Science AMA Series: We're a group of scientists who use genomic sequencing technology to understand how viruses spread. Ask Us Anything!

Zika$_{G}enome^{1}andr/ScienceAMAs^{1}$

[1]Affiliation not available

April 17, 2023

Abstract

EDIT: Thank you everybody for all the GREAT questions! Some of us will have to go do some sciencing, but we'll keep checking in and continue to answer your questions - please keep 'em coming! Hi Reddit, We are a group of scientists who use genomic sequencing technology to study the spread of viruses during outbreaks. Most recently we've been exploring the spread of Zika virus across the Americas. In order to understand how the virus has spread, we sequenced the virus genome from samples obtained from infected individuals, as well as from the mosquitoes that transmit the virus. Analysis of the genomic data allowed us to show how Zika virus spread across South America and Central America, into the Caribbean, and from there into Florida in the United States. Our papers on Zika virus can be read for free here: Zika virus evolution and spread in the Americas by Metsky et al. Establishment and cryptic transmission of Zika virus in Brazil and the Americas by Faria et al. Genomic epidemiology reveals multiple introductions of Zika virus into the United States by Grubaugh et al. The following scientists will be participating in this AMA: Kristian Andersen, PhD, an Assistant Professor at The Scripps Research Institute and Director of Infectious Disease Genomics at the Scripps Translational Science Institute. Kristian has a background in host-pathogen evolution and immunology. Nathan Grubaugh, PhD, a Research Associate at The Scripps Research Institute. Nathan is a postdoc in the Andersen Laboratory and is an expert on mosquito-borne viruses, such as Zika, chikungunya, and West Nile. Hayden Metsky, a member of the Sabeti Lab at the Broad Institute of MIT and Harvard. Hayden is a graduate student in computer science at MIT and is interested in computational biology, machine learning, and their applications in viral genomics. Shirlee Wohl, a member of the Sabeti Lab at the Broad Institute of MIT and Harvard. Shirlee is a graduate student in Systems Biology at Harvard and is interested in using genomic approaches to understand viral disease transmission. Bronwyn MacInnis, PhD, is Associate Director of Malaria and Viral Genomics at the Broad Institute of MIT and Harvard, with experience in combining genomic technologies and epidemiology to understand and control infectious diseases affecting global health. Jason Ladner, PhD, a member of the Center for Genome Sciences at USAMRIID. Jason is an evolutionary biologist who uses genetic data to understand the emergence and spread of pathogens. Nick Loman, PhD, is a Professor of Microbial Genomics and Bioinformatics at the University of Birmingham. His research focuses on the use of sequencing for the diagnosis and surveillance of infectious diseases. He has applied portable nanopore sequencing in field conditions in Guinea during the Ebola epidemic and in a mobile laboratory that travelled through Brazil to investigate Zika. Steve Schaffner, PhD, a senior staff scientist at the Broad Institute of MIT and Harvard. He is an ex-physicist who applies computational tools to study the population genetics of humans and their pathogens. Nathan Yozwiak, PhD, is Associate Director of Viral Genomics at the Broad Institute of MIT and Harvard with experience in using genomic technologies to detect and understand viruses and expanding these capabilities to regions at risk of serious outbreaks. We'll be back at 1pm EST/ 10am PST to answer your questions. Ask us about genetics, genomics, virus biology, outbreak surveillance - ask us anything!

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REDDIT

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ZIKA_GENOME R/SCIENCE

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The following scientists will be participating in this AMA:

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Nathan Grubaugh, PhD, a Research Associate at The Scripps Research Institute. Nathan is a postdoc in the Andersen Laboratory and is an expert on mosquito-borne viruses, such as Zika, chikungunya, and West Nile.

Hayden Metsky, a member of the Sabeti Lab at the Broad Institute of MIT and Harvard. Hayden is a graduate student in computer science at MIT and is interested in computational biology, machine learning, and their applications in viral genomics.

Shirlee Wohl, a member of the Sabeti Lab at the Broad Institute of MIT and Harvard. Shirlee is a graduate student in Systems Biology at Harvard and is interested in using genomic approaches to understand viral disease transmission.

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READ REVIEWS

WRITE A REVIEW

CORRESPONDENCE:

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Florida resident here and I teach Microbiology and Pathophysiology. We recently hosted a mosquito-borne illness seminar on my campus.

I'm curious regarding the mutations and the resulting pathogenicity of ZIKV. From what I have seen, the FL cases of ZIKV were relatively mild compared to South American countries for example. Aside from surface glycoproteins and the 3' UTR, do we have a sense of the phenotypical changes in the virus and how it may affect pathogenicity?

Second, how does the mutation rate in ZIKV compare to other viruses such as Influenza?

Thanks for doing this, I will be using this in class this term!

