Epidemiology and Disease Outbreak

Nicole C. Close

October 30, 2014

Nicole C. Close, Ph.D., Class of 1992, is founder and president of EmpiriStat, Inc., a clinical research organization specializing in biostatistics for regulated clinical trials.

Epidemiology — we just don't get much press until there is some sort of outbreak that we are all talking about. And now we are the important people again. We're usually behind the scene doing our day-to-day activities but this again is our time.

FINDING YOUR PASSION IN EPIDEMIOLOGY

Let me say a few words about epidemiology and how I got into it. That started here at Juniata College. I was a biology and political science Program of Emphasis (or major), and for biology I took a number of different courses here. I studied ecology, and I went to the Duke Marine Lab and did hands-on marine biology for one of the trips with Dr. Bob Fisher. I explored different areas. I had the mindset that I wanted to be an athletic trainer for the Pittsburgh Steelers, and then I kind of realized that that wasn't likely to happen. I also took a biometry class, which hadn't been offered before and I really liked it. Then we had a guest speaker come in to talk about epidemiology and I was like, "I think it's really cool." It is important when you have guest speakers to take advantage of the opportunity and go, because that could spark an interest, and that is what it was for me. I was like, "This is cool, epidemiologists are like spies." I saw that they do some neat things, and I could be a spy, and I could handle what they are doing.

Unfortunately we didn't have epidemiology at Juniata so I thought, where am I going to get this experience? How am I going to know if I really like epidemiology, whether it is really my passion and could be my career? I reached out to see if I could do an internship or an externship and get credit here at school. I went to the Pennsylvania Department of Health in Harrisburg — very naïve as a junior— called a person and said, "I am at Juniata College and I would like to learn about epidemiology and I would work for you for free." So I thought free would get me through the door. I was very persistent, and I got an internship with the Department of Health as an acute infectious disease epidemiology intern.

They were nice to me, probably because I called them every day for a while, but I was able to go there on Tuesdays and Thursdays during the semester. The head of the infectious communicable diseases branch handed me an epidemiology book and said, "Read this because it is what you are going to be working on." I knew nothing, and he was a great mentor after I read the book. I worked on their

Morbidity and Mortality Weekly Reports, or MMWR, for the Department of Health. I worked on a case of rabies and I was actually assigned later in the semester to be able to work partly with the federal Centers for Disease Control and Prevention, or CDC. There was an infectious disease outbreak on one of the cruise ships and whenever anybody got off the cruise ship they dispersed to wherever they came from. We had some Pennsylvania residents who came off that particular cruise ship and we needed to do some tracking of where those people lived and if they still had or ever had any of the symptoms of disease and so forth. We had a CDC representative come up from Atlanta, Georgia that assisted in the investigation, who I was able to get some hands-on experience with there. They let me do everything. It was where and when I decided that graduate school in this field was in my future.

BUILDING YOUR FOUNDATION

When I left Juniata I went to Case Western Reserve University and earned a masters degree in epidemiology and biostatistics. Mostly at that time I did a lot of chronic disease work. I worked on case control studies, taking a look at different types of chronic diseases, but I was not able to get back into infectious diseases until I went to work for the U.S. Army at Fort Detrick, Maryland. I am going to talk further about my experience there.

When we talk about epidemiology, there are a lot of definitions. You can break down the word into its meaning, and you can also say epidemiology is the study of disease, and the distribution of disease in the population, but I like this one from one of the epidemiology books. It said that it is a quantitative discipline that builds on a working knowledge of probability, statistics, and sound research methods.[1] And I like that because epidemiology is multi-disciplined in what you have to understand and know. You have to know about probability. You have to be able to manipulate the data and understand how to manipulate the data that you do collect. You also have to have good, sound research methods when you work in epidemiology.

The second part of the definition says that it's a method of causal reasoning based on developing and testing hypotheses pertaining to the occurrence and prevention of morbidity and mortality. This part is interesting because when we think about traditional research design or clinical trials or testing a new drug, we start with a primary hypothesis. That hypothesis is set in stone: this is what we collect the data for, and this is what we test in the end. One of the important things about epidemiology is that first we're developing and testing. Sometimes through that developing and testing we learn new things, and we have to develop and test again as we gather the data. That makes epidemiology different from clinical research. And that's an important part. I like the thinking involved in the developing part, and we're going to talk about that a little bit more.

