



OPINION ARTICLE

REVISED Yellow fever in the Americas: the growing concern about new epidemics [version 2; referees: 2 approved]

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Abstract

Yellow fever (YF) is a haemorrhagic viral disease with a high case fatality rate. It is considered a reemerging infectious disease of remarkable importance. During the last outbreaks in Brazil (2016-2017), many cases of YF emerged despite high YF vaccination coverage in some areas. However, there are many areas and populations worldwide where vaccination coverage has been low for years (e.g. Nigeria), which increases the risk of major epidemics in such areas, as would be the case in many of the American territories. Several factors, including the vast border and migratory status of Brazil, the widespread distribution of *Aedes* mosquitoes and the lack of efficient health policies and surveillance systems, favor this complex epidemiological scenario of reemergence. Therefore, mass vaccination of the population at risk, public health awareness and preparedness are urgently needed in this region. This opinion article describes the current global epidemiological situation of YF, focusing especially on the Americas, as well the risk and vulnerabilities in the region that would be of concern for major expansion to other countries apart from Brazil. Also, imported risk from endemic area outside of Americas (i.e. Africa) are of current concern.



This article is included in the **Zika & Arbovirus Outbreaks** channel.

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	Invited Referees	
	1	2
REVISED		
version 2	report	
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published 30 Mar 2017	report	report

- Jean-Paul J. Gonzalez**, Kansas State University USA, **Juergen Richt**, College of Veterinary Medicine, Kansas State University USA
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REVISED Amendments from Version 1

This new version considered the interesting comments of both reviewers regarding the situation of yellow fever in Brazil, and has been carefully revised and extended, attending all the suggestions. The data regarding the ongoing epidemiological, ecological and entomological scenario in Brazil has been updated, and its implications for expansion to other countries in the Americas.

See referee reports

Introduction

Yellow fever (YF) is a haemorrhagic viral, vector-borne disease with a high case fatality rate (CFR), spread by infected mosquitoes caused by the YF virus, an arbovirus belonging to the genus *Flavivirus*, family *Flaviviridae*. It has reappeared as a threat to global public health, evidenced by new epidemics in several countries in Africa and South America through autochthonous transmission, and in Asia with imported cases¹. In Asia, but also Europe and North America, potential spreads beyond the borders of the endemic countries is a matter of global concern. Currently, there are around 1 billion people, from 49 endemic countries, that are considered at risk^{1,2}. In this opinion article, we would like to express our concern regarding the expansion of YF in Latin America, beyond Brazil. In that country there is currently an epidemic situation, where, since the beginning of the outbreak in December 2016 up to 29 March 2017, there have been 1,987 cases of yellow fever reported (574 confirmed, 926 discarded, and 487 suspected under investigation). This included 282 deaths (187 confirmed, 24 discarded, and 71 under investigation) with a CFR of 33% among confirmed cases.

Recent outbreaks outside the Americas

Although relatively wide scale YF vaccination has been applied, a growing number of outbreaks have been documented in several African countries in the last decade¹⁻³. The most recent outbreak occurred in Angola, resulting in 7,344 suspected cases, 962 laboratory-confirmed cases and 137 deaths (with a CFR of 14.2%), and lasting from December 2015 to October 2016². In addition to spread of YF by autochthonous transmission, confirmed imported cases of YF were identified in China and Kenya¹⁻³. Other countries, such as Chad, Ghana and Guinea have also reported outbreaks or sporadic cases not linked to the outbreak in Angola¹⁻¹⁵. On Mar 12, 2016, the first imported case of YF was confirmed by China CDC. The patient was a 32 years old Chinese male who worked in Luanda and had fever and chills on Mar 8, 2016. He arrived to Beijing, where he was immediately hospitalized. Eleven imported cases of confirmed yellow fever occurred in China from March of 2016, prompting calls to strengthen surveillance systems at the border (<http://www.who.int/csr/don/6-april-2016-yellow-fever-china/en/>)¹⁶.

The risk of Yellow Fever in the Americas, with a focus on Brazil

Even though no new cases have been confirmed since the last year in Angola, Africa, the global threat continues, indeed now with its epicentre in Brazil, South America. An ongoing outbreak of YF has started in Brazil since December 1, 2016. Up

to February 22, 2017, a total of 1,336 cases of YF infection have been reported (292 laboratory confirmed, 920 suspected and 124 ruled out), resulting in 215 deaths (101 confirmed, 109 suspected, 5 ruled out) across six states of the country (Bahia, Espírito Santo, Minas Gerais, Rio Grande do Norte, São Paulo and Tocantins). The current CFR is 35% (from confirmed cases) and 12% (from suspected cases)³.