Yurastupidbitch

Considering the variances in reporting and the time it takes before birth defects appear, there is not yet enough evidence to support that disease from Zika infections are more severe in one region compared to another. So far, we do not know of any Zika virus mutations that occurred in the Americas that directly alter pathogenicity. Our new genetic dataset, however, now allows us to identify mutations that are specific to different regions and directly test their fitness in the lab. That is exactly what we are planning on doing and we'll make those results available as soon as we can. My guess is, however, that mutations are not responsible for the severe disease observed in the Americas. - Nathan

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Yurastupidbitch

In answer to your 2nd question, from our genomic surveillance work, we can not directly measure the mutation rate, which is the rate at which the viral polymerase incorporates errors when replicating the viral genome. Instead, we measure the rate at which changes become fixed in a population, or the substitution rate. The substitution rate is related to the mutation rate, but is also influenced by other factors including natural selection. The substitution rate observed for Zika virus (~0.001 substitutions per site per year) is very consistent with substitution rates for other viruses with RNA genomes (typically 0.01-0.0001 substitutions per site per year). -JL

How much variance did you notice in the DNA sequence between carriers, or even within the same carrier of the virus? Due to the rapid multiplication even within the same host I would imagine the virus would look very different from day to day.

Also, given the scale of the variance (be it large or very minimal), does this make it easier to treat/prevent Zika?

hnglmkrnglbrry

The amount of variance observed in the DNA sequence depended on exactly what we were

comparing. There was enough variance in the sequence that we could relatively easily determine the country or region in which the person carrying the virus got infected (e.g. a person infected in Colombia might have a Zika virus sequence with on the order of ~100 sites differing from someone infected in Honduras). Within a country we observed less variation in the sequence, and within a carrier we observed even less.

We had a few opportunities to sequence the virus on different days from the same carrier, and we didn't see much variation between days. Even though the virus is mutating rapidly, most of the mutations disappear (i.e. aren't found in subsequent virus particles) because they don't help the virus survive.

Viruses with a lot of variance (like influenza) can be difficult to treat or create vaccines for because they change so rapidly that it's hard to develop a treatment that will be successful for all the different versions of the virus. We don't currently have treatments designed specifically for Zika, but the amount of variance in the virus sequence shouldn't have a big effect on our ability to develop such a treatment. -SW

How do viruses with multiple hosts evolve? Specifically what are the evolutionary constraints of Zika in humans and mosquitos. Are there ways to exploit these constrains? In other words, can you promote a non-infectious human zika virus to persist over the type that is circulating right now in mosquitos. Thanks for the Ama!

ancyk

Viruses are under very different selection pressures during infection of mosquito vectors and vertebrate hosts (e.g. mammals and birds), see:http://www.sciencedirect.com/science/article/pii/S1879625716301365. In general, the virus diversifies in mosquitoes, generating lots of genetic variations that decrease the fitness of the virus, see: http://www.sciencedirect.com/science/article/pii/S1931312816300944. During transmission to hosts, like humans, the virus must be purified of all of the deleterious mutations picked up in the mosquito. Therefore, mosquito-borne viruses cycle through periods of genetic diversification and purifying selection. Could this be manipulated? Good question. There are examples of mosquito-borne viruses that lost their ability to infect vertebrates and now only infect mosquitoes, and we could use these as vaccines: http://www.nature.com/nm/journal/v23/n2/full/nm.4253.html. - Nathan

How much can you find out by looking at the DNA of a virus? For example, does it tell you how dangerous it is our how infectious it is?

jgmdb

A lot! One of the most important things we can do, and central to the Zika studies that we did, is compare the genomes across patients. We start to see that genomes from patients in one geographic region look very similar to each other, and all of these look different from the genomes in another region. This is because the genomes accumulate mutations over time as they spread. For example, the genomes in country A may have some mutation, and the genomes in country B might have that mutation and also more mutations; that could suggest that the virus traveled from A to B. Furthermore, by estimating how fast the mutations are accumulating and considering how many are in the genomes in different regions, we can estimate when the virus was introduced into those different regions. We made those estimates for Zika virus in regions throughout the Americas.

Knowing the genomes of the virus in different places over time can also tell us if there are mutations coming up that might impact the function of the virus -- e.g., as you suggested, by making it more

dangerous or infectious. Often these kinds of mutations occur in particular genes of the virus. For example, a team found a mutation in Ebola that made the virus infect human cells more efficiently, and that mutation dominated the epidemic in West Africa. Another team found a mutation in Zika that increases Zika's ability to infect mosquitos. Having the genetic code of the virus, especially seeing how it's changing over time, is critical for these kinds of experiments.

-HM

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jgmdb

The virus' genome does not directly tell you how dangerous or infectious it is. You can use the information to compare to other viruses to formulate hypotheses, but ultimately this needs to be tested in the lab using cells and animal models. - Nathan

From an evolutionary stand point, what does the virus gain from causing such a severe effect on foetal brain development? Also, are there any advantageous genetic variants in the human population that prevents some of the effects of the Zika virus?

thedwarf30

I doubt the severe fetal effects provide an evolutionary advantage to the virus. The fetus represents a dead-end for the virus, since any virus replicating there is unlikely to be transmitted further. More likely, fetal neurons are just unfortunately vulnerable to infection and damage from Zika. It's too early to tell whether particular human genetic variants affect how likely you are to become infected or to suffer different effects. Answering that question would (or will) require a large study, comparing the genetics of people with and without symptoms. -SS

At one point early in the period of the Brazilian outbreak, I had heard about the deaths of some monkeys that were unexplained. But then I never heard any more about those.

