Early Transmission Dynamics and Forecasts of the Yellow Fever Outbreak in Angola, 2015-16

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ABSTRACT

EARLY TRANSMISSION DYNAMICS AND FORECASTS OF THE YELLOW FEVER OUTBREAK IN ANGOLA, 2015-16

By

THINH TRAN

August 2017

Introduction. Yellow fever is an infectious disease endemic in Africa and South America, and it is a vaccine-preventable disease. The outbreak of yellow fever in Angola, 2015-2016 posed a risk to the global health. In the early phase of the outbreak, mathematical modeling can be a useful tool to predicting how the outbreak might spread and what factors affect the course of the outbreak so that health policy makers and health organizations can react effectively. In this project, two mathematical models, generalized-growth model and generalized Richard model, were applied retrospectively to predict the case rises in the early phase and to forecast the short-term trend of the outbreak.

Data and method. The data was extracted from the WHO weekly outbreak situation reports, for the period from Dec 04, 2015 until Sep 29, 2016. The analysis was focused on the data of 3 provinces including the capital Luanda, Huambo, and Benguela. The generalized-growth model (GGM) was applied for fitting the model into the early phase of the outbreak. GGM and the generalized Richards model (GRM) was applied for short-term forecasting the trend of the outbreak’s peak. Simulations to project the uncertainty of the epidemic trend was conducted with MATLAB R2017a (The Mathworks, Inc.).

Results. Fitting GGM to the data of 3 provinces shows the patterns of case rises in the early phase widely vary from above-constant to sub-exponentially growth. Short-term forecasting with GGM becomes less capable after the epidemic reach its peak. GRM is more advantageous for the forecasting period containing the epidemic peak. However, it can be less effective when the outbreak is partly controlled or there are some interventions on the epidemic transmission.

Conclusion. GGM and GRM can be the useful tool to characterize the dynamic growth of an infectious outbreak in the early phase and produce a short-term forecast of dynamic patterns that shape the guidance and action for the outbreak control and interventions.

Key words: Angola, Yellow Fever, generalized-growth model, GGM, generalized Richards model, GRM, phenomenological modeling.
EARLY TRANSMISSION DYNAMICS AND FORECASTS OF THE YELLOW FEVER OUTBREAK IN ANGOLA, 2015-16

by

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THINH THI VAN TRAN
Signature of Author
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INTRODUCTION AND BACKGROUND

Yellow fever. Yellow fever is a mosquito-borne zoonotic disease, transmitted through the bite of the infected mosquitoes, *Aedes* or *Haemagogus* species, as the vector. The disease is endemic and intermittently epidemic in many countries in Africa and Central and South Americas. 2015-16 witnesses the worst yellow fever outbreak in Angola in the last three decades, resulted in 4,347 notified cases and more than 377 deaths, reported until the end of September 2016 (1). The disease was spread to the Democratic Republic of the Congo, and imported cases from Angola were reported in Kenya, China, and Brazil. In 2017 the disease has been emerging in South Africa, and some countries have cases notified, including Brazil, Bolivia, Peru, Columbia and Ecuador.

The pathogen. Yellow fever virus (YFV) is an *Arborvirus* that belongs to the family *Flaviviridae*, and related to dengue virus, Zika virus, West Nile virus, and tick-born encephalitis virus. The spread of YFV occurs through three transmission cycles: in the jungle (sylvatic) cycle, the infection is transmitted among non-human primates and to human by different mosquitoes, and in the intermediate (savannah) and urban cycle, yellow fever is transmitted from an infected human to a susceptible one by *Aedes Aegypti* bites. Although savannah transmission is more dominant in Africa, it is expected to shift to urban yellow fever if the environment becomes more facilitating for mosquitoes flourishment and the population immunity is vulnerable (2). In 2016 Angola outbreak, the cases were found mainly in cities, suggesting that the transmission occur through urban cycle. The transmission dynamic of YFV is associated with climatic conditions. Infection occurrence is most common during the months of heavy rainfall and high temperature. While high temperature is supposed to facilitate the survival and reproduction rate and shorten extrinsic incubation period in mosquitoes, increased precipitation might expand the existing larval habitats and create new breeding grounds.