The geographical spread of the cases in Brazil has led to major concern, because cases are no longer being reported just in the jungle, but also in the most densely populated cities and states such as Minas Gerais and São Paulo. Fortunately, these regions have a long history of high YF vaccination coverage in young people (at least in urban areas), in contrast with the low vaccination rates in other major urban centres of Brazil⁴. Nevertheless, the lack of YF vaccination coverage was raised several times by the Brazilian provincial health authorities back in the early 2000s, but they were unable to reach the remote western zones of Minas Gerais.

Although the epidemiology and clinical manifestations of YF should be familiar to healthcare workers in endemic countries, where clinical manifestations can overlap with other acute viral haemorrhagic fevers and other etiologies of the febrile syndrome, a rapid spread of misinformation about this harmful disease in social media and a lack of online training for healthcare workers has been reported in the recent outbreak of 2016–2017 in the Americas^{5,6}. In addition to limited health resources, this highlights that early identification could be a challenge in Latin America, as has been observed in the past with Zika and chikungunya virus outbreaks in this region, particularly in countries such as Brazil and Colombia^{7,8}.

Given the current YF situation in Brazil, and the emergence of new cases in areas where YF has not occurred for several years, the Brazilian health policies have been oriented to continue efforts to detect, confirm, and adequately and timely treat cases of YF (<http://portalsaude.saude.gov.br/index.php/o-ministerio/principal/secretarias/svs/febre-amarela>). To this end, health care workers should be kept up to date and trained to detect and treat cases, especially in areas of known virus circulation. Furthermore, they should also take the necessary actions to keep travelers, heading to areas where YF vaccination is mandatory, informed and vaccinated.

Conclusions

There seems to be an almost imminent risk of YF outbreaks turning into a large epidemic⁹. Unvaccinated travelers heading to the affected states in Brazil are at risk of spreading the virus in to areas where YF risk factors (human susceptibility, prevalence of competent vector, and animal reservoirs) are present. The geographic area of human cases has expanded recently to Rio de Janeiro, São Paulo, and Pará states. Ecological factors and enzootics would promote the necessary spillover that would lead to an epidemic¹⁰⁻¹², and unfortunately, nothing can be done to halt the infection of non-human primates in the affected areas. Moreover, the vast border of Brazil, with 10 neighboring countries/territories (Uruguay, Argentina, Paraguay, Bolivia, Peru, Colombia, Venezuela, Guyana, Suriname and French Guiana), the lack of

efficient health policies and surveillance systems, and the distribution of *Aedes* vectors (as well the uncontrollable sylvatic vector species in the genus *Haemagogus* and *Sabethes*), raise the possibility of the widespread YF throughout the Americas, including the USA. The USA has suitable conditions for autochthonous cases in areas such as South Florida, where *Aedes albopictus* is present and has been linked to transmission of dengue virus (another flavivirus), chikungunya and possibly Zika. These entomological factors should strongly emphasize the risk of imported cases in temperate zones (i.e. Central and North Americas) during the boreal summer and *Aedes spp.* activity in Central and North America. It has been documented elsewhere for Dengue virus (New Mexico or Texas) and, even in the case of vectors for other diseases, such as *Anopheles*, the case of airport malaria in the US.

The risk of imported cases in temperate zones

Mass vaccination of the at-risk population¹³, and public health awareness and preparedness is urgently needed to control the current 2016–2017 outbreak in Brazil and prevent a possible epidemic related to this deadly disease. Nevertheless, these recent outbreaks and the lack of YF vaccine stock piling (WHO) means that YF vaccine availability needs to be strategized by the countries health authorities and international community. Also, the lifelong protection of the vaccine, its innocuity and the reduction by 1/10 of the immunity dose are new and of extremely high importance for global and public health.

More studies, as well as new innovative strategies for vector control (e.g. involving community participation), early prevention (e.g. sampling in risk areas to look for asymptomatic subjects),

warning and enhanced surveillance (using smart phones), are necessary in order to improve the scenario of this reemerging arboviral threat^{14,15}. Mosquito biosurveillance is an important issue to control the epidemic risk. *Haemagogus* and *Sabethes* are specific for South America and have been well studied; the risk and ability of *Aedes albopictus* expansion to transmit the virus in the Americas needs to be assessed, and an entomological priority set up when needed (i.e. public health priority in at-risk areas).