Were there cases of other primates being affected by Zika in the South American outbreaks? Are they a reservoir?

mem_somerville

It is pretty clear that Zika virus can indeed infect non-human primates, however, it is currently unclear exactly how big a role this play for starting human epidemics. During epidemics like what we're observing in the Americas, infections are sustained via human-mosquito infection cycles, and non-human primates likely play a very minor - if any - role in sustaining the epidemic. As for the South American outbreak, while there were some papers that observed "unexplained" events in monkeys early on, there's currently no data to suggest that these are linked to the Zika outbreak.

Kristian

Do you have a better idea yet of how Zika gets to a fetus? Is it through the placenta? Through sperm? Is the CDC guidance to avoid all countries w Zika risk if you might become pregnant on the conservative side?

Is there a reliable Zika test yet for contraction?

Booked a 3 week honeymoon in Indonesia, Malaysia, and Bali. Hadn't been planning to use contraception (husband is Catholic). Can't get a feel for the actual risk of contracting Zika and then how risky it is to an early stage pregnancy (like if I got pregnant on wedding night). Don't want to cancel but fiancé is worried.

emrducks

Once a pregnant woman becomes infected, the virus can likely find its way to the fetus via the bloodstream. This can happen irrespective of the way that the woman was infected - e.g. from an infected mosquito or from sexual transmission via sperm. The CDC guidelines are currently to "Consider avoiding nonessential travel to areas with a CDC Zika travel notice".

Those areas can be found here: https://wwwnc.cdc.gov/travel/page/zika-information

The most up-to-date CDC guidelines can also be found here: https://www.cdc.gov/zika/pregnancy/women-and-their-partners.html

As for the specific countries you mention, Indonesia (including Bali) and Malaysia are not currently on the 'Zika Travel Notices' list, but they are on the 'Other Areas with Zika Risk', so precaution should be taken. My recommendation would be to go talk to your doctor about your specific concerns.

Kristian

Hi! First off I'd like to thank all of you for taking the time to do this AMA. I personally want to study genetics so this interests me greatly. What is the most interesting and or amazing thing you have learned in your field especially in regards to your latest research?

StormLord_654

You're very welcome, it is always fun to talk about science :) And I encourage you to pursue your interest in genetics, there's still so much to discover!

One interesting thing we learned was just how little Zika virus there typically is in a patient, compared to other viral infections, even though it can cause such devastating effects. In addition to being interesting, this posed a significant challenge for our work, since we were trying to sequence "a needle in a haystack", meaning very small amounts of Zika virus compared to human and other DNA in the samples -- Zika was as little as 0.0001% or even less in some cases. This was a big technical challenge but we learned a lot about how to sequence and analyze low titer viruses, which will be very useful for Zika or other low titer virus outbreaks in the future.

Another interesting thing we learned is that our approach of genome sequencing showed that Zika was circulating in many regions long before it was detected by local public health systems. While the fact that Zika was present in an area before it turned up clinically isn't necessarily surprising, it is exciting that genome sequencing has the potential to help detect viral threats at a much earlier stage in the future. We look forward to someday using genomic surveillance to help prevent an outbreak from ever occurring! - BM

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StormLord_654

Not exactly the answer to your question but something that is very exciting in genetics research particularly for infectious diseases is our new found ability to sequence the genomes hundreds of related viruses or bacteria with next-generation approaches. This means we can see evolution happening virtually in real time with fast evolving viruses like Zika and Ebola. This both has practical implications for epidemiology, and is also incredibly exciting for understanding forces of selection acting on the genome.

NJL

Are there any new emerging viruses we should worry about?

How do you think we can help stop the anti vaxx movement?

Hausofkristin

There are many emerging viruses (and bacteria) that have potential to cause us harm. There's a good chart over here if you want to scare yourself: https://www.nap.edu/read/18975/chapter/2#4 It's hard to know which ones to worry about in advance, as we are very bad at predicting which will 'break out'. We had very little idea that Zika would be one to worry about just a few years ago. One way we can buy a little more time is to improve our global response system through much more untargeted diagnostic surveillance (perhaps using sequencing). We need a global system that can act as sentinel so we can pick up emerging threats more quickly and deal with them.

NJL

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Hausofkristin

Vaccines represent one of the true victories of the human scientific endeavor. In a way though, they're a victim of their own success, and we now too often face collective amnesia of the dangers of infectious diseases, especially childhood illnesses. It's important to remember that all parents want what's best for their children, and maintaining rates of vaccination that confer community benefits requires continued vaccine education efforts. But that's not enough. Scientists must remember that using data will only take us so far, and often the most resonating arguments we can make for vaccines are through personal physician recommendations, and the importance of storytelling to share personal experiences. For the most part, people value their doctor's recommendations and what their peers experience. If you get your child vaccinated, spread the word!