Clinical manifestation. In human, most of cases are asymptomatic, however if the symptoms occur after the 3-6-day incubation period, the progress is typically through 3 phases. The first phase (acute phase) can last for 3-4 days, characterized by non-specific, flu-like generalized symptoms such as fever and chills, loss of appetite, headache, muscle aches, nausea, vomiting. The second phase (remission) lasts for 48 hours when the symptoms relieve, and most of patients recover. After the second phase, approximately 10-15% patients develop to the third phase (toxic phase) (3). In the toxic phase, the acute hemorrhagic syndrome appears, with manifestations of high fever, internal bleeding, damage of liver, kidney, and circulation system, shock, and multiple organ failure. Death is estimated 25-50% of those progressing to this phase (3)(4). In the 2015-16 outbreak, the death rate among confirmed cases is high, nearly 14% (121/884) (1).

Epidemiology. Yellow fever is one of major public health issues in Africa, and most of the cases in the world have been reported in Africa. In Africa, while the endemic area spreads from the South edge of Sahara Desert in the North to Angola in the south, there have been more cases reported in the West countries. Most of the outbreaks and the large outbreaks of YF also occurred in the West countries. Over 70 years before the outbreak in Angola (the South Africa) in 2015, there were 2 major peaks of YF reported in Africa. The early peak was in 1960-1962, mainly due to the outbreak in Ethiopia (the East Africa), and the later in 1985-1995, mainly due to the outbreak in Nigeria (the West Africa) (5).
YF is one of diseases required to report to WHO. However, the actual number of cases is suspected to be 10-500 times higher than the reported number. The underestimated burden of YF is due to the limitation of surveillance and healthcare system of the affected countries (6). In addition, there is a challenge in differentiating YF from other hemorrhagic fevers prevalent in the endemic regions. A previous WHO estimation based on data source from 1990s reported that the annual number of cases and death of YF in Africa were 200,000 and 30,000 respectively (3)(6)(7). Recently, a modeling study using data of yellow fever cases reported in Africa for 25 years, 1987-2011, provided an estimation with a high level of uncertainty that there were annually 130,000 cases including 78,000 deaths (8). In Angola, before the 2015-16 outbreak, there were two small outbreaks over one hundred years. One was in 1971 with 65 cases and 41 deaths, and one was in 1988 with 37 cases and 14 deaths. Then there was no any cases reported in Angola over 27 recent years (2)(9).

Vaccination and population immunity. Vaccination is the single key measure for yellow fever prevention. The vaccination for yellow fever is 17D, an attenuated live vaccine that has remained a safe and highly efficacious vaccine over 60 years. A single dose of vaccination provides immune protection after 7-10 days in 95% of people vaccinated, and in 99% after 1 month (6). The protection lasts for at least 10 years. Some studies showed that it can provide protection for many years or even for a whole life (3)(10). In resource-limited settings, a single dose is acknowledged as a long-life protection. Due to the shortage of vaccination stockpile in the Angola 2015-16 outbreak, a smaller dose or fractional dose of vaccine (a fifth of standard dose) was applied as a short-term measure in the emergency setting. A single fractional dose of vaccination can provide the protection for at least 12 months (11).

Preventive vaccination campaigns can help to reduce cases and death up to 27% in areas covered by these campaigns (8). To prevent outbreaks, vaccination coverage should reach 60%-80% of the target population (7). However, there were few countries in Africa reporting to reach this coverage. By the end of 2006, it is estimated that only a half of high-risk countries in Africa achieved vaccination coverage of 80%, while the situation was better in South America, the coverage rate was obtained at more than 80% in 10 endemic countries (3).

Foreseen global threat after increases of YF reports in West Africa and South America led to activities of The Yellow Fever Initiative launched in 2006. This aimed to reduce to global risk of yellow fever outbreaks through ensuring the global vaccine supply and increasing the population immunity in high-risk areas (7). According to that, routine childhood vaccination and preventive vaccination campaigns were implemented in high-risk countries defined by the Yellow Fever Initiative, mostly in West Africa and South America. After implementing YF Initiative, the routine vaccination coverage of the targeted high-risk population significantly increased, from 16% (2000) to 43% (2008) in Africa; and from 64% to 91% in South America (7). Before the 2015-16 outbreak, Angola and DRC were not classified as in high-risk areas and preventive vaccine campaign was not implemented through The YF Initiative. The estimated vaccine coverage in the country increased over the last decade from 29% (2000) to 64% (2013) but still not reach the level to prevent an outbreak (9). After the outbreak, both Angola and DRC were benefited from
massive vaccination campaign. However, the preventive campaign is still in high demand in some other high-risk countries in Africa and South America.

