RESEARCH NOTE

Seasonality of birth defects in West Africa: could congenital Zika syndrome be to blame? [version 1; referees: 3 approved with reservations]

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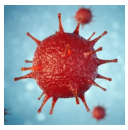
v1 **First published:** 07 Feb 2018, **7**:159 (doi: 10.12688/f1000research.13858.1)
Latest published: 19 Jul 2018, **7**:159 (doi: 10.12688/f1000research.13858.2)

Abstract

The link between Zika virus infection during pregnancy and microcephaly and other neurodevelopmental defects in infants, referred to as congenital Zika syndrome (CZS), was recently discovered. One key question that remains is whether such neurodevelopmental abnormalities are limited to the recently evolved Asiatic ZIKV strains or if they can also be induced by endemic African strains. Thus, we examined birth registries from one particular hospital from a country in West Africa, where ZIKV is endemic. Results showed a seasonal pattern of birth defects that is consistent with potential CZS, which correspond to a range of presumed maternal infection that encompasses both the peak of the warm, rainy season as well as the months immediately following it, when mosquito activity is likely high. While we refrain from definitively linking ZIKV infection and birth defects in West Africa at this time, in part due to scant data available from the region, we hope that this report will initiate broader surveillance efforts that may help shed light onto mechanisms underlying CZS.

Keywords

Zika virus; ZIKV; birth defects; microcephaly; congenital Zika syndrome; West Africa; seasonality



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Referee Status: ? ? ?

	Invited Referees 1	2	3
REVISED version 2 published 19 Jul 2018			
version 1 published 07 Feb 2018	? report	? report	? report

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Competing interests: No competing interests were disclosed.

Grant information: This work was partially supported by the Research Seed Award from Kent State University (to HP) and by Research For Health, Inc. (to RH).
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Majumder MS, Hess R, Ross R and Piontkivska H. **Seasonality of birth defects in West Africa: could congenital Zika syndrome be to blame? [version 1; referees: 3 approved with reservations]** *F1000Research* 2018, **7**:159 (doi: 10.12688/f1000research.13858.1)

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Introduction

Since 2015, when an initial link between Zika Virus (ZIKV) and microcephaly was discovered in Brazil, the term congenital Zika syndrome (CZS) has been coined to reflect a broad range of Zika-linked neurodevelopmental damages[1] beyond microcephaly[1–3], including ocular[4,5] and auditory defects[6,7]. The overall risk of Zika-linked birth defects has been estimated at ~10% and 15% for infections during the 1st trimester[8], potentially impacting thousands of infants in the US and US territories alone. Concerns exist that ZIKV-related outcomes are underreported, particularly when ZIKV infections result in neurodevelopmental abnormalities without visible microcephaly (e.g., developmental delays and learning disabilities that would not be immediately noticeable[9–11]). Such outcomes are likely not recorded, particularly if the causative infection was asymptomatic[12]. Further, a recent CDC report that examined birth defect records from 15 US jurisdictions showed a statistically significant increase in prevalence of birth defects potentially consistent with CZS in areas with documented local ZIKV transmission in the second half of 2016[13]. Notably, the majority of infants and fetuses with birth defects potentially related to ZIKV infection in this report lacked ZIKV infection testing, which may be in part attributed to lack of known maternal exposure or other such indicators[14]. Nonetheless, these findings are alarming and underscore not only the need for continued monitoring and surveillance, but also the need to better understand the full extent – as well as mechanisms – of neurodevelopmental defects associated with CZS.

Can we expect to find cases of congenital Zika syndrome in the African Continent?

Currently our understanding of the mechanisms that underlie CZS remains limited, including the possibility that ZIKV infection is a necessary but insufficient condition for CZS[15]. One key question is whether ZIKV-mediated birth defects are associated with a specific strain of ZIKV, which, for example, could have evolved after ZIKV migrated from South East Asia to French Polynesia and Brazil[16]. However, other studies suggest that African strains are likely to be as pathogenic as the Asiatic strains (e.g., 17,18). Thus, the lack of connection between ZIKV infection in pregnancy and birth defects prior to the 2015–16 Brazilian outbreak may instead be attributable to the benign nature of ZIKV infection in adults[19] and lack of surveillance, among other factors. This can be illustrated by a report of a handful of birth defects in Hawaii in 2009–2012, which now has been shown to be associated with ZIVK infection, but was undetected as such until the Brazilian microcephaly epidemic brought ZIKV into the spotlight[20].