In terms of what emerging virus keeps me up at night - a highly contagious avian influenza strain. Highly lethal bird flu cases periodically jump into humans, but fortunately for now they do not spread very well. If this changes, we need to be prepared to detect and respond as soon as possible. This risk is on many outbreak researchers radar. -NY

Nice work. A few questions:

1. For Metsky, et al., and Grubaugh et al.: It looks like you used exclusively Illumina sequencing. Is there a reason you did not also try other sequencing methods? Faria, et al. used Nanopore, which seems faster/cheaper/better for long reads that would be useful for assembling whole genomes from sparse input material like clinical samples where the viral titers may be low. Is Nanopore

sequencing too noisy, is the analysis too different, or is the output too low for useful assemblies? Similarly, to Faria et al.: Why did you go with Nanopore sequencing?

2. To all three groups: Is your Zika work ongoing, or if not, what's next? Are you starting to run down some of the functional implications of the variants you observed?

3. What were the greatest challenges in this work? Acquiring the samples quickly enough so they weren't degraded? Import control at the border? Actually sequencing the samples?

4. This was clearly a large, and international, group effort. Do you have any fun stories from the work that you would be willing to share?

5. Have you been able to suggest changes to policy in response to this work for outbreak control (i.e. symptomatic screening at borders, more surveillance at hospitals, etc.), and for everyday people what can we do to help? Should we avoid traveling when we're sick?

6. Not specific to the science, but this is a question for the authors of all three papers: What tools or software did you use to create the figures for your papers, and what is the process like to prepare figures for a prominent journal like Nature? Are the editors picky about formatting, and do they alter what you submit to them like they might edit the text?

sciencequestions2017

Great questions! Here's a partial answer to your first one.

In some ways the choice of sequencing method wasn't the most important decision to be made here. One technical problem all the teams faced early on was that it was very difficult to sequence Zika on any platform. This was due to the fact that clinical samples like blood typically had vanishingly small amounts of Zika virus in them. It would be too laborious to culture each virus in the laboratory so this left us with quite a big problem to solve in order to recover full genome sequences from the samples. The first time we attempted our standard methods we really struggled to get any good results. A breakthrough came over the summer of 2016 when Josh Quick who works in my laboratory spent a lot of time optimising polymerase chain reaction methods in order to coax out even very small amounts of virus. This was really a trial and error process but we eventually came up with something that worked well by focusing on short 'primer' sequences that binded very specifically to the virus and not to host DNA. One lovely result of this project was that it was carried out in the open. We published our protocol on our Zibraproject.org project website and it was picked up by the other teams who also took it and improved it and ported it to other platforms like Illumina. What's great about genome sequencing is that the results can be compared across platforms readily (with a few technical caveats).

Our choice of nanopore sequencing reflected the fact that our project involved a mobile bus trip around Brazil, and we knew that at the end we wanted to have a number of fixed laboratories that would continue the sequencing. We were operating with a reasonable budget from the Medical Research Council and Wellcome Trust in the UK (~$200,000) but we wanted to spend that on reagents and not new equipment!

NJL

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sciencequestions2017

2) Yes, we are starting the test individual Zika virus mutations that we observed during the epidemic. Hopefully we'll have results soon, and we'll post them on our website: http://andersen-lab.com/secrets/ - Nathan

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sciencequestions2017

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can we do to help? Should we avoid traveling when we're sick?

I think we (the international community) missed the boat rather on Zika. One of our major findings was that Zika had been circulating for a long time in Brazil and Americas prior to detection. There was a significant number of cases in 2015 and 2016 and this seems very likely to relate to the high numbers of microcephaly cases in affected areas. It is interesting to consider what will happen in 2017, early indications are that there will be far fewer cases in Brazil, likely due to immunity. What I think it says to me is that we need to get much better at detecting emerging infectious diseases that are circulating in humans and make earlier interventions if warranted. I think the main thing we can do better is mosquito control of Aedes populations, as there is no specific treatment for Zika and it will take a while to develop a vaccine.

NJL

Is it possible to study ancient viral DNA? There were several papers last years about finding DNA of Yersinia pestis in human remains from the Bronze Age to Middle Ages. Is it possible to study viral DNA in the same way?

adalhaidis

This is a really interesting question. As you mention there have been numerous studies of ancient DNA sequencing of bacteria, from Yersinia pestis (the cause of the black death) and other scourges of mankind including Mycobacterium tuberculosis and the leprosy-causing bacterium Mycobacterium leprae. I was involved in a study that sequenced TB from well-preserved mummies from the 18th century. As a general rule, this approach gets harder as the sample gets older, and it also depends a great deal on sample preservation. Recently Michael Worobey and his team successfully sequenced HIV-1 samples from just the 1970s but it was very technically challenging to do (https://www.ncbi.nlm.nih.gov/pubmed/27783600). Despite the samples being stored in the freezer the samples had degraded significantly. The prospect of sequencing RNA viruses that are very ancient may prove difficult. However, if the samples are well preserved for example in permafrost, it may be possible. Some viruses like retroviruses incorporate their genomes into the host genome and therefore it may be possible to sequence fragments from these from ancient DNA. It's a very interesting area - I am currently reading Svante Paabo's book Neanderthal Man: In Search of Lost Genomes and strongly recommend it for those interested in ancient DNA.