**The 2015-16 yellow fever outbreak in Angola.** The outbreak of yellow fever in Angola started in the first week of Dec 2015 among Eritrean and Congolese citizens in Viana municipality, a suburb by 20 km to the East of the capital Luanda (12). The place was an area with a high density of Aedes Aegypti, the primary vector for yellow fever transmission. The index case was notified in early of Dec 2015, and confirmed later outside Angola with the PCR test at the Zoonosis and Emerging Disease Laboratory of the National Institute for Communicable Diseases in Johannesburg, South Africa and at the Pasteur Institute in Dakar, Senegal.

By January 2016, four weeks after detecting the index case, WHO was notified of the potential outbreak of yellow fever in Angola. By this time, there were 23 cases confirmed, and the rapid increase of infected cases was anticipated. There were quick responses from the public health authorities in Angola and WHO to contain the outbreak, including outbreak response coordination, clinical case management, enhanced laboratory testing and surveillance, social mobilization and vector control measurements, and financial support. The outbreak of YF in Angola also spread to the neighbor country of DR Congo after a sport event of football between two countries, and YF imported cases were also notified in China and Kenya. By April 2016, four months after starting of the outbreak, WHO declared the YF outbreak in Angola as a global threat. The capital Luanda was the province with the highest confirmed cases. The following provinces were Huambo and Benguela where the first notified cases there occurred in 6-7 weeks after the index case in Luanda.

In Luanda, by early of February, 8 weeks after the index case, the massive vaccination campaign was initially implemented. By early of March, 4 weeks later, the vaccination coverage reached nearly 80% of Luanda target, and the trend of incidence cases in Luanda dramatically decreased. By this time, 9 out of 15 provinces in Angola reported confirmed cases, and the yellow fever still spread to other provinces. In Huambo and Benguela, by the middle of April, EW19 of the outbreak, the massive vaccination was implemented.

After May, Luanda completed its massive vaccination. The vaccination in Huambo and Benguela also reached 80% of their target population, and there were just a few new cases reported in those provinces after then. The estimated total population in Angola in 2015 was approximately 28 million people (13). By the end of July, the population vaccinated in Angola was about more than 13 million people, 86% of target population (14). By the end of September 2016, 16 million people were vaccinated. By early October 2016, two more million people were vaccinated to reach the vaccine coverage of 18 million people.

According to WHO final situation reports, during ten months from Dec 2015 to Oct 2016 in Angola, there were more than 4300 suspected cases, 880 confirmed cases, and 370 deaths. Suspected cases were found in all 18 provinces, and confirmed cases found in 16 out 18 provinces of Angola.

<table>
<thead>
<tr>
<th>Calendar timeline</th>
<th>Epidemic week (EW0-EW43)</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 05, 2015</td>
<td>EW0</td>
<td>Index case notified in the capital Luanda, Angola</td>
</tr>
</tbody>
</table>
Study rationale. The control of yellow fever outbreak required the collaboration from different stakeholders including the local health authorities, emergency response from international organizations, vaccination providers, environment and vector control agencies, health education, health policy makers, etc. In the early period of the outbreak, mathematical modeling can be a helpful method in predicting of how the outbreak might spread and what factors affecting the course of the outbreak so that health policymakers and relevant organizations can provide appropriate responses. In this project, two mathematical models, generalized-growth model and generalized Richard model, were applied retrospectively to predict the spread of the outbreak in the early phase and to forecast the short-term trend of the outbreak after the peak.