Earlier studies from the African Continent – where ZIKV is endemic – have documented a relatively high prevalence of ZIKV antibodies in human populations (e.g., Nigeria[21], Sierra-Leone[22]). Despite this, there exists negligible data regarding CZS across the African Continent; nevertheless, lack of evidence should not be taken as definitive proof of absence[17]. Thus, here we examine birth registries from one particular hospital in West Africa from a country considered by the WHO to be at medium risk of a ZIKV outbreak[23]. As there are ongoing security concerns in this location, to ensure the safety of the hospital and staff, the hospital name and location have been kept anonymous. The study was approved by the Committee on Administration of the hospital in lieu of a functioning Ethics Committee.

Case study: seasonality of CZS-type birth defects in a hospital in West Africa

Risk of major neurodevelopmental defects, such as microcephaly, appears to be particularly high if vertical transmission occurs during the first trimester, especially within a "vulnerability window" around 12 weeks (10 to 14 weeks) post-conception[8,24]. Thus, we hypothesized that – similar to seasonal malaria infections, which peak a few weeks following abundant rainfalls during the "rainy" season, typically from August through October in the study region[25,26] – seasonal variations in the number of CZS-type birth defects would be detectable from the aforementioned hospital data. Such expectations are consistent with prior findings from Senegal (West Africa)[27] and Kenya (East Africa)[28], where Rift Valley Fever epizootics were associated with heavy rainfalls. Our hypothesis was further informed by the temporal relationships between the number of ZIKV infections and microcephaly cases reported in Brazil[29]. We expected that the peak of CZS-type birth defects (such as documented cases of microcephaly and/or stillbirth) would coincide with vertical ZIKV transmission at around 12-weeks post-conception during the peak of the rainy season, assuming an approximate 3-week lag between maternal infection and vertical transmission[30], as suggested by data from Brazil in 2015[31].

Methods

A total of 13445 birth registries (2009–2015) from a non-governmental hospital in West Africa were examined to determine whether we could identify a seasonal pattern of birth defects potentially attributable to ZIKV infection (i.e., CZS-type birth defects). The number of births and respective outcomes (i.e., live birth versus stillbirth) and reported complications (i.e., fetal malformation, breech, etc.) were collated by month/year. Reporting standards for birth complications varied between years; thus, we focused exclusively on visible neurodevelopmental complications (such as microcephaly) and pregnancy losses (such as stillbirth) that could be attributed to potential CZS[1,2] (Supplementary Table 1 and Supplementary Table 2). To infer the "vulnerability window" of 12 weeks (spanning 10 to 14 weeks) post-conception, we assumed that births that were not reported as premature in the records were full-term, thus enabling us to infer the likely month of conception[29].

We also considered national average monthly temperature and rainfall data for the study years, collected from the World Bank Climate Change Knowledge Portal database. These values were treated as proxy indicators for mosquito activity in the hospital catchment area at time of maternal infection. To visualize any relevant trends, we plotted these data, as well as the average percentage of birth defects consistent with potential CZS by month.

Results and discussion

As shown in Figure 1, the average percentage of births consistent with potential CZS demonstrates a marked peak between March and July, which places maternal month of infection between August and December of the previous year. These months encompass the peak and latter half of the warm, rainy season (August–October) as well as the first half of the cool, dry season that immediately follows (October–December) in the study region, which likely represent months with considerable mosquito activity. Notably, the hospital from which these birth defects data were acquired generally experiences a peak in childhood malaria cases every October, which falls squarely in the middle of the August to December range of presumed maternal month of ZIKV infection determined here.

With this in mind, the early months of the cool, dry season (October–December) are likely hospitable enough for mosquito vectors to thrive and spread pathogens, including ZIKV; this may explain why the range of our presumed maternal month of infection (August–December) extends past the rainy season, given that mosquitoes require a balanced environment for survival, including both moderate rainfall and optimal temperatures[32].