NJL

Hi there! I used to work in the Hay lab, where we were trying to build a MEDEA Complex to perpetuate disease resistance genes at higher than Mendilian ratios in *Aedes aegyptai*. So while I've mainly done animal genetics, I've always been interested in virology!

Two questions:

- 1) How long do you give it before Zika evolves the ability to jump to*Aedes albopictus*?
- 2) This is more of a disease prevention question, but I was toying with ideas on how to make a mosquito net more portable. I designed a way to make the net have an adjustable opening and weighted bottom hem, so it can be draped over an umbrella and used for safe travel outside. It got some positive comments when I shared it with the mosquito researches I know, and a patent firm helped me file a patent pro bono. **Here's the design** and the instructions to make one, do you think this could actually work for people in Zika-infested countries?

solinaceae

1) Zika virus can already infect and by transmitted by Ae. albopictus, albeit not very efficiently (as determined in the lab). It could, however, adapt to increase transmission, like chikungunya virus. Predicting if or when this might occur is extremely difficult and likely depends on many virus, mosquito, and environmental factors. 2) Anything that could prevent mosquito bites and people would want to use could be beneficial. However, I cannot directly assess how well your net might work without using the actual product. - Nathan

I am a computer science graduate looking into getting into the field of computational biology. What steps should I take for this route? Any particular course I should look at etc

batmanox

Awesome! People who think well computationally can have a big impact in tackling biological problems, which is part of what makes the work very exciting.

In terms of courses, having a strong foundation in algorithms is critical in the field. In addition, a course in machine learning will be super helpful because it's being applied more and more to problems in biology, with a lot of success (and those same problems can help to motivate advances in machine learning); there are many online courses (e.g., through edX or Coursera) that I hear good things about. A background in statistics can also be very helpful, particularly in interpreting results, and is sometimes left out of CS curricula.

It's also a good idea to have some base in biology if you weren't exposed to that as an undergraduate. I took 7.01 at MIT and enjoyed it a lot. It's available online here. You could also try to keep an eye on recent papers in the field -- bioRxiv is a great resource -- and see if there's any area in particular that excites you, and dive further into the biology of that.

If you're not interested in graduate school or academia, there are many companies (e.g., in biotechnology) and startups (e.g., in personalized medicine) that are doing exciting work and would be hiring CS graduates.

-HM

How common is it for a virus to evolve into a new virus? Such as a virus becoming airborne when before it was not.

hendrixma

For a virus to change the way it is transmitted, e.g. moving from transmission through contact with secretions to airborne is incredibly unlikely. It is worth saying that RNA viruses may evolve quickly, i.e. there are observable changes in genomes over short timescales like weeks and months, but the vast majority of those changes are neutral (the deleterious ones will usually not be passed from generation to generation). Large changes of life cycle are vanishingly unlikely to occur over the timescales we are investigating.

NJL

Hi, thanks for the AMA. Are you able to map geographical movement of the virus using rates or mutation of certain genome loci? In other words, does the virus mutate fast enough for statistically meaningful relationships to be drawn from different sample sequences? Woo geophylogenies!

Rangelus

We do this a little bit in the three papers. For example, in the Grubaugh et al. paper, we showed how the virus moved from the Caribbean to Florida multiple times. For future studies we're hoping that there'll be enough data so we can start doing similar analyses to the ones we and others did for Ebola. E.g. this paper:

Virus genomes reveal factors that spread and sustained the Ebola epidemic
https://www.ncbi.nlm.nih.gov/pubmed/28405027

Kristian

Hi! Pharmacy student here, currently thinking about dedicating my life to research, just a simple question: What interest do the public institutions show on new viruses research? Like every time a new and dangerous virus appears we get a month or so of reports and as soon as the cases begin to decrease, it seems like the disease has leaved forever. Of course it is not the case, but do institutions such as universitys continue investig time and money into their study? Or do they abbandon de idea when the media forgets about the disease?

inigoansa

Once researchers become interested in a virus (or in any scientific question) they tend to stick with it and study it for years. Public health agencies like the CDC also tend to think in the long term about threats. What is sometimes more fickle is funding — the money you need to actually do the research. Public worry about an outbreak can drive governments to respond with funds during a crisis, and those funds can dry up when the crisis passes. For example, during the Zika outbreak, the US government shifted funds intended for Ebola research to address Zika instead. This is unfortunate, since a lot of the research needs to be done after the publicity has died down. Steve S.