DATA AND METHODS
The epidemiological data was extracted from the WHO outbreak situation reports available on the open-accessed WHO website, for the period from Dec 04, 2015 until Oct 28, 2016 (1). The reports include confirmed and probable cases weekly in each province, target population and dose of vaccination administered weekly in each province. The analysis was focused on data of 3 provinces, the capital Luanda, Huambo, and Benguela that are the three highest-case provinces in Angola. We assumed that the data from those provinces probably be presentative for the data of the whole Angola (Graph 1). The data of vaccination coverage were also considered. The number of target population for Huambo and Benguela slightly altered during the massive vaccination campaign. To have another comparison of the vaccination situation, the percentage of vaccinated population was estimated base on the number of vaccine doses administered from the situation reports and the population of each province collected from the record of Angola population in 2016 (15). In the context of the limited-resource setting of the Angola, the cases include probable and confirmed cases to avoid underestimating the extent of the outbreak.

The exponential growth model can be applied to predict the pattern of case rise in the early period of an epidemic. This model basically assumes that the cumulative number of cases (probable and confirmed) has an exponential growth in the early phase. The cumulative number of cases is described by the exponential equation: \( C(t) = C(0) e^{rt} \), where \( C(t) \) is the cumulative number of cases at the time \( t \), \( C(0) \) is the
number at the beginning of the outbreak, \( r \) is the growth rate of cases per unit of time (day). This equation is solved by the differential equation: \( C'(t) = dC/dt = r*C(t) \) for the exponential growth model.

When this assumption is not fully satisfied, the early pattern of case rise becomes sub-exponential growth rather than truly exponential growth. The generalized-growth model (GGM) is considered in such settings. This model is given by the differential equation: \( dC(t)/dt = C'(t)=r*C(t)^p \), where \( p \) is the parameter of “deceleration of growth” with the values ranging between 0 and 1. When the incidence of cases increases exponentially, the assumption is fully satisfied, \( p \) reaches to 1, and the pattern shows an exponential growth. When the incidence of cases keeps constant, \( p \) reaches to 0, and the pattern shows a horizontal line. When \( p \) is in the middle of the range (0,1), the pattern shows a sub-exponential growth. This model GGM was demonstrated useful in forecasting infectious outbreaks, including Ebola and food and mouth disease (16).

The generalized Richard model (GRM) is given by the differential equation \( C'(t)=r*C^p(1-(C/K))^\alpha \), where \( p \) is the deceleration of growth, ranging from 0 to 1, \( r \) is the intrinsic growth rate, \( K \) is the epidemic size, and \( \alpha \) is the parameter modulating the timing of the pandemic peak. This model is applied to fit to an S-shaped growth curve that allows the early curve to change in a wide range of sub-exponential growth, with \( 0<p<1 \). This model was also used in forecasting the Ebola outbreak (17).

In this project, GGM was used to fit into the data of early few weeks of each province, and GRM was applied in forecasting a short-term period of 4 weeks. The parameter \( r \) and \( p \) were estimated using the nonlinear least-square fitting method by fitting the observed cumulative number of cases into the curve modeled by \( C'(t) \) of GGM in the early weeks of the outbreak. The numbers of confirmed and probable YF cases available in weeks were switched into the numbers of cases in days. The initial numbers of cases based on the initial observed numbers of cases for each province (2 in Luanda, 1 in Huambo and Benguela). The 95% confidence intervals of estimated parameters were calculated based on simulating 200 realizations of the best-fit curve of the model.

The period of early phases of 3 provinces was subjectively considered as the period before the massive campaign, the key measure of control for the outbreak, implemented. In Luanda, the early phase was the period from the epidemic week (EW) 0 (the week of index case found) to the epidemic week 9. The period of early phases in Huambo and Benguela were the EW 6 – 19 and EW 7 – 19, the early 12 and 13 weeks from the first local cases found in Huambo and Benguela until the vaccination campaign started in each province, respectively.

