referrals to other facilities. All green boxes have dark green arrows leading to reporting to the health zone. Twenty-one paths were identified for a case to be reported to the health zone. We have indicated the number of cases that would be reported onwards or would not be reported in each box. Once cases make it to the health zone –there is direct vertical reporting.
4.6 REFERENCES


26. de Vos CJ, Saatkamp HW, Nielen M and Huirne RB. Scenario tree modeling to analyze the probability of classical swine fever virus introduction into member states of


Chapter 5: Concluding Remarks

5.1 Outcomes and Implications

This dissertation provided information on a number of factors related to the surveillance system and how cases are identified and reported, including changes in disease occurrence and factors related to reporting. Additionally, it provides a platform for expanding these methods to other reportable diseases that may have components that make reporting more or less complete. For example, polio eradication is in the final stages, and the importance of recording every case of AFP is crucial. Additional funding for disease eradication activities may improve the surveillance system temporarily, but will not be sustainable in the long-term after declaring polio eradicated. Thus, other gaps within the system and recommendations for how to reduce the gaps may be highly beneficial in a resource limited setting.

Based on the studies presented here, there are implications for future studies which use multiple sources of data available within the same surveillance system. The surveillance data is collected regularly, however, due to time constraints and limited resources, these extensive analyses are rarely accomplished. Results of these types of studies should be used for identifying gaps and providing recommendations to the national health system that can be disseminated throughout the country in a clean and understandable format for improving the system.

5.2 Limitations

Overall, there were a number of limitations encountered in each paper, much of the data used is population based. Thus they are ecological studies and cannot be generalized to the individual level, in order to provide factors which could impact individual disease acquisition. A major limitation of using the aggregated ecological data available, will be the limited ability to make causal inferences due to ecological bias, lack of ability to control for confounders,
misclassification within the groups, and the potential for temporal ambiguity.\textsuperscript{1} The case
definition for MPX has a low specificity, thus suspected cases will represent true cases and other
rash-illness like diseases, laboratory confirmation would be the only way to differentiate between
these diseases. However, the studies can provide insight for the geographic regions described in
broader terms for disease risk and overall changes in the system and disease occurrence.

Data from the surveillance system may represent data with significant time delays that
will not be realized since each data year is formatted just by week and health zone, and will not
include additional information if there were multiple reports or delayed reports. It may also
represent incomplete and incorrectly coded data. There are limited checks in the data entry
system, and data can be digitalized at the health center, health zone, district, province, or national
level as there is not a standardized system for receiving data. This non-standardization for data
entry will incudes errors such as transposing the numbers for case counts and consistently
spelling health zone names. There is not a clear role in the system for correcting these errors at
the national level, which is where the data is compiled and distributed.

Additionally, due to the structure of the surveillance system at the local level, there is
often some discrepancy as to when reporting at each level should take place, thus each location
may have a slightly different definition of the epidemiologic week – as to when it begins and
ends, and when reporting does not happen on a regular basis, reports could be combined to
include multiple weeks of data, making the appearance of clusters, when it may represent
multiple isolated cases. Additional problems that arise with reporting at the most local level
include:

- Not having paper to record cases, or other needed supplies;
- If only one person is available for sending the report, and they are sick or away, no one else is delegated with the task
- Seasonal issues making some areas completely inaccessible
- Lack of available transportation or means of communication, and if available elsewhere nearby, may not be sustainable due to cost. They can rent bikes, and pay to use high frequency radios for reporting,
- Lack of trained personnel at this level, and many reportable and non-reportable disease have similar clinical characteristics, but need to be laboratory diagnosed for confirmation,
- Lack of motivation, results from samples and data sent is rarely received at the aire de santé level. Monthly meetings at each health zone are supposed to take place where the nurses from all health centers meet and receive results.

Finally, there was a lack of a consistent source of population data to calculate incidence. While the standard is the 1984 census, the EPI population data has provincial, health zone and health areas population estimates, and was thus used for this analysis.\textsuperscript{2} \textsuperscript{3} \textsuperscript{5} These estimates may lead to a further underestimate of MPX incidence, as the population is based on ensuring that 100% of children will be vaccinated against a number of vaccine preventable diseases which have mass campaigns including polio and measles, thus they include an overestimate for vaccine loss and population movement.

5.3 Conclusion

We observed an increasing trend for MPX reporting throughout DRC. Our evidence is based on factors including change in geographical regions reporting, such as once areas which have been targeted for active case searching, and in comparison to other reportable diseases. From
2008-2013, the “stable reporting phase”, MPX was the only disease showing a significant increase in incidence compared to other reportable diseases during the same time period. When exploring other trends, apparent increases in reported annual MPX cases, and trends in weekly reporting, may be artifacts of improvements in disease surveillance as there were no significant trends.

Further, our analyses indicate that while the system should be integrated based on published manuals at the national level which includes disease detection and confirmation for reportable diseases, that each component may only work within the specific diseases. Additionally, we found that these single disease systems such as the one implemented for Polio eradication efforts which was implemented as a parallel system, may be diverting attention from other components of the system causing disruption of passive reporting system. Further exploration is needed to look at other components of the eradication strategy that should impact the system, including the reporting in the system during the mass vaccination campaigns, which include a mass deployment of money for training and services for the whole population.

Each missed case of a person with a suspected disease reduces the true incidence of that disease, leading to underestimates of disease burden. We estimate that only about 10% of the actual suspected cases of MPX are making it to the national level. This could significantly limit the ability to detect emerging public health problems. Further research is necessary to learn how the system could be better understood for more complete integration and improved capacity of the health service system in resource limited settings, such as the DRC.
5.4 References