I have a daughter going into her sophomore year of high school. She is in all honors classes and her unit on genetics last year changed her perspective on what she wants to do with her life - it's all about genetics! What should she study, and what should she look for in a college? I hope that's not too off topic!

BYs19thwife

It's great that she was exposed to genetics so early, it really is a fascinating field! Not all colleges will have a genetics major, so studying some sort of biology might be the best way to get exposed to more genetics. Genetics comes up in many fields of biology (evolutionary biology, molecular biology, etc.) so she can choose whatever aspect is most exciting to her. Choosing a college in which students are able to and encouraged to do research might be something to look for, but that research doesn't have to be specific to genetics. Any sort of biology-related research experience will be very useful if your daughter wants to continue on in the field. Finally, more and more of genetics research is computational or requires some computational skills -- taking computer science and statistics classes in college will definitely give your daughter a leg up! -SW

When I was in high school, I did independent genomics research into algorithm prediction for viral evolution and spread. The central topic I was trying to address was how to determine family trees of viruses when they mutate so fast. My work was eventually accepted by the Intel science competition in 2010. It was titled High-Variance Comparative Genomic Methodology: A Bacteriophage Case Study.

In my work, instead of going from a purely traditional genomics comparison method, I took into account the conservation of individual genes but accepted that their positioning was mobile. My algorithm

categorized genes by function into Phams using a hook into BLAST and then measured distance between the genes to determine as a surrogate the number of times it had been shuffled. Based on these distances, I generated a subscore of how related different bacteriophages were, and used this value to weight my normal DNA-based genomic alignments and cluster analysis. I also made a further adjustment using silent mutations as a further measure of genetic distance, comparing both top level DNA sequence against translated sequence. In addition to this, I made a prediction algorithm based on the geographical coordinates of where the viruses were found to try and match distance of spread to genetic age and predict future genetic drifts.

I have since left bioinformatics to pursue wet-lab work. I have never received much feedback about my method in the last 7 years. To my knowledge, nobody was using something like that at the time. My question is: is there a similar modern approach and if it is still applicable. How are people addressing the problem that viruses have such a fast turnover and evolution rate that most genomics methods for larger organisms do not work correctly? Is such a method usable for the Zika virus?

zhandragon

Hi zhandragon, sounds like a cool project! I'm not aware of any specific phylogenetic approaches that utilize genomic rearrangements as markers of genealogy in the way you describe. This type of approach could be useful for studying distantly related groups of viruses. However, within viral families, we typically see very high conservation of gene order. –JL

Hi , thanks for doing AMA on this topic

My question is

Zika virus is transmitted by Aedes mosquitoes which is also a vector for yellow fever viruses and Dengue fever viruses. Is there a possibility that sometimes two viruses recombine their genomic material to become a deadly virus?

I ask this question because major host of Zika viruses are primarily monkeys, not humans. Maybe the co existence of a virus that infects human(yellow fever virus) and Zika virus over a period of time made humans susceptible to Zika virus?

Thanks

gaprmaka

Genetic recombination does occur with flaviviruses (genus that includes yellow fever, Zika, West Nile, and dengue viruses). Recombination can help a virus with a deleterious mutation, one that reduces fitness, by switching part of its genome to remove the mutation. Usually it occurs with members of a species, i.e. dengue virus with another dengue virus. It is possible for 2 different viruses to recombine, but the outcome will not likely be a "deadly super virus". There must be an advantage for the virus to become deadlier, and often there is not. - Nathan

During your genetic analysis, did you find anything to support the idea that the severity of South American infections (with regards to microcephaly especially) could have been caused by co-infection with another member of the flavivirus family?

Cross reactivity for immunoassays between most of the flavi constituents is high, so I was curious if you were seeing similar genomic overlap or anything else like that. Considering you did a QIAmp extraction and then created a cDNA library, I figured you might have picked up one or two anomalous samples that didn't totally fit the ZIKV genomic profile after analysis.

Background: I'm also a Zika researcher, though my focus is Zika diagnostics.

jquiz1852

This is a popular hypothesis. Our study did not specifically set out to test it as we were focused on Zika infected patients. Interactions with other related arboviruses is conceivable, particularly with dengue which is very closely genetically related to Zika. At the moment the jury is out as to the importance of previous arbrovirus infection on Zika pathogenesis (through, e.g. antibody-dependent enhancement). This is an active field of research. We think there is a role for more genomic epidemiology and serology surveys to help unpick this idea.

NJL

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jquiz1852

The Metsky et al. study used metagenomic sequencing to look for similarity between sequencing results and dengue and chikungunya virus sequences, among other viruses. We did not find evidence for coinfection of Zika virus with any other flavivirus, though we did find that one patient who came into the clinic to be tested for Zika virus actually was infected by dengue (both the sequencing results and initial qPCR assays showed this).

How do you think CRISPR will effect us, the human race, in 50-100 years from now?

dwarfbear

It's going to have a profound effect. Personally I have no idea what it's going to look like.