Our results suggest that a seasonal pattern exists with respect to CZS-type birth defects reported in the study region (Figure 1), where the largest fraction of said defects appear to occur in the months of March through July. Furthermore, this pattern can be linked to ecological evidence, such as rainfall and temperature trends that likely facilitate maternal ZIKV infection. While consistent with the expectation that some of these defects might be attributable to (unreported) ZIKV infections that occurred early in pregnancy (and indeed resemble temporal patterns from studies in Brazil[29]), our findings stop short of definitively linking ZIKV infection and birth defects in the study region, in part due to scant data. Instead, by reviewing the

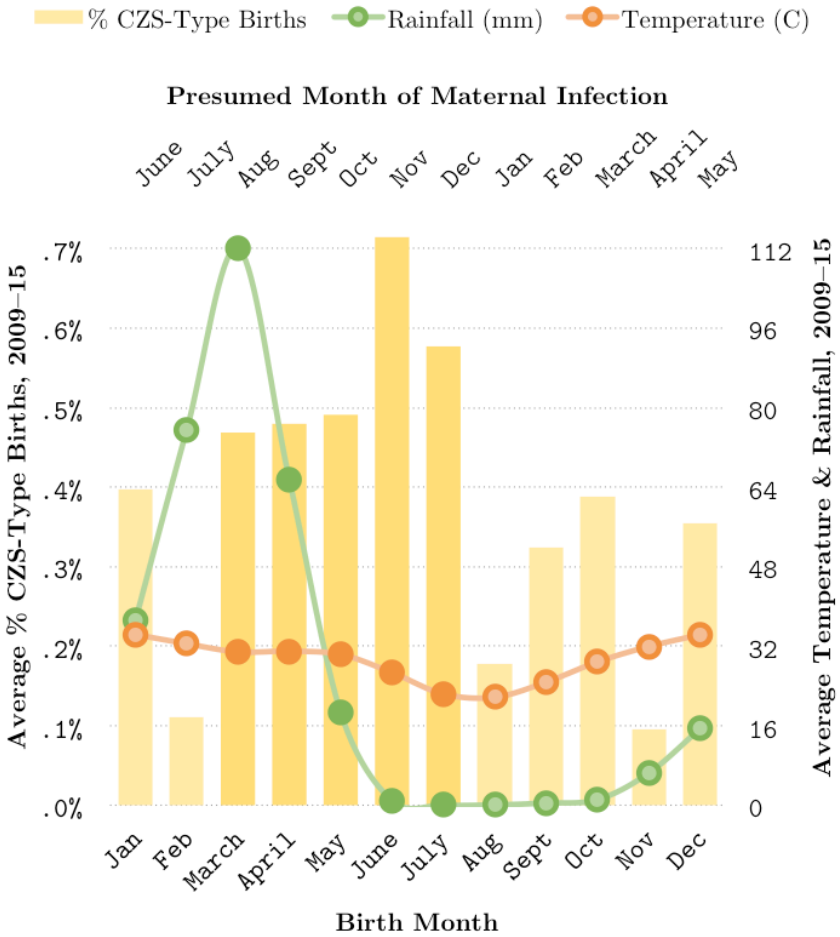

Figure 1. Average birth defects consistent with congenital Zika syndrome per month, with corresponding average daily temperatures and rainfall during presumed maternal month of infection.

potential limitations of the data analyzed here, we hope that this report will initiate broader surveillance efforts that may help shed light onto mechanisms that underlie CZS, including utilization of data that might already be available across various African countries where ZIKV is endemic and/or competent vectors exist (e.g., Gabon[33], Central African Republic[34]). For example, a recent WHO Bulletin on Outbreaks and Other Emergencies[35] reported a number of microcephaly cases from Angola (a country listed in the High risk category[23]) that appear to be linked to ZIKV infection, despite the lack of direct PCR confirmation from the specimens. Due to only recent implementation of active surveillance in the country, the true magnitude of the event is not yet clearly understood. Nonetheless, it is important for insights into a broader pattern of potential CZS defects, despite the lack of experimental ZIKV infection confirmation or lack of evidence of ongoing active ZIKV transmission in Angola (i.e. only two ZIKV cases were reported from Angola in early 2017[36]).

