PLOS Science Wednesday: Hi reddit, my name is Gene, and the results of our cross-sectional serosurvey indicates that many Ebola cases were minimally symptomatic and likely undetected during the Sierra Leone outbreak – Ask Me Anything!

PLOSScienceWednesday [1] and r/Science AMAs[1]

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Abstract

Hi Reddit, My name is Gene Richardson and I am and infectious disease physician and anthropologist at Brigham and Women's Hospital and Harvard Medical School. I use biosocial approaches to conduct research on infectious disease epidemics in sub-Saharan Africa. I recently published an article titled "Minimally Symptomatic Infection in an Ebola 'Hotspot': A Cross-Sectional Serosurvey" in PLOS Neglected Tropical Diseases. The study provides further evidence that Ebola, like many other viral infections, presents with a spectrum of clinical manifestations, including minimally symptomatic infection. The findings also suggest that a significant portion of Ebola transmission events may have gone undetected during the recent outbreak in West Africa. I will be answering your questions at 1pm ET – Ask Me Anything!

the WINNOWER

REDDIT

PLOS Science Wednesday: Hi reddit, my name is Gene, and the results of our cross-sectional serosurvey indicates that many Ebola cases were minimally symptomatic and likely undetected during the Sierra Leone outbreak – Ask Me Anything!

PLOSSCIENCEWEDNESDAY R/SCIENCE

Hi Reddit,
My name is Gene Richardson and I am and infectious disease physician and anthropologist at Brigham and Women's Hospital and Harvard Medical School. I use biosocial approaches to conduct research on infectious disease epidemics in sub-Saharan Africa.
I recently published an article titled "Minimally Symptomatic Infection in an Ebola 'Hotspot': A Cross-Sectional Serosurvey" in PLOS Neglected Tropical Diseases. The study provides further evidence that Ebola, like many other viral infections, presents with a spectrum of clinical manifestations, including minimally symptomatic infection. The findings also suggest that a significant portion of Ebola transmission events may have gone undetected during the recent outbreak in West Africa.
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Does this mean there could be hundreds of typhoid Marys and that they could still be out there "waiting" for a particularly vulnerable individual to infect?

Trumpstered

So far there is only one report documenting transmission from a minimally symptomatic individual: see https://academic.oup.com/cid/article-abstract/doi/10.1093/cid/ciw793/2666520/Ebola-Virus-Persistence-in-Breast-Milk-After-No Given there have only been a few flare-ups (mini-outbreaks) due to sexual transmission from survivors (after they convalesced), my sense is that minimally symptomatic individuals pose little concern for future transmission of virus. But more research needs to be done.

Is it possible that the results are measuring exposure to TWO strains of Ebola that were present in Sukudu, Kono District, Sierra Leone, from October 2015 to January 2016... One strain that was very deadly, and one strain that is not?

I note that the log (anti-GP) of the 14 minimally symptomatic individuals (yellow dots) in figure 3, is lower on average than the positive controls (green dots)... could that be because of a small genetic divergence between the surface antigens of a minimally symptomatic strain relative to the base Zaire strain?

Lucretius

I don't think strain variation played a part in whether one is symptomatic or not, but rather host defenses. There were families with individuals that ran the gamut of infection.

Although there was a trend for the minimally symptomatics to have lower titers, the difference was not significant (but our sample was on the small side). We hope to answer this question with a larger study.

Hi Gene and thank you for doing this AMA.

How do Ebola titers (by ELISA) in non-symptomatic carriers compare to Ebola titers in symptomatic patients?

Why do you think the Ebola virus is constrained in a minimally symptomatic state in these study participants? Is it an Ebola autonomous feature, or is the host immune system keeping the virus in check?

If it is the latter, do you have plans to isolate plasma cells from these volunteers, with the intent of antibody/vaccine discovery?