NJL

Hi I'm in year 10 currently studying this line of work My question is:

What do you hope to achieve by doing this? (what is your overall goal)

FreshPomp

My personal view: infectious diseases cause severe misery and mortality across the globe. A single case of a new emerging pathogen (perhaps from an animal reservoir) can rapidly spread and turn into an outbreak. Next it can become an epidemic (across multiple countries). Without being controlled further you can have a pandemic, and some diseases can even become endemic in human populations. A good example fitting this progression is HIV. What if we could have stopped HIV at the first case? Or when it was confined to a small number of people.

Diagnostic and surveillance methods (we think - using genome sequencing) is what gets me excited. Such techniques combined with a bunch of other tools including treatments, vaccinations, traditional epidemiology and infection control - could work in concert to help break chains like this in future. So this is what I hope to be able to achieve with work like this.

NJL

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Viruses spread in a few different ways, and the key to understanding how they spread is understanding that viruses need a "host" to survive -- they only can replicate inside of another plant or animal and cannot survive for very long outside of their host (viruses usually are specific about what host(s) they can infect and also what part of the host they can infect, but that's a story for another time).

In humans, viruses are typically spread in 3 ways: direct/indirect contact, through the air, or via a vector. Direct contact means that a bodily fluid in which the virus lives (like blood or saliva) directly contacts bodily fluid of another person. A great example of this is Epstein-Barr virus, which causes mono (aka "the kissing disease"): when two people kiss, virus inside the saliva of one person can move to the saliva of another person, thus infecting them and spreading the virus.

Some viruses are spread through the air. These viruses are usually very tiny and have adapted to be able to survive outside a host for several hours, so they can be carried around in air currents until they are inhaled or ingested by another person. Luckily, not too many viruses can be spread this way, since this often leads to rapid spread.

Finally, some viruses are spread by another animal called a vector. This is often a mosquito or tick that can carry the virus but isn't affected by it. The mosquito, for example, picks up the virus when biting a human, and then the virus is passed on to the next human it bites, thus transmitting the virus. -SW

Considering only 20% of cases are symptomatic, is there something present in the DNA that controls the expression of the virus. (I.e different strains)

CrunchitizeMeCaptn

Whether or not a person has symptoms following Zika virus infection likely has more to do with the host's immune response than the virus. Certainly different virus strains could generate more symptomatic cases, but we currently do not have any evidence to support that claim. - Nathan

Recent graduate in microbiology here--can I have a job? ;)

My actual question is: in my experience working with SINV, another mosquito-borne virus, mammalian cells will display significant morphology changes once infected while mosquito cells would remain relatively healthy. Is this true for ZIKV as well? Do mosquitos carrying the disease display any cytopathic effect or other indication that they are infected? And do other mammalian models display ZIKV infection in the same way that humans do?

Finally, what methods for preserving RNA integrity would you recommend for people collecting clinical samples?

durcula

In my experience working with mosquito-borne viruses, like West Nile, chikungunya, dengue, and Zika, yes - they primarily cause cytopathic effects in mammalian cells (like primate Vero cells), but not mosquito cells (like C6/36). Mosquito infection is chronic and usually does little harm to the vector (the degree of harm is debatable).

There are mouse Zika models, but for mice to become infected with high enough titers for research, their immune systems usually needs to be compromised. The net result is often a lethal model, which is useful but does not represent human infection. The best models are non-human primates, but they are obviously difficult to work with and may not 100% reflect human infection. - Nathan

HS bio teacher here. I still teach the molecular clock hypothesis using HIV strains as an example. How well has this held up over time? Any updates I should include? Thanks.

FUZZY_BUNNY

Hi FUZZY_BUNNY, many viruses do indeed evolve at a relatively consistent rate over time (at least over certain time frames), as predicted by a molecular clock. And, in fact, it is this temporal signal that we used to date the introduction of Zika virus to Florida.

However, viruses don't always evolve according to a molecular clock. Rates of replication can change, for example, depending on the host species or tissue type in which the virus is replicating. Some viruses can also enter into latent phases, in which the virus is not actively replicating. Changes in the rate of viral replication will result in changes in the rate of evolution and therefore deviations from the molecular clock. -JL

What is the rate of mutation of such viruses? At what time do you say it has evolved to a new organism completely?

jgmdb

Viruses are extremely diverse, and so there's also a large range across viruses in how fast we see mutations accumulate. Roughly, we might see anywhere from about 10^{-6} to 10^{-2} substitutions per site per year. That gives the number of mutations that we see accumulating at each site in the genome over the course of each year (so you could multiply by the length of the virus's genome to determine how many there are). At a high-level, RNA viruses generally mutate more quickly than DNA viruses. Influenza viruses have some of the fastest rates (poliovirus is also exceptionally fast). For Zika, we estimated that within this outbreak the rate is about $1x10^{-3.}$

It's difficult to say when they've evolved to a new organism because viruses are very different than, say, mammals. But it does bring up the interesting question of how to classify viruses. It's complicated because of their diversity; right now, there might be many strains of the same species of virus, or different species of viruses that are closely related. Furthermore, there are many novel viruses being discovered all the time (this paper found 1,445 new ones) and it's not obvious to determine how to classify these new ones. It's an open debate.