Finally, another matter of concern that is also important to mention is the trans-border risk. Ultimately traveler's to/from endemic areas need to be covered by a mandatory international certificate of vaccination to protect the borders (trans-border risk). The long-time mystery of the absence of YF in South East Asia up to 2016 is also an issue to keep in mind for the future - particularly in term of global risk, with new imported cases, for example those reported in China, now occurring.

Author contributions

YOM, AMPB and AJRM all participated in the writing and editing of the manuscript. All authors have agreed to the final content of this opinion article.

Competing interests

No competing interests were disclosed.

Grant information

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Current Referee Status:  

Version 2

Referee Report 26 April 2017

doi:[10.5256/f1000research.12397.r22240](https://doi.org/10.5256/f1000research.12397.r22240)

 **Jean-Paul J. Gonzalez¹, Juergen Richt²**

¹ Center of Excellence for Emerging and Zoonotic Animal Diseases (CEEZAD), College of Veterinary Medicine, Kansas State University, Manhattan, KS, USA

² Center of Excellence for Emerging and Zoonotic Animal Diseases (CEEZAD), College of Veterinary Medicine, Kansas State University, Manhattan, KS, USA

I agree with the version 2 of the manuscript and I approved it for publication.

Competing Interests: No competing interests were disclosed.

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Referee Report 18 April 2017

doi:[10.5256/f1000research.12169.r21389](https://doi.org/10.5256/f1000research.12169.r21389)

 **Paola Barato^{1,2}**

¹ Veterinary Pathobiology Group, Laboratory of Veterinary Pathology, Institute of Biotechnology, National University of Colombia, Bogotá, Colombia

² CEO and Scientific Director, CORPAVET, Bogotá, Colombia

In general, it is an interesting and well written opinion article. Some comments:

TITLE: Okay.

ABSTRACT: Okay.

INTRODUCTION:

1. I consider it to be desirable to include in the introduction the name of the virus (species) which causes yellow fever.

2. Please review the punctuation of this sentence: .."In Asia, but also Europe and North America, Nevertheless, potential spreads beyond the borders of the endemic countries is a matter of global concern."

RECENT OUTBREAKS

3. Because this section is referring only to information outside of Americas, I respectfully suggest modified the subtitle as: RECENT OUTBREAKS OUTSIDE OF AMERICAS

THE CONCERN RAISED FROM BRAZIL

In the introduction was stated.."the lack of efficient health policies", however in the development of this idea in this section there is very little (a sentence) about what are the Brazilian health policies for yellow fever or for vector-borne disease.

This information could be very useful to go in deep to discussion about the "lack of efficient health policies"

CONCLUSIONS

Again, the statement "the lack of efficient health policies" needs a deeper discussion in the previous section to be included in the conclusions.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I strongly recommend to include the comments outlined above.

Is the topic of the opinion article discussed accurately in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Partly

Are arguments sufficiently supported by evidence from the published literature?

Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Yes

Competing Interests: No competing interests were disclosed.

Referee Expertise: Infectious diseases

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 19 Apr 2017

Alfonso Rodriguez-Morales, Universidad Tecnológica de Pereira, Colombia

Dear Dr. Barato

Thank you very much for your valuable assessment and comments. Regard the specific

comments:

INTRODUCTION:

1. I consider it to be desirable to include in the introduction the name of the virus (species) which causes yellow fever.

Agree, we will include it.

2. Please review the punctuation of this sentence: .."In Asia, but also Europe and North America, Nevertheless, potential spreads beyond the borders of the endemic countries is a matter of global concern."

Agree, we will review it.

RECENT OUTBREAKS

3. Because this section is referring only to information outside of Americas, I respectfully suggest modified the subtitle as: RECENT OUTBREAKS OUTSIDE OF AMERICAS

Thanks for your comment, we will modify it.

THE CONCERN RAISED FROM BRAZIL

In the introduction was stated.. "the lack of efficient health policies", however in the development of this idea in this section there is very little (a sentence) about what are the Brazilian health policies for yellow fever or for vector-borne disease.

This information could be very useful to go in deep to discussion about the "lack of efficient health policies"

We will include information about the Brazilian health policies for yellow fever and vector-borne diseases.

CONCLUSIONS

Again, the statement "the lack of efficient health policies" needs a deeper discussion in the previous section to be included in the conclusions.

Ok, we will go deeper in the discussion regarding that point.