RESULTS

Applying GGM fitting the model in early phase of the outbreak

When applying GGM fitting in early phase for the data for each province and 3 provinces combined, the growth of case rises varies widely from nearly constant to exponentially (Figure 1 and 2). For Luanda, the visualization of growth shows more exponentially fitted in 9 weeks than in 7 weeks. The \( p \) values shift towards 1, and the 95% confidence intervals of \( p \) values narrow down and include 1. For 7 weeks, \( p = 0.912 \ (0.590, 1.000) \) and for 9 weeks, \( p = 0.965 \ (0.839, 1.000) \) (Table 2). For Huambo, the case rise shows
a linear growth in 7 weeks and 9 weeks with p values around 0.5, p = 0.451 (0.157, 0.782), and p = 0.402 (0.166, 0.650), respectively. In Benguela, the growth shows a slightly linear rise in early 7 weeks. However, the rise moves close to the constant growth in the data of 9 weeks, p values decrease toward 0 and with a large uncertainty, p = 0.270 (0.000, 1.000).

Table 2. Estimated parameters for r and p in GGM:

<table>
<thead>
<tr>
<th></th>
<th>For early 7 weeks</th>
<th></th>
<th>For early 9 weeks</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r (95%CI)</td>
<td>p (95%CI)</td>
<td>r (95%CI)</td>
<td>p (95%CI)</td>
</tr>
<tr>
<td>Luanda</td>
<td>0.089 (0.062, 0.204)</td>
<td>0.912 (0.590, 1.000)</td>
<td>0.082 (0.070, 0.121)</td>
<td>0.965 (0.839, 1.000)</td>
</tr>
<tr>
<td>Huambo</td>
<td>0.457 (0.154, 0.940)</td>
<td>0.451 (0.157, 0.782)</td>
<td>0.500 (0.200, 1.162)</td>
<td>0.402 (0.166, 0.650)</td>
</tr>
<tr>
<td>Benguela</td>
<td>0.239 (0.063, 0.552)</td>
<td>0.398 (0.000, 1.000)</td>
<td>0.274 (0.051, 0.571)</td>
<td>0.270 (0.000, 1.000)</td>
</tr>
<tr>
<td>3 Provinces</td>
<td>0.092 (0.064, 0.187)</td>
<td>0.917 (0.638, 1.000)</td>
<td>0.084 (0.073, 0.122)</td>
<td>0.970 (0.850, 1.000)</td>
</tr>
</tbody>
</table>

Applying GRM forecasting the short-term period of the outbreak

For Luanda, the trajectory area can capture fairly the trend of the observed data. When the epidemic peak falls in the forecasting period, there is a shift of the observed trend from the upper limit of the uncertainty estimation area before the peak to the lower limit of the uncertainty estimation area after the peak. (Figure 5). For Huambo, GRM captures more faithfully the trend of the pandemic. For Benguela, GRM predicts well in early weeks. However, in later weeks (week 9 and 10), GRM fails to capture the second peak of the case rise when the case rise moves up abruptly.

DISCUSSION

Luanda was the place where the outbreak started before spreading to other provinces. The number of cases in Luanda (confirmed and probable) constitutes a significant portion of the total cases in Angola. Therefore, the trend of case rise of Luanda closely describes the trend of case rise of the combined three provinces and of the whole Angola (Graph 1). For Luanda data and 3 provinces data combined, applying the GGM and GRM, to fit the observed data into the model and forecasting short-term period, it exhibited analogous trends and forecasting trajectories.

The GGM can be considered as a useful method to describe the case rise in the early phase of infectious outbreaks (16). In this project, the results of fitting observed data of each province and 3 provinces combined to the GGM again demonstrated this capacity of the model. The model can fit into the case rises varying from above-constant growth to closely exponential growth. In Luanda, the growth pattern of the first 9 weeks (EW0-EW9) is very close to exponential growth, p=0.965 (0.839, 1.000). This phenomenon is consistent with a high reproductive number of yellow fever. The basic reproductive number of the disease was estimated to vary from 1.7 to 3.6 (18), and in a recent study also using the data of this outbreak, the reproductive number was estimated up to 4.8 (4.0, 5.6) (19). The high case rise in Luanda was also because the outbreak occurred initially there when the effective measures to control the disease were not fully established in this early period. Massive vaccination campaign started in Luanda in EW9, and 2 weeks later, the epidemiological curve of incidences in Luanda reached its plateau in EW10-11 (Graph 2).