Lastly it's a tool for public action: to promote and protect the public's health based on science, based on that causal reasoning — and I love this part because people tend to forget about this— a dose of practical common sense. If you're following the media regarding Ebola right now, do you think that that last part, a dose of practical common sense, is sometimes left out?

Those three parts of that definition really talk about that area of epidemiology and why I particularly love it. I like that you're able to use a lot of different skill sets when you're working in the field. When I talk about epidemiology, there are different areas of epidemiology that you can go into and you'll see, especially when you go into grad school, there are different specialty tracks. Most commonly, when people think of epidemiology they think of public health and a public health track. Epidemiology could be part of it, or it may not be part of it.

DEVELOPING YOUR SKILLS

Epidemiology, then, can mean a number of things. It could be applied epidemiology; it could be the monitoring of reports of communicable diseases in the community. That is what we did at the Department of Health. We monitored diseases in the community: how often they're occurring, and taking a look at the distribution of disease. It could be a study where we're looking at a particular dietary component and how it influences your risk of developing cancer; that could be a different area. It could be the effectiveness of a cholesterol awareness program that you implement throughout the community through a quasi-experimental design. That's applied epidemiology. We could also look at historical trends and current data to project future public health resource needs; that's another type of applied epidemiology. We can even conduct clinical trials randomizing entire communities into different strategies for risk reduction.

I worked on a large program in Africa for male circumcision. For a lot of African communities, male circumcision is just not part of the culture. We know that male circumcision reduces the rate of HIV/AIDS transmission. What we did in this particular epidemiological study is that we had a mobile male circumcision van, and we would go to a particular community where we had we talked to the elders already. We got cultural support for being able to implement this community health program of male circumcision and implemented the program there. Then we would take the mobile van to a different community where we did not perhaps get as much support for the circumcision program but they really wanted some STD education, so that community then received the STD communication and educational messages and components from that.

When we think about those disciplines that I've mentioned you'll see epidemiology is a track of its own. You can also pursue environmental and occupational health. There's also veterinary public

health, public policy and management, and other different components. Tonight I'm focusing on my area, which is epidemiology and biostatistics.

Before many of you were born, there was a big nuclear accident at Chernobyl in the former Soviet Union. This is one of the major epidemiological cluster of cases that could be occupational or environmental hazards that has been followed since this accident, especially for thyroid cancer and leukemia. The richest epidemiological data come out of, unfortunately, this particular incident. These are the types of things that could be environmental or occupational things that we hear about for epidemiological studies.

Another classic epidemiological case is the radium girls. One company manufactured radium dials for watches. When you're putting the watches together you need really small hands so they hired younger females to be able to put these watches together with the different components. To be able to actually paint the radium, what they would do is they had these really thin paintbrushes, but to keep a really fine tip on it, they were taught to do a little licking procedure with their tongue to get a really fine point on their little paintbrush. They were constantly licking the paintbrush to paint and to do the dial measurements on the watches.

This was no single epidemiological study. It took almost two decades for this occupational exposure to be identified, studied, and then to convince the company that this was an occupational hazard. So this is one of the most famous cases because it's compared to Chernobyl. The amount of radium that these women and young girls took in, I think, was equal to about a hundred times more than if you were standing next to the Chernobyl accident when it happened.

Now, do you ever visit the CDC website? I do, especially when I'm traveling. I always take a look at what's going on in the country that I'm going to visit. Any time that you want to know if there are any current outbreaks that the CDC is investigating, it's always on their website. They will have U.S. based outbreaks and those that are international. So you can go through, and if you're excited about those things you can click on the case, you can read about what they did. And then for the international traveler page they always have any outbreaks that are going on, on that website on the right-hand side to take a look at. The CDC is good, and it is quite interesting to see what they are reporting and what is going on in different countries compared to what you're hearing or what you're seeing in the literature of your science journals too.

BUILDING YOUR CAREER

One of the things I wanted to do is talk about common epidemiology terms, because I think sometimes they are used and misused. In epidemiology we often discuss a case, as in "a case was reported." What is a case? It's a countable incident in the population of a particular disease, a health

disorder condition, and it could be sometimes just an individual at that particular date. So they have identified a case, and that's how we use that word. You may also hear about a cluster; it's an aggregation of cases of a disease or another health-related condition, particularly cancer or the effects. We'll hear about those cases, which are closely grouped by time and place.