SirT6

There was not a statistically significant difference in titers between survivors and minimally symptomatic individuals in our cohort, but we had a small sample size. I don't think inoculum plays a role in how sick someone becomes. Rather I think there is a genetic component, coupled with nutritional status, age, etc. We are beginning collaborations with other investigators to explore genetic determinants and whether we can isolate effective neutralizing antibodies from previously infected individuals.

Typically we think of Ebola as self limiting, because the lethality tends to kill the host before they can infect many others. How does the discovery of these less symptomatic serotypes affect both our current model for how Ebola spreads, as well as current and future treatment models?

Noninex

This discovery means that all previously published transmission chains were inaccurate, since none of them included undocumented survivors or minimally symptomatic individuals. We have a paper currently under review which will show the transmission chain for this hotspot village, which includes these individuals.

Given the success of the ring vaccine strategy, I'm hoping the implications of these transmission dynamics become moot.

The findings also suggest that a significant portion of Ebola transmission events may have gone undetected during the recent outbreak in West Africa.

What does this mean for how we should consider treating future outbreaks of the disease? What do you think the risk of transmission is for people who are minimally symptomatic? And does having a less extreme response (i.e. they survive without medical intervention) give people any immunity to future outbreaks?

firedrops

I think the risk of onward transmission for minimally symptomatic individuals is very low, potentially

only through sex. For future outbreaks, I would extend safe sex recommendations for those individuals who are contacts of EVD cases or suspects.

I know that ebola would have a particularly difficult time eradicating large amounts (by large I mean millions) of people due to it being lethal quickly, and thus making the window for infection relatively small.

Are there concerns that a new ,slightly weaker strain could arise where it is not as QUICKLY lethal (thus increasing the window for transmission) but is still deadly?

This is worrisome for me because it could mean that, on a person by person basis, there may be a slightly higher likelihood of survival, but on a societal basis, there could be much more potential for death, as many more could be infected with a slightly less lethal variant

JaDinklageMorgoone

I don't think Ebola virus will turn out like HIV because survivors are not similarly viremic (despite some maintaining reservoirs of infection). The next virus (TNV) is on always on the horizon, though, meaning that we should focus on strengthening health systems and address structural inequities as our primary mode of prevention.

First off, thank you for doing this AMA. My question to you is, as a junior finishing up my undergrad with plans of going to medical school and also specializing in infectious diseases, what is some of the best advice you received early in you medical career and how did you apply that in order to get to your position you are in currently?

sqLc

Sounds hokey, but follow your heart…good things will happen. Listen to the advice of your teachers and mentors. Send me an email once you're in fellowship, and we'll find some good work for you.

Given this information, is it possible that we actually were at a greater threat to ebola in the U.S. than many suggest (aka, was the fear actually not exaggerated?)

EmDashxx

I think the fear was greatly exaggerated given that we have a very robust public health infrastructure to contain outbreaks in the US and strong intensive care services in most hospitals.

Was it a weaker strain of the virus that mildly-symptomatic patients had, or are some people naturally more resistant than others?

Does this also mean that the death rates are actually over inflated, because I'd assume non/mildly symptomatic patients would rarely if ever have been counted in the statistics?

Could natural resistance to Ebola be used to help synthesise better treatments?

JoeyClaire

I don't think strain variation played a part in whether one is symptomatic or not, but rather host defenses. The mortality rate for EVD cases wasn't inflated, but the rate for all infected individuals was.

Even so, my sense is the total number of deaths is much higher than the 11,000+ currently reported due to poor surveillance (especially early in the outbreak). We are beginning collaborations with other investigators to explore whether we can isolate effective neutralizing antibodies from previously infected individuals.

How bad is it if you get ebola in a western country (in my case Finland), and what are the percentages of death in this kind of countries?

Also, how badly would this kind of undetected carrier damage others around him/her?

Tuuumas

You would very likely survive given Finland has excellent hospitals. Our research did not discover "undetected carriers," but rather individuals who were infected during the outbreak, but who weren't detected by the surveillance system in place. There is no evidence that these individuals are current "carriers."