-HM

Do viruses communicate with each other to "share" properties (sorry, not a scientist; I know bacteria share properties/capabilites/whateverthescientificwordforitis)? Do they "share" with bacteria?

preachers_kid

Hi preachers_kid, bacteria generally have much larger and more structurally flexible genomes than viruses. So, many bacteria will regularly acquire new genetic material from other bacteria. This is one way in which they can "communicate". Viruses typically have much smaller and less structurally flexible genomes, so it is unusual for them to acquire completely new genetic material. However, if two viruses coinfect the same cell, it is possible for the viruses to recombine to create hybrid progeny viruses. This is common, for example, in the virus that causes flu. -JL

How dependant in your research upon other (such as epidemiological) information? For example, how useful is genomic data from patients if you are unfamiliar with their medical record and information surrounding their likely time of infection? Essentially, how useful is viral genomic data on its own?

NippPop

Our research isn't dependent on additional information, though having detailed epidemiological information and patient records definitely helps us better understand viruses and how they are spread! On its own, viral genomic data can help us identify key mutations and develop hypotheses about viral spread. Knowing basic information, such as the country or region where the patient got infected and the approximate date of infection, greatly increases the value of this data. With this basic epidemiological information, we can now identify what the virus looked like in a particular time and place. For example, knowing the difference between Zika virus found in Honduras and Colombia could help us identify where a patient was most likely infected. And knowing the dates of each sample can help us determine how fast mutations are occurring. In the case of these Zika virus studies, in many cases we did not have detailed medical records available for patients, and were still able to understand spread of the disease on a large scale. Having these detailed records would allow us to answer more specific questions related to how individuals respond to Zika virus infection, how exactly they got sick and from whom, etc. -SW

Can you explain the cluster of points in the graph shown?

Viruses mutate really quickly, among other things that make it very difficult to understand viral evolution. What assumptions/measures were used to allow making a phylogenetic tree?

What kind of genes are important in viral evolution? That is, what parts of the genome do you look at specifically to make your conclusions, and what biological function do they serve for the virus?

How are ss/ds RNA/DNA viruses related? That is, what parts of their genome/proteome/etc. would you specifically look at in order to build a phylogenetic tree from these?

How well can we predict viral evolution? How would we best improve vaccine effectiveness? Also, do you think we could ever prevent a global pandemic by administering a preemptively engineered vaccine?

Thanks!

hikariwomotomeru

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What kind of genes are important in viral evolution? That is, what parts of the genome do you look at specifically to make your conclusions, and what biological function do they serve for the virus?

Hi hikariwomotomeru, viruses do tend to evolve quite quickly, relative to their hosts. However, this is actually a benefit for tracking the spread of viruses over short time frames because these mutations

provide high resolution markers of ancestry.

The Zika virus genome is relatively small (~11 kb) and we utilized nearly the entire genome for our analysis because mutations anywhere in the genome can be useful for reconstructing the viral family tree, or genealogy. However, different regions of viral genome tend to evolve at different rates due to differences in selection pressures. The surface proteins, for example, tend to evolve more quickly because they are often the targets of the host immune system.

What's your favorite virus? I remember being totally blown away learning about some of the amazing things they do like overlapping genes on the sense and anti-sense strands and ribosomal frameshifts.

Notasurgeon

I'm a bit biased, but one of the most intriguing viruses to me is Guaico culex virus. Not only does this virus have overlapping genes and utilize ribosomal frameshifting, but each of its genome segments are separately packaged into viral particles and one of the segments appears to be optional, at least within certain contexts. -JL

Is there any remote possibility of an ancestor's memories being passed down to their descendants through their DNA? Even if they're naturally inaccessible to the bearer of those genes.

Xangr8

An interesting theory but sadly I don't think there's any evidence to support this idea!

NJL

Has there been any developments in your community regarding the advent of CRISPR?

Could genetic alterations of known viruses be possible? I know viruses don't function genetically like organisms, but is there any way to use this advantageously?

ljjpaulsen

Recently there was an awesome paper in Science based on CRISPR in which the authors developed a platform, called SHERLOCK, for detecting and monitoring nucleic acid. A graduate student and post-doc in our lab, Catherine and Cameron, helped in its development and are advancing it. It has lots of applications in infectious diseases, and in viral outbreaks in particular. A lot of the testing that has been done and is ongoing is on clinical Zika virus samples. The platform can be used to detect viruses by fluorescing when there's cleavage with a target (like a Zika virus genome). By using guides that incorporate particular mutations of the virus, it can be used to determine whether a sample has a particular strain of a virus. And finally, it has applications in therapy by cutting up (destroying) a virus genome that we're targeting. It provides a new path forward in diagnostics and surveillance of viral infections. -HM