When we talk about epidemiology, especially defining what a case is, we talk about three things: who, where, and when. If we're thinking about disease outbreaks, we always want to know who it was, where did it occur, and when did it occur?

For a cluster, the number of cases may not exceed the expected number. Frequently the expected number is not known though. One of the things we hear about in the U.S., you may not know, is that a cluster of cases is something common. One is power poles and cancer clusters. We live near the power poles, and maybe five kids have cancer. These are the things that we look at to try to determine if there is cause and effect. To say there's a cluster going on, we have to know the expected number of cases we would get, just out of probability, before we know if it's a cluster of cases that are related to something else.

Then there are the two big ones that are sometimes misused: an epidemic and a pandemic. When we think about epidemiology we think about numerators and denominators for math: number of cases for the numerator, after the number of people for the denominator. An epidemic is the occurrence of more cases of a disease than expected in a given area, or in a specific group of people over a period of time. Remember my who, when, and where? We have to have more cases of a disease than expected in a particular area, in a particular group of people, over a specific period of time. So that's when we have an epidemic.

When we say it's a pandemic . . . when was the last time we heard that word used? We heard it a few years ago heavily associated with the flu. That's an epidemic occurring over a very wide area, often several countries or continents, usually affecting a large portion of the population. And again remember, it's more than what's expected. Just because we have disease cases doesn't mean it's more than expected. That could be the number that we expect in a given population at a given time. So it's important when you see and read those words that you understand what is being explained, and if they're being explained correctly.

The fun thing, especially related to infectious disease, is an investigative outbreak. We can outline some basic steps that you would do, and these are some things I was able to do as an intern to learn about epidemiology. If we have a possible outbreak of a disease, the first thing of course is to identify the investigative team and the resources we're going to use, and who needs to be on that team. Now, just because we think there's an outbreak going on, that doesn't mean that it is an outbreak. We may expect those cases already. So we have to determine if an outbreak exists. We have to verify the

diagnosis, and why is that important when we're thinking about identification of disease? We want to make sure we're not undercounting or overcounting from that diagnosis because a lot of people may present with the same symptoms of a disease, but it doesn't mean that they have the disease.

We know that there are a lot of diseases that may have flu-like symptoms. If we are studying one of those diseases we want to make sure that we have an actual diagnosis of the disease to know if there is a case or not. So we really do have to verify, which is not just if you do an interview with a person who says, "Well, I had a high temperature, I felt lethargic, I was throwing up." We need some clinical test to know and verify that diagnosis. We also want to construct that case definition of who the person is, the place, and the time.

Let us turn to the Ebola cases now. Constructing that case definition, there has been a lot of controversy associated with healthcare workers coming back to the U.S. and having a quarantine or not. What do we know about the quarantine or the incubation period for symptoms of Ebola? We've all heard them. The incubation period is twenty-one days. We're going to talk about twenty-one days and how we calculate those days. When we think about the case's definition, when we think about person, place, and time, we have to think about that incubation period: where they were, when they were there, and who they were in contact with, and we are defining that case period.

Remember, you've got to work backwards. Somewhere you were exposed to something, even if it was the infamous church picnic and you ate something bad, right? We have to find that and then symptoms occurring, and then the disease outbreak. What's fun about the investigative process is that you have to find those cases systematically and develop that line listing of information such as, "how was that process," and "what was that timeline," in order to be able to find those people. And what can be hard about that since we live globally? Right, travelling and tracking.

I did an investigation of an outbreak of hepatitis B when I was at the internship during college and what made that hard was that we had around twelve cases so we had to go through this step of determining if that was an outbreak. We had twelve different reports to the Health Department, and we had to verify that they were seen and they tested positive for hepatitis B. Then we had to start constructing that definition and that case period of finding out where they were, what they did, and who they came in contact with. Finding those cases systematically was difficult. We couldn't find every single contact from that line item, but it ended up that it was a Burger King worker that had Hepatitis B and had transmitted it to six of our cases who had visited that Burger King. We were able to start tracing it back to the different people from that contact who had visited the same Burger King. It's highly systematic. So if you like doing those kinds of things and figuring out the puzzle, and then tracking, this is your thing.