However, GGM can be more useful to project the rise trend in the primary outbreak location rather than in secondary outbreak location. In Huambo and Benguela, the trends in early phase were not typical or
closely exponential growth. The epidemics in those sites occurred in EW6-7, when emergency responses might already have some effects on containing the transmission, particularly the vaccination coverage in Luanda attained 80% in just few weeks after being implemented. It is consistent for the data of 3 provinces that the incidence curves run down when the curves of vaccination coverage go up (Graph 2,3,4).

In Benguela, the early pattern of case rise shows an above-constant growth, with a wide range of uncertainty estimation containing the 0 and 1 value of p, $p=0.398 (0.000, 1.000)$, for early 7 weeks, and $p=0.270 (0.000, 1.000)$ for early 9 weeks. This conforms to that the epidemiologic curve of incidences in Benguela fluctuate in the early weeks (EW7-EW17) and increase dramatically later by (EW18-21). When applying GGM for the longer epidemic period covering the epidemic peak of Benguela, the trajectory pattern changes to sub-exponential growth with a narrower uncertainty estimation of p value, $p = 0.871 (0.634, 1.000)$ (Figure 3).

GGM can be helpful in forecasting in the very early phase of the epidemic. However, after the epidemic reaches to its peak, GGM becomes less capable to capture the decreasing patterns into its trajectories (Figure 4). GRM showed to be more advantageous than GGM in forecasting the short-term periods including the peak of epidemic. However, in case of the fluctuating early phase of Benguela, GRM misses the real peak of the pandemic (Figure 5). It should be cautious to apply GRM to predict the case rise when the outbreak is partly controlled or in secondary pandemic sites.

The challenge is how those mathematical models can work as a useful tool in practice, particularly from the beginning of outbreaks to support the control of infectious outbreaks. In this project, with those mathematical models applied retrospectively and the main intervention of the outbreak already known, the uncertainty of the model can be easily assessed. In term of practical utility, a large uncertainty of trends of case rise might be an disadvantage when applying the method for emergency responses.

CONCLUSIONS

The case rise of yellow fever in Angola in the first early weeks was characterized by a sub-exponential growth, ranging from the above-constant growth to the close-to-exponential growth. The case rise in the primary pandemic site before the outbreak was partially controlled is closely exponential growth. The intervention of implementing vaccination has significant influence on the trend of case rise.

GGM is the useful tools to describe the dynamic growth of an infectious outbreak in the early phase, and GRM is helpful to produce a short-term forecast of pandemic trend. It should be careful when applying GRM in case that the epidemic is influenced by some intervention effects or has a fluctuating early phase, GRM can fail to capture the real peak of the epidemic.

It is vital to bringing mathematical modeling into practice during infectious dynamics that cases should be early notified, and the data should be more accessible to modeling epidemiologists. In settings with more available data and advanced data managing system, those phenomenological models can be integrated into strategies of emergency responses to predict the outbreak patterns that provide prompt guidance and shape actions for the outbreak control.
Graphs and Figures

Epidemiological Curve of Incidences (Confirmed and Probable) and vaccination in 3 provinces: Luanda, Huambo and Benguela

Graph 1. Weekly Reported Cases in Angola and 3 provinces

Graph 2: Luanda Vaccination (the vaccination started from EW9, however the data of vaccination coverage percentage available from EW16)
Graph 3: Huambo Vaccination

![Huambo Vaccination Graph]

Graph 4: Benguela Vaccination

![Benguela Vaccination Graph]
Graph 5: Confirmed and Probable cases of 3 provinces and some key events

- Starting vaccination in Luanda, EW19
- Vaccination coverage achieved 80% target population in Luanda, EW15
- Starting vaccination in Huambo and Benguela, and Vaccination coverage achieved 90% in Luanda, EW19
- Vaccination coverage reached 80% of target population in Huambo and Benguela, EW25

Data extracted from the WHO situation report of calendar week 39, Sep 26, 2016
Figure 1. Fitted GGM in early phase of 7 weeks for Luanda, Huambo, Benguela and 3 provinces combined.

Figure 2. Fitted GGM in early phase of 9 weeks for Luanda, Huambo, Benguela and 3 provinces combined.
Figure 3. Fitted GGM in early phase of 14 weeks for Benguela.
Figure 4. Forecasting with GGM
Figure 5. Forecasting with GRM
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