Several conservative assumptions made in this analysis, such as assuming a gestation period of ~9 months, or not classifying "low birth weights" (which may represent full-term births of ZIKV-infected fetuses) as a CZS-type birth defect, would likely lead to underestimation of potential trends, if any. We also assumed that the available birth records were representative of the pregnancy/birth patterns that occur across the entire region. Other limitations of the available data are related to the standard of care that is feasible in much of West Africa, including (i) lack of family history and/or genetic testing for mutations in loci responsible for primary microcephaly; (ii) lack of laboratory evidence or testing for ZIKV and/or other infections, including TORCH agents[37,38], often due to inability to pay for testing (e.g., 39); and (iii) lack of detailed clinical prenatal history, including whether rash and/or other symptoms of Zika infection were present at any point during pregnancy. This final limitation may be considered minor, given that the majority of ZIKV infections are asymptomatic[19,24]. Additionally, no data were available regarding other clinically relevant factors that are also associated with microcephaly[40], such as history of excessive alcohol consumption or recreational drug use, and/or prolonged exposure to pesticides, such as pyriproxyfen. However, the former life-style factors are unlikely to have a seasonal effect spanning several years, and the role of the latter factor as a causative agent of microcephaly remains unclear[41]. There is also a lack of precise ecological data, including estimates of rainfalls in the hospital catchment area, the distribution and feeding habits of mosquitoes, and whether or not said mosquitoes carry ZIKV, as well as data regarding ZIKV prevalence in the human population.

Despite these limitations, our findings suggest that using the data we already have – even in the absence of formal surveillance systems for CZS – can provide compelling, introductory insights. In the future, work that employs existing data from hospitals across the African continent – which encompasses countries with a variety of climates, dry and rainy seasons, and suitability for widespread mosquito habitats – should be pursued.

Data availability

Figshare : Data for Figure 1. Average birth defects consistent with congenital Zika syndrome per month, with corresponding average daily temperatures and rainfall during presumed maternal month of infection. doi: 10.6084/m9.figshare.5387029.

Competing interests

All authors declare that they have no competing interests.

Grant information

This work was partially supported by the Research Seed Award from Kent State University (to HP) and by Research For Health, Inc. (to RH).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Supplementary material

Supplemental Table 1. A list of birth complications (as recorded in the health records) consistent with potential congenital Zika syndrome.

Click here to access the data.

Supplemental Table 2. A list of birth complications (as recorded in the health records) that are not consistent with potential congenital Zika syndrome and/or missing.

Click here to access the data.

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Publisher Full Text

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Version 1

Referee Report 25 June 2018

doi:10.5256/f1000research.15063.r35015

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Massachusetts Department of Public Health (MDPH), Boston, MA, USA

The authors present an analysis of birth defects by season from a single hospital in an unnamed West African country relative to a purported mosquito season. Their conclusion is that the seasonality of certain types of birth defects, consistent with CZS, could be explain by Zika virus transmission in the area. This is an interesting attempt to use available data to speculate about the impact of Zika virus on congenital defects in an endemic area. Although this is certainly thought-provoking and supports the authors recommendation to improve surveillance for Zika virus in endemic areas, there is insufficient discussion of all of the limitations to this particular analysis which, if included, would cast doubt on their proposed conclusion.

The limitation that the data are from a single hospital in an un-named location make it impossible to make any generalizable conclusions and to understand any limitations completely.

Data do not exist on the underlying sero-prevalence of Zika virus infection in this population (I assume). However, given that Zika virus infection likely results in lifelong immunity, one might not expect to see any change in CZS-like defects simply due to a low number of susceptible pregnant women. Were the women with infants with birth defects generally younger and therefore less likely to have been previously infected? And why wouldn't we expect children to have a high rate of infection resulting in immunity as they reach child-bearing age?

Again, although difficult to determine given the lack of geographic specificity provided, there is minimal discussion in the paper of other potential causes of microcephaly; most notably rubella and malnutrition. Although rubella-related birth defects might not be expected to show any seasonality, malnutrition might. As might toxoplasmosis.

The time period covered by this report encompasses both the Ebola outbreak and significant Yellow fever activity; both of these could cause confounding in the data.

Mosquito species are quite variable in their feeding habits, optimal climactic conditions and in their vectorial capacity. Relying on patterns of malarial disease to represent what is likely to happen with a flavivirus like Zika which is transmitted by different species of mosquitoes should be considered to be a limitation. What about using Yellow fever or dengue disease patterns?

Lastly, while I understand the argument the authors are making, I found the assertion that the maternal infection period of August through October encompassed the peak and latter half of the warm, rainy

season confusing. Based on the presented data, August through October had minimal rain and lower than average temperatures. October through December was described as the cool, dry season although temperatures peak for the year in November through January (according to the data presented by the authors).

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

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 have significant reservations, as outlined above.

Author Response 16 Jul 2018

Helen Piontkivska, Kent State University

>>>The limitation that the data are from a single hospital in an un-named location make it impossible to make any generalizable conclusions and to understand any limitations completely.