What is a biosocial approach? For example, how did that affect the article you linked?

unhappychance

Check out our article in Health and Human Rights: https://www.hhrjournal.org/2015/12/biosocial-approaches-to-the-2013-2016-ebola-pandemic/

Hello, thank you for the work you are doing first of all. My question is what prompted you to get into this field? Also what if any opportunities are there for someone with a background in Bacterial Vaccinology to get into BSL4 Virology?

Demaculus

Reading Infections and Inequalities by Paul Farmer got me interested in this field.

Could the minimally susceptible people be studied to find out why they were minimally affected, then use that knowledge to develop a drug treatment?

blackeneth

We are beginning collaborations with other investigators to explore whether we can isolate effective neutralizing antibodies from previously infected individuals as a potential therapeutic.

Would it be possible to extrapolate your research to come up with an estimate of how many people in the "hot zones" in Africa are carriers of the Ebola virus?

And a more general question: Was there a high school or undergrad instructor who made you think, "Yeah, I want to do this for the rest of my life" - What was the experience/relationship like?

SlopDaddy

Again, our research did not discover “undetected carriers,” but rather individuals who were infected during the outbreak, but who weren’t detected by the surveillance system in place. There is no evidence that these individuals are current “carriers.”

Hello! Is it thought that these non-symptomatic patients may be elite controllers, as is observed with HIV? If so, would this resistance trait have emerged due to co-evolution of Ebola and local populations (akin to the higher proportion of sickle cell anemia carriers observed in populations impacted by malaria)? Are there any actionable lessons that can be distilled from this population's mechanism of resistance?

Thanks for doing this AMA!

axolotlfarmer

Although, infection with Ebola virus is not analogous to infection with HIV (no long term viremia, etc.), there are investigators working on whether there is a genetic component that associates with severity of illness. IMO, health systems strengthening is the most important "mechanism of resistance."

Hey Gene - Thank you for your research.

- In your paper you list study limitations and caution against generalizing your results. Do you think that'll happen? I mean, is Ebola an active area research currently? My reading is a bunch of money was poured into researching it during the outbreak but it's been mostly forgotten; I'm hoping that's wrong.
- How do you think your results should impact public policy? I'm specifically thinking of things like travel bans and quarantines which were largely seen as overkill (at least in US) under the assumption asymptomatic transmission's not possible.

martydertz

Ebola is still an active area of research, although promised funds for research and health systems strengthening are quickly being diverted to “The Crisis Caravan” (I recommend the book), including Zika, etc.

I think the problem with research money during the outbreak was that it was channeled through clinical research organizations (CROs), instead of straight to investigators associated with clinical delivery platforms.

Hi Gene, I have a few questions.

Since these cases show no symptoms, does this mean that the risk of having Ebola in the U.S is actually greater than we once thought?

Could the virus be "waiting", for lack of a better term, for someone with a weaker immune system?

How will this affect future outbreaks?

Thank you for your research and for doing this AMA!

reallyweirdperson

I don't think there's any risk of having Ebola in the U.S.

It's is widely believed that people aren't infectious until the onset of symptoms. Do you have findings on the infectiousness of these minimally symptomatic persons (a relative r-naught, for example) compared to "traditionally" sick people w diarrhea vomiting (projecting viruses)?

burkulosis

My sense is that minimally symptomatic infections are a very rare source of onward transmission. However, a recent case report https://academic.oup.com/cid/article-abstract/doi/10.1093/cid/ciw793/2666520/Ebola-Virus-Persistence-in-Breast-Milk-After-No suggests that there's more research to be done.

I actually worked in Liberia during the outbreak and at one point came down with a huge fever, a headache, and diarrhea. After a time, this subsided. Are there any tests available that I can take to check and see if I had the disease or rather just a terrifying flu as I originally concluded?

eljefehunter

Ebola serology is not commercially available, nor FDA approved, so you would need to be tested as part of research.