Usually when we are doing an investigative outbreak, especially for infectious diseases, we know the cases and we know when they're identified as a case, the verification of the diagnosis, and when they

start seeing symptoms. Also, every disease is going to present itself differently. We have to start calculating that time period even if we don't know a lot about a disease.

INFECTIOUS DISEASES

What do we know about Ebola and how it's spreading in Africa? It has a lot to do with cultural practices such as funeral processions, how they handle the body after death, and contact with bodily fluids. Those practices are different in our community. These constructs will look a little bit different and could vary in different communities and environments. What we have to do is to know over the time period when those cases were verified as a case—the diagnosis. Then we have to work backwards, finding out when this estimated exposure period occurred. Usually we have a narrow window of when the maximum and minimum incubation period could be. There is overlap when we're doing that estimate because we know that the incubation period is not going to be exactly the first period of that case. Whenever you see an infectious disease and the incubation period, it's usually a minimum and maximum. When we think Ebola then, twenty-one days, it's probably a range. For every other disease you have a range, so you've got to think about that. Could it be plus or minus five days? When you're constructing this as an epidemiologist you know that you have a range on those times, that it's not an exact time period. For public health measures we may take that maximum range while predicting.

When we collect those data in the investigation of an outbreak we perform descriptive epidemiology. We develop hypotheses—what is the cause and effect, when did it occur, with whom did it occur—and we evaluate those and perform additional studies if necessary. If we have to go take more environmental samples, maybe we have to implement some other measures to collect, especially if you're looking at environmental hazards or occupational health items. You might have to go into the factory and take air quality samples, or whatever it may be.

Of course when we're getting down to the end we want to implement control measures. Why do all this work, with identification of cases? We want to prevent the spread of the disease now that we know what's happening so we want to implement those control measures, whether it's telling people we have to get a quarantine, we have to do better hand washing, we have to do whatever that is. Looking at that, we need to communicate those findings, and more importantly we want to maintain surveillance of the disease. Do we see any more cases over the next period of time? And continue that tracking across that time.

I think the fun part is that you have to be systematic. You always have to be asking questions, and when you ask questions especially of cases, you have to ask the same questions each time. There's always some environmental aspect that's part of the investigation. There are also cultural aspects that could be part of the investigation because people and communities do things differently and this is the important

part that we talked about in the beginning. We're always assessing and reassessing based on the information that you learn, and gathering more data as we synthesize that information.

When I worked for the U.S. Army Medical Research and Materiel Command (USAMRMC), I was with the U.S. Army Surgeon General and I handled the portfolio of our medical research for the army. What does medical research look like for the army? What do they study? A lot of different diseases, right? Why do we study a lot of different diseases, mostly infectious diseases? Yes, bioterrorism, but also because our military serves in a number of different places around the globe. It's vital for the U.S. military to look at a lot of these different diseases and try to develop vaccines for them. A large part of the military research program is for vaccine development. As a result, many of the diseases that we were looking at were ones where our troops were deployed and where they're going to be in those environments for a long period of time. It benefits not only those U.S. soldiers going in, but also we work with the partner, the ministries of health in that country as well, so that it benefits the civilians living in that country too.

In my first year on the job at USAMRMC I was told, "Oh, you need to go meet with Colonel Hoke. He has a study he needs some help on." And I said, "Oh, what is it in?" They said, "Chikungunya." I'm like, "I've never even heard of it. This is a disease? What's going on?" So I always laugh because I like the name of it, "Oh, Chikungunya." And lo and behold, it pops its head up six to eight months ago in the Caribbean. I said, "Oh, my gosh, all that work I did eight years ago, it's close. Who would have thought?" Who gets excited when a disease comes close?

Chikungunya has human-to-human transmission through female mosquitos, and is actually in forty countries. The onset of illness is within four to eight days after getting infected by the mosquito but can be up to twelve days. There are many diseases that go with mosquitos, if you don't know it already. When you work in all these areas, you think, "I am spraying myself with DEET and taking my chances with the chemical."

There is no cure for Chikungunya, only treatment for the illness or the symptoms if you get it. This makes it interesting. That was when we looked for a vaccine, and we're still working on a vaccine for that portfolio. With that particular study, we worked with the French military, who have an excellent lab in Paris. They're on the forefront of a vaccine for Chikungunya when I was working with USAMRMC, and they did a lot of partnerships with the French military.