Competing Interests: None.

Referee Report 04 April 2017

doi:[10.5256/f1000research.12169.r21529](https://doi.org/10.5256/f1000research.12169.r21529)



Jean-Paul J. Gonzalez, Juergen Richt

Center of Excellence for Emerging and Zoonotic Animal Diseases (CEEZAD), College of Veterinary Medicine, Kansas State University, Manhattan, KS, USA

Title: Although the title is appropriate and clearly leads to the risk of YF re-emergence in the Americas, the manuscript is more centred to South and eventually Central Americas. Also, for this matter (i.e. maintain the title), the authors could emphasize strongly on the risk of imported cases in temperate zone (i.e. Central and North Americas) during the boreal summer and *Aedes* spp. activity in Central-North America (e.g. as it is documented elsewhere for Dengue virus - New Mexico or Texas – and, Airport malaria in the US).

Abstract: “Angola” appears at first, also if the authors want to focus on the Americas, it will be better, in my opinion, to have a short sentence at the end of the abstract that focus on imported risk from endemic area outside of Americas (i.e. Africa).

The authors wrote “despite high YF vaccination coverage”, this is not accurate: Indeed, in many areas and populations worldwide, YF vaccination coverage is discouraging low for years (e.g. Nigeria). This needs to be clear: YF vaccine is certainly the best live attenuated vaccine among all, the less expensive and the first of its kind, consequently there is no reasons today – except politics and funding allocation - to have the people of endemic areas not yet entirely immunized with a real 100% vaccine coverage.

Introduction: For the reader, CFR needs to be expressed as a number of a general historical consensus. Needs also to document the historical dimension of multiple consistent re-emergence of Yellow fever since its discovery beside the excellence of the vaccine(s). While frequency and size of outbreaks are recently (a decade ago) increasing.

Recent outbreaks: China emergence needs to be more specific (i.e. risk) from where (climatic zone) these imported cases were observed.

“Concern raised from Brazil”:

- From the general title or this of such chapter section, one is misleading “Americas (title) or Brazil (this section)”? I suggest something like: “From Brazilian experience, a concern of YF risk for the Americas”
- Line 3: “epicentre:” this needs to be more precise geographically or the sentence clearly linked to the following one, starting by “Indeed, ...”
- Second section, line 4: “a long history of high YF vaccination coverage”, I am not sure this is applicable to Minas Gerais’s remote areas, at least for “long history”. The lack of YF vaccination coverage was raised several times by the Brazilian provincial health authorities back in the early 2000s, unable to reach the remote western zones of the province.
- Section 3, line 3, top of the page: to be politically correct we do not use anymore “Latin America” but “South America”.

Conclusions: Main concerns, regarding the YF risk of emergence/re-emergence, seems to be missing:

- Vaccine: 1/ The recent outbreaks and the lack of Yellow fever vaccine stock piling (WHO). This needs to be strategized (YF vaccine availability) by the country health authorities and international community. 2/ Also the lifelong protection of the vaccine, its innocuity, and the reduction by 1/10 of the immunity dose are new and of extremely high importance (i.e. for the public & public health).
- Biosurveillance needs to be stressed: Mosquito biosurveillance is an important issue to control the epidemic risk, also *Haemagogus* and *Sabethes* are specific for South America and have well studied, the risk and ability of *Aedes albopictus* (expansion) to transmit the virus in the Americas needs to be assessed and an entomological priority set up when needed (i.e. Public health priority in at risk areas).
- Trans-border risk. Ultimately traveler’s from/to endemic areas need to be covered by a mandatory international certificate of vaccination to protect the borders (trans-border risk).

- The long time mystery of the absence of YFV in South East Asia can be also stressed in term of global risk.

Competing Interests: No competing interests were disclosed.

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 04 Apr 2017

Alfonso Rodriguez-Morales, Universidad Tecnológica de Pereira, Colombia

Dear Drs. Gonzalez and Richt

Thanks for you valuable comments. The first thing that should be pointed out is that this is not a Review Article, is a short Opinion Article. Nevertheless, we fully agree to carefully revise our manuscript for a new version (Version 2), considering all the comments you made and based on that correct it accordingly base on each of them.

Regard your comments:

Title: Although the title is appropriate and clearly leads to the risk of YF re-emergence in the Americas, the manuscript is more centred to South and eventually Central Americas.