Have you read "The Hot Zone" about the Ebola outbreaks in the 90's? If so, how relevant is the book still today?

front2back2

I have read the Hot Zone. Well written, but I think it sensationalizes the field. I'd recommend Pathologies of Power by Paul Farmer as an alternative.

Hello, from what I understand, the size of the inoculum is predictive of the severity of infection with Ebola virus. Do you suspect, given your findings, that this may be put to question, as there are numerous patients who have probably not been diagnosed skewing the results that led to the conclusion above?

iTyrosinekinase

I personally don't think inoculum determines severity of infection. My reasoning is that I assume that all expats with EVD were infected by small innocula due to errors in doffing PPE, but they exhibited a range of symptom severity.

Is there any indication of cross-neutralization of the virus due to previous exposure to similar antigens from the Taï Forest or Sudan viruses?

Is this lack of immunogenicity in any way compounded by burial rituals, and what advances have been made in convincing families of the deceased to be more flexible in regards to contact with corpses?

Thank you for taking the time to read, Dr. Richardson.

TheDeakness

I'm not sure about the level of protection afforded by exposure to other species of Ebola.

I do think there was excessive focus on "funerary ritual" as an amplifier of infection, when, in the final analysis, Ebola is a caregiver's disease. The large majority of the survivors I interviewed said they knew about how Ebola was transmitted, and they knew their loved ones had EVD, but they couldn't leave them to suffer without care.

Thanks for doing this AMA, I'm applying to get my PhD in Immuno and work on vaccines so this is really cool.

Are the Abs typically cross-neutralizing between symptomatic and asymptomatic cases? Do you think that the display of symptoms correlates to an individual's immune system, different strains of Ebola, or another factor? And finally, are there any promising vaccination targets? I don't know much about ebolavirus so I don't know if they mutate a ton or have conserved regions for easy targeting.

yosoyellogan

My sense is that both symptomatic and minimally symptomatic Ebola virus infections result in immunity. Not sure about the durability though. There is a vaccine that was 100% efficacious in a recently published ring vaccination trial http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)32621-6/fulltext Whether it will be effective as a scaled-up routine vaccination remains to be determined.

Very interesting study, thank you. My question is, how accurate did you determine the self diagnosis of fever to be? Or were medical personnel checking the patients as well?

I've always had a fascination / fear of Ebola since reading the Hot Zone while living in Africa. So thanks for working to better understand and protect us from these diseases.

photoengineer

One limitation of the study is that we asked people about symptoms one year after the outbreak in their village; however, during the outbreak, most quarantined households were monitored daily by surveillance teams that conducted symptom screens and measured temperatures, and individuals were brought to treatment facilities for EBOV testing if they screened positive.

What do you think about the possibility that the current strain of Ebola is more virulent than previous strains?

laurus22

There is a recent paper that suggests a strain with increased infectivity appeared during the outbreak http://www.cell.com/fulltext/S0092-8674(16)31397-6

I think it's important to highlight that this study looked at IgG antibodies. When we see these antibodies present, we cannot tell when the person was infected. It could have been this particular outbreak, or some other previous exposure. This means that it is possibly equally likely that these individuals weren't infected at the time of the outbreak and therefore weren't contributing to the transmission of the disease during the recent outbreak.

Additionally, I think it's also important to highlight the definition of 'minimally symptomatic' in this study. It doesn't mean all 14 were actually sick in any way:

"We considered participants to have had minimally symptomatic EBOV infection if they 1) had an anti-GP ELISA above the cut-off as determined in the validation sub-study and 2) denied symptoms consistent with EVD during the period of active transmission in the village."

Essentially, you were considered 'minimally symptomatic' if you *weren't* sick with what looked like Ebola (perhaps not sick at all) and you have IgG antibodies (which, as above, you cannot pinpoint if someone was infected during the outbreak or years before). The two that had fever ... fever is common, especially in areas where there are other endemic diseases like Malaria. Actually, there are some districts that ended up treating for Malaria before assuming ebola towards the end.