We appreciate these limitations, and they were requirements for us to access the data. Specifically, the Committee on Administration of the hospital required us not to name the hospital or the country. We added a statement clarifying this. Our goal was to spur further discussion and further research from larger sample sizes in multiple locations in order to access the generality of this pattern.

>>> Data do not exist on the underlying sero-prevalence of Zika virus infection in this population (I assume). However, given that Zika virus infection likely results in lifelong immunity, one might not expect to see any change in CZS-like defects simply due to a low number of susceptible pregnant women. Were the women with infants with birth defects generally younger and therefore less likely to have been previously infected? And why wouldn't we expect children to have a high rate of infection resulting in immunity as they reach child-bearing age?

It is still unclear whether in humans (versus non-human primates) Zika infection confers life-long immunity (Siedner, Ryan and Bogoch 2018). However, age distribution of mothers of infants with CZS-like birth defects indicates that such birth defects appear across multiple age cohorts, from 15 to 37, with the mean number of CZS-like cases per each age group of 2.39 (± standard error of 0.42). Further research of larger cohorts across different locations is needed to definitively test whether there are any maternal-age related effects.

>>> Again, although difficult to determine given the lack of geographic specificity provided, there is minimal discussion in the paper of other potential causes of microcephaly; most notably rubella and malnutrition. Although rubella-related birth defects might not be expected to show any seasonality, malnutrition might. As might toxoplasmosis. The time period covered by this report encompasses both the Ebola outbreak and significant Yellow fever activity; both of these could cause confounding in the data.

We agree that there are many human health issues that could display seasonality. This underscores the need for widespread comprehensive test for infectious agents and prenatal care, although implementation of such tests in Africa will require significant investments to be feasible.

>>> Mosquito species are quite variable in their feeding habits, optimal climactic conditions and in their vectorial capacity. Relying on patterns of malarial disease to represent what is likely to happen with a flavivirus like Zika which is transmitted by different species of mosquitoes should be considered to be a limitation. What about using Yellow fever or dengue disease patterns?

In our inferences we did not rely on the malaria pattern to infer seasonality; instead, it was referenced to indicate consistency in the inferred activities from the temperature and rainfall data. Regretfully, no data regarding yellow fever or dengue infections were available. However, the temperature ranges of the peak transmission of malaria and dengue are overlapping [mid 20's ºC for malaria, per (Beck-Johnson et al. 2013); 23-34ºC for DENV, per (Mordecai et al. 2017)]. Therefore, we expect that the transmission patterns would be similar.

Beck-Johnson, L. M., et al. (2013). "The effect of temperature on Anopheles mosquito population dynamics and the potential for malaria transmission." PLoS One **8**(11): e79276.
Mordecai, E. A., et al. (2017). "Detecting the impact of temperature on transmission of Zika, dengue, and chikungunya using mechanistic models." PLoS Negl Trop Dis **11**(4): e0005568.

>>> Lastly, while I understand the argument the authors are making, I found the assertion that the maternal infection period of August through October encompassed the peak and latter half of the warm, rainy season confusing. Based on the presented data, August through October had minimal rain and lower than average temperatures. October through December was described as the cool, dry season although temperatures peak for the year in November through January (according to the data presented by the authors).

We revised the figure 1 legend to make it clear that the bottom axis corresponds with the birth month (depicted with yellow bars) and therefore with the left Y axis that shows % CZS-type birth defects, while the top axis corresponds with the month of maternal infection (i.e., with the rainfall and temperature shown on the left, depicted in green and red, respectively). We have also added color guides to the figure to make it visually clear.

Competing Interests: No competing interests were disclosed.

Referee Report 25 June 2018

doi:10.5256/f1000research.15063.r35010

Diana Valencia
Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA

Thank you for the opportunity to review this article. I have the following questions/suggestions for the consideration of the authors:

1. The following important reference is missing from the article, please include: Rasmussen et al. (2016)[1]

2. Authors should mention that Zika migrated not only to Brazil but to the Americas.

3. What are the characteristics of the chosen hospital? Why only one hospital was chosen? Does the hospital has a good reliable birth defect registry?

4. There is no description of the birth defects taken into account for the paper; which CZS-type birth defects were chosen form the hospital registry? Were the birth defects confirmed? Was any description available in medical records? Were X-rays available for review?