Yes, certainly this was focused on the concern of expansion in Latin America beyond Brazil where currently is an epidemic situation, where, since the beginning of the outbreak in December 2016 up to 29 March 2017, there were 1,987 cases of yellow fever reported (574 confirmed, 926 discarded, and 487 suspected under investigation), including 282 deaths (187 confirmed, 24 discarded, and 71 under investigation). The case fatality rate (CFR) is 33% among confirmed cases.

Also, for this matter (i.e. maintain the title), the authors could emphasize strongly on the risk of imported cases in temperate zone (i.e. Central and North Americas) during the boreal summer and Aedes spp. activity in Central-North America (e.g. as it is documented elsewhere for Dengue virus - New Mexico or Texas – and, Airport malaria in the US).

We agree with this comment. This will be definitively included in our new version.

Abstract: “Angola” appears at first, also if the authors want to focus on the Americas, it will be better, in my opinion, to have a short sentence at the end of the abstract that focus on imported risk from endemic area outside of Americas (i.e. Africa).

Fully agree, we will change the abstract according those considerations.

The authors wrote “despite high YF vaccination coverage”, this is not accurate: Indeed, in many areas and populations worldwide, YF vaccination coverage is discouraging low for years (e.g. Nigeria). This needs to be clear: YF vaccine is certainly the best live attenuated vaccine among all, the less expensive and the first of its kind, consequently there is no reasons today – except politics and funding allocation - to have the people of endemic areas not yet entirely immunized with a real 100% vaccine coverage.

We would rephrase that, in order to make clear that although in some areas of some countries at risk, there is a high YF vaccination coverage, there are many areas and populations worldwide, where that is low for years (e.g. Nigeria).

Introduction: For the reader, CFR needs to be expressed as a number of a general historical consensus.

We will explain more about the CFR historical reports.

Needs also to document the historical dimension of multiple consistent re-emergence of Yellow fever since its discovery beside the excellence of the vaccine(s). While frequency and size of outbreaks are recently (a decade ago) increasing.

Ok. We will also comment on this, according to your recommendation.

Recent outbreaks: China emergence needs to be more specific (i.e. risk) from where (climatic zone) these imported cases were observed.

Ok. Now is more detailed available information about it, then we will address this in the revised version.

“Concern raised from Brazil”:

From the general title or this of such chapter section, one is misleading “Americas (title) or Brazil (this section)”? I suggest something like: “From Brazilian experience, a concern of YF risk for the Americas”

Well, the concern is for Americas, Brazil is already with epidemics. Then, given that, we will change the title of section to “From Brazilian experience, a concern of YF risk for the Americas”.

Line 3: “epicentre:” this needs to be more precise geographically or the sentence clearly linked to the following one, starting by “Indeed, ...”

Ok, we will correct it.

Second section, line 4: “a long history of high YF vaccination coverage”, I am not sure this is applicable to Minas Gerais’s remote areas, at least for “long history”. The lack of YF vaccination coverage was raised several times by the Brazilian provincial health authorities back in the early 2000s, unable to reach the remote western zones of the province.

Agree, we will make such clarification.

Section 3, line 3, top of the page: to be politically correct we do not use anymore “Latin America” but “South America”.

Well, that is not really accurate, both terms are correct. But Latin America includes both Central and South America. You can consult any reference and you will realize this. South America is not exchangeable to Latin America, with this you will be excluding Central America and Mexico.

Conclusions: Main concerns, regarding the YF risk of emergence/re-emergence, seems to be missing:

Vaccine:

1/ The recent outbreaks and the lack of Yellow fever vaccine stock piling (WHO). This needs to be strategized (YF vaccine availability) by the country health authorities and international community.

This will be included in our new revised version.

2/ Also the lifelong protection of the vaccine, its innocuity, and the reduction by 1/10 of the immunity dose are new and of extremely high importance (i.e. for the public & public health).

This too.

Biosurveillance needs to be stressed: Mosquito biosurveillance is an important issue to control the epidemic risk, also Haemagogus and Sabethes are specific for South America and have well studied, the risk and ability of Aedes albopictus (expansion) to transmit the virus in the Americas needs to be assessed and an entomological priority set up when needed (i.e. Public health priority in at risk areas).

We will add comments about this.

Trans-border risk. Ultimately traveler's from/to endemic areas need to be covered by a mandatory international certificate of vaccination to protect the borders (trans-border risk).

Ok, agree. We will include comments about this.

The long time mystery of the absence of YFV in South East Asia can be also stressed in term of global risk.

Ok, we will make also comments on this.

Competing Interests: None.