All this to say that for some of you panicking about asymptomatic cases, please just keep in mind that you would need a whole lot more evidence to link the detection of IgG antibodies to assuming actual transmission of the disease from those 14 in this current outbreak.

As for my question: Dr. Gene, When you cross checked records with DERC, were you able to have a look at the notes from the quarantine/ surveillance officers? I guess it depends on the district and period, but officers were taking records and doing daily temp monitoring at quarantine houses and just wonder whether that could be used to triangulate on any symptoms, rather than trying to solely rely on people who may want to avoid stigma or where there is recall bias.

petitefleur12

The retrospective symptom interviews were a limitation of the study. The DERC records did not include notes on symptoms in quarantined individuals; however, I was the clinical lead for Partners In Health's Ebola response in that district at the time, lived 10 km from that particular village, and attended the nightly DERC meetings, so I have a reasonable sense of how effective surveillance was at the time. As we have been expanding the study, we're realizing there are many more undocumented survivors (and minimally symptomatic infections) in less "well-surveilled" villages.

So if they were minimally symptomatic, is there any way to isolate the specific strain and use it as a vaccine, or would that be a terrible idea?Or is this the exact same strain that just happens to have different effects on different people?

jaleel131

There is a vaccine that was 100% efficacious in a recently published ring vaccination trial http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)32621-6/fulltext Whether it will be effective as a scaled-up routine vaccination remains to be determined.

So, given that transmission in these individuals is still being studied, what are your thoughts on medical personnel who work with Ebola patients, but insist it is impossible for them to have the virus because they are asymptomatic. I'm thinking of Kaci Hickox: A quote from her op-ed: "No one should be victimized by being placed in a quarantine if they do not have any symptoms of Ebola, because asymptomatic people are not a health risk."
https://www.theguardian.com/commentisfree/2014/nov/17/stop-calling-me-ebola-nurse-kaci-hickox

alewifery

I think the current CDC guidelines for observation and quarantine are adequate. I also think that early in the outbreak, it would have been reasonable to allow the American public and its elected officials

some time to sift through our (still) incomplete knowledge about Ebola virus.

If possible, Dr. Gene, could you also address if in current literature there is evidence of transmission from asymptomatic cases? Apart from those involving recovered, known cases i.e. via sexual transmission.

petitefleur12

See https://academic.oup.com/cid/article-abstract/doi/10.1093/cid/ciw793/2666520/Ebola-Virus-Persistence-in-Breast-Milk-After-No for the only report I know of.

In your line of work did you ever come in to direct contact with the virus?

ProffesorFinesser

While working as a clinician in Ebola Treatment Units, I'd tried to be as fastidious as possible with my personal protective equipment (PPE). I myself am seronegative which suggests I was not infected.

So would this mean that the deadly cases of disease were due to the virus straying from "normal" pathogenesis? I do recall reading that the paralytic effects of polio were due to the disease "accidentally" reaching the CNS and only occurred in 1/100 cases of infection.

lina-beana

I don't think strain variation played a part in whether one is symptomatic or not, but rather host defenses.

I'd read about ebola well before the most recent outbreak, and one thing that struck me is its infection rate is much lower than I would expect, given how often in the early stages you had massive hemmoraging while doctors and nurses were elbows deep in blood trying to save teh patient, unaware of the exposure; not to mention the Northern VA outbreak that wiped out lab monkeys but only gave the humans sharing the holding space minor flu symptoms. I became suspicious that some percentage of humans have developed a genetic resistance to the virus (I understand that many europeans have a resistance to the Plague as those susceptible were wiped out in the middle ages); has there been any investigation into this possibility?

temp1876

There's no evidence of evolved resistance to Ebola virus. I think the infection rate is lower than one would expect because individuals must come into direct contact with the bodily fluids of a sick individual, which means infection will cluster by household (or health facility), with more limited transmission between households.

Any advice for someone thinking about going into your field/ pathology?

TheFallen__

Read Paul Farmer's books, get involved locally or abroad in addressing health inequities.

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