5. I agree with the authors on the importance to have birth defects surveillance systems in place. I hope that this article will contribute to the awareness of public health authorities regarding this important issue.

6. Birth defects surveillance is needed to identify Zika related defects. As the authors mention, the majority of infected pregnant women are asymptomatic.

7. I think it will be important to differentiate in the article between Zika virus surveillance and birth defects surveillance, and the difficulties of implementing them in Africa.

References

1. Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR: Zika Virus and Birth Defects--Reviewing the Evidence for Causality.*N Engl J Med*. 2016; **374** (20): 1981-7 PubMed Abstract | Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Referee Expertise: Birth defects surveillance in low and middle income countries

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 have significant reservations, as outlined above.

Author Response 16 Jul 2018

Helen Piontkivska, Kent State University

>>> 1. The following important reference is missing from the article, please include: Rasmussen et al. (2016)

Thank you for pointing out our oversight. We added this important reference to the paper.

>>>> 2. Authors should mention that Zika migrated not only to Brazil but to the Americas.

Done.

>>>> 3. What are the characteristics of the chosen hospital? Why only one hospital was chosen? Does the hospital has a good reliable birth defect registry?

Additional identifiable characteristics were not included in order to protect the identity of the hospital; however, we now added several broad characteristics of the hospital to the manuscript. These were the only data that were available to us, and we are confident in the quality of the birth defect registry. We are excited that we were able to demonstrate this trend even with the relatively small sample available to us. We hope this study will spur further comprehensive analyses of larger datasets.

>>> 4. There is no description of the birth defects taken into account for the paper; which CZS-type birth defects were chosen form the hospital registry? Were the birth defects confirmed? Was any description available in medical records? Were X-rays available for review?

The description of birth complications that we categorize as a CZS-type (i.e., birth defects consistent with potential congenital Zika syndrome) are listed in the Supplementary table 1, while Supplementary table 2 lists the non-CZS-type complications. We did not have access to individuals' medical records beyond the descriptions listed in Supplementary tables. The hospital does not routinely perform X-rays on newborns with birth defects; thus, no further description of cases or X-rays were available to us.

>>> 5. I agree with the authors on the importance to have birth defects surveillance systems in place. I hope that this article will contribute to the awareness of public health authorities regarding

this important issue.
6. Birth defects surveillance is needed to identify Zika related defects. As the authors mention, the majority of infected pregnant women are asymptomatic.

Thank you, we completely agree.

>>> 7. I think it will be important to differentiate in the article between Zika virus surveillance and birth defects surveillance, and the difficulties of implementing them in Africa.

We agree, and have added statements to that effect. Enhanced birth defect surveillance within hospitals are potentially feasible with the current resources, although they may require additional personnel and/or training. However, the surveillance of birth defects outside of hospital settings would be problematic, though potentially possible. On the other hand, Zika virus surveillance per se, as well as surveillance of other viral diseases, would require substantial financial investments globally, as well as overcoming other challenges related to the implementation of such surveillance.

Competing Interests: No competing interests were disclosed.

Referee Report 03 April 2018

doi:10.5256/f1000research.15063.r32204

? **Matthew T. Aliota**
Department of Pathobiological Sciences (PBS), University of Wisconsin-Madison, Madison, WI, USA

The authors have produced a paper speculating that African lineage Zika virus has the same capacity to cause congenital Zika syndrome (CZS) as more recent Asian/American outbreak isolates. This was accomplished by analyzing birth outcome reports from one hospital in West Africa and temporally linking outcomes consistent with CZS to seasonal patterns when mosquito populations would be abundant. The paper is well written and certainly addresses an outstanding question in the field. In sum, this article's major purpose is to create a discussion and provide a rationale for broader Zika surveillance activities in Africa, which I I believe has been accomplished, however, there are a few minor details that could be changed to facilitate understanding by the reader.

1. I understand the need for security and thus not naming the hospital but would naming the country truly jeopardize security?

2. While I agree that it is possible that African ZIKV has always had the capability of causing CZS and that it is likely underreported or unrecognized, an alternative explanation is that in Africa where ZIKV is endemic girls and women are exposed early in life and subsequent immunity provides protection against CZS during child bearing years. Is there any age distribution that can be associated with the outcomes presented here?

3. Throughout comparisons are made to Malaria which is transmitted by Anopheles mosquitoes, whereas, ZIKV is likely transmitted by an Aedes species mosquito. Therefore, the same environmental factors may not drive transmission of both equally. Do the authors have any data on, for example, dengue cases that were reported at the same hospital during the study period?

4. The data are from a country that is at "medium risk for a Zika outbreak". I believe it is more important to know what the estimated seroprevalence of Zika exposure is in this country. This suggests that perhaps Zika is not endemic in the country.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Referee Expertise: Virology, medical entomology, evolution and transmission dynamics of arthropod-borne pathogens

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 have significant reservations, as outlined above.

Author Response 16 Jul 2018

Helen Piontkivska, Kent State University

>>> 1. I understand the need for security and thus not naming the hospital but would naming the country truly jeopardize security?

We agree with you in principle; however, the Committee on Administration of the hospital required us not to name the hospital or the country. We added a statement clarifying this.

>>> 2. While I agree that it is possible that African ZIKV has always had the capability of causing CZS and that it is likely underreported or unrecognized, an alternative explanation is that in Africa where ZIKV is endemic girls and women are exposed early in life and subsequent immunity provides protection against CZS during child bearing years. Is there any age distribution that can be associated with the outcomes presented here?

We agree with the reviewer that the question of whether early exposure to ZIKV and/or other flaviviruses may offer subsequent long-term protection against CZS during childbearing years

warrants further attention. CZS-type defects analyzed in our study were found in women of ages 15-37 years old; the average number of cases per maternal age class is 2.39 (± standard error of 0.42). Thus, these data are not well suited to test this hypothesis, which we hope can be tested in the future with appropriate power.

>>> 3. Throughout comparisons are made to Malaria which is transmitted by Anopheles mosquitoes, whereas, ZIKV is likely transmitted by an Aedes species mosquito. Therefore, the same environmental factors may not drive transmission of both equally. Do the authors have any data on, for example, dengue cases that were reported at the same hospital during the study period?

There are no data on dengue cases available from the hospital. However, the temperature ranges of the peak transmission of malaria and dengue are overlapping [mid 20's ºC for malaria, per (Beck-Johnson et al. 2013); 23-34ºC for DENV, per (Mordecai et al. 2017)]. Therefore, we expect that the transmission patterns would be similar.

Beck-Johnson, L. M., et al. (2013). "The effect of temperature on Anopheles mosquito population dynamics and the potential for malaria transmission." PLoS One 8(11): e79276.
Mordecai, E. A., et al. (2017). "Detecting the impact of temperature on transmission of Zika, dengue, and chikungunya using mechanistic models." PLoS Negl Trop Dis 11(4): e0005568.

>>> 4. The data are from a country that is at "medium risk for a Zika outbreak". I believe it is more important to know what the estimated seroprevalence of Zika exposure is in this country. This suggests that perhaps Zika is not endemic in the country.

Unfortunately, there are relatively scant data available from the region, most of which comes from the decades-old studies. Specifically, antibodies to ZIKV were found in human blood samples collected in 1960-ies in Senegal, Burkina Faso, Cote D'Ivoire, Guinea-Bissau, Cameroon, Mali, Niger, Benin, Gabon (Brès 1970), in Senegal (Renaudet et al. 1978) and Nigeria (Adekolu-John and Fagbami 1983) in 1970-ies and 1980-ies, supporting the premise that ZIKV is present across multiple countries in West Africa region (reviewed in (Kindhauser et al. 2016)). We hope that this study will motivate the collection of such data in the future. We added these references to the manuscript, to the "Can we expect to find cases of congenital Zika syndrome in the African Continent?" section.

Adekolu-John, E. O. and A. H. Fagbami (1983). "Arthropod-borne virus antibodies in sera of residents of Kainji Lake Basin, Nigeria 1980." Trans R Soc Trop Med Hyg **77**(2): 149-151.
Brès, P. (1970). "Données récentes apportées par les enquêtes sérologiques sur la prévalence des arbovirus en Afrique, avec référence spéciale à la fièvre jaune [Recent data from serological surveys on the prevalence of arbovirus infections in Africa, with special reference to yellow fever]." Bulletin of the World Health Organization **43**(2): 223-267.
Kindhauser, M. K., et al. (2016). "Zika: the origin and spread of a mosquito-borne virus." Bull World Health Organ **171082**.
Renaudet, J., et al. (1978). "[A serological survey of arboviruses in the human population of Senegal]." Bull Soc Pathol Exot Filiales **71**(2): 131-140.

Competing Interests: No competing interests were disclosed.