Leishmaniasis: who's heard of that bad boy? Leishmaniasis is caused by protozoan parasites, and there are more than twenty different Leishmaniasis species that are transmitted to humans by sandflies. Which unit of our U.S. military do you think gets this the most? Special forces, because of their extended periods of time lying in the sand. They're burying in for long periods of time on their missions, so they are being affected by the bites of the sandflies. The sandflies get down in their boots, so you'll see all the

bites of the phlebotomine sandflies: heels, foot-related, leg, and so forth. It's actually a pretty bad disease. There are two main types of Leishmaniasis that we look at—visceral and cutaneous. There have been reported one million cases of cutaneous Leishmaniasis over the last five years, and there have been over 300 million cases of visceral Leishmaniasis cases, and over 20,000 deaths annually from this one.

I worked in Tunisia for this study. We were looking at cutaneous Leishmaniasis. We worked with the Ministry of Health as this is an important disease in Tunisia. Yet Leishmaniasis cures itself. You get a wound, and there is a lot of superficial scarring, and the scarring of course doesn't go away. You do get cured of these protozoan parasites but it takes time. Our vaccine program takes a while and we've got to get our troops out and get them healed. But more importantly we worked with the Ministry of Health there because a lot of women in the population get Leishmaniasis. If they get it on an area like the face, the hands, and so forth, it detracts from their ability to get married. Because they have that scarring, it takes on cultural weight. We worked with them to see if we could heal them faster, and we could then look at the wounds and see that there was less scarring and a more natural progression of the skin, so this would be a benefit to that population as well.

EDUCATION AS A MISSION

When I talked about cases and you talk about outbreak, we have to know what incidence cases are. Incidence is the number of new cases that present in a population. Prevalence is the number of existing cases in the population. A lot of times when you go into countries, they don't keep good health statistics, so we don't know what the prevalence rates of diseases are because they don't have a current surveillance system. At my company now I do a lot of capacity building, meaning that I go into countries and I help their physicians and nurses and their health ministries develop surveillance systems. I help the doctors and nurses collect the data and teach them methodology to be able to collect those prevalence numbers and to start conducting epidemiological studies and clinical trials.

I went to Abuja, Nigeria, almost five years ago. I worked on capacity building in Nigeria, Kenya, Tanzania, and Uganda. This is with their military, across all branches, and is funded by our U.S. government as well. Basically, our goal was to go in and have a whole series of lectures in epidemiology, to have clinical trials, and to talk about conducting surveillance systems for HIV, AIDS, tuberculosis, malaria, all of the basic communicable diseases.

I visit them every year and a half and we do updates to their trainings. We see what studies are going on and assist with those studies. Right now they have sixteen protocols, sixteen studies that they're running because they have a good surveillance system in place. It's rewarding to see that system being put in place, because they are able to track things a lot better at this time.

CASE EXAMPLE: EBOLA

This is what's going on now, for Ebola. You hear of healthcare workers going in and the group called Doctors Without Borders, but there's also Statistics Without Borders. Almost three weeks ago, there was a huge data set sent out to all of the group members and they're asking for people to work on model building. There were four prediction models that they wanted help on building from the community of statisticians. The first one took a look at the African countries and mapping the funeral processes among ethnicities because, as we know, the funeral practices are very different, and the spread of disease is quite different.

We are also looking at mapping the connectivity between villages, including the number of neighboring villages and how they're connected by roads, because when you think about spread of disease, it's not just you going and being near somebody. You have to think about the infrastructure, the environment, and how it's spreading. We have a lot of data about where the cases are, which villages, and the infrastructure between those villages and also the neighboring villages. There was another one where we wanted to start mapping the mortality rates. Currently, those mortality rates are only crude predictors of the death in cases. So we'll have when they died, but it is tough to track backwards, given that there is a two week lag, and there are discrepancies in the data collection that are going on the ground now with these Ebola cases in Africa.

Currently we're trying to figure out if there is a more accurate way to statistically derive a rate from these lags of the data. They have also asked us to look at prediction models for death in cases of the current out-of-control state to see if response is having an effect. We do have one country right now where no control measures have really been implemented, and they are putting in place one response and trying to see if that's having an effect on their rates now. A request came out earlier this week for help to build these four models. They're also looking for this to be a student project too. One of the good things about these data coming out of Africa is that they're publicly shared. There is a website, and both government and non-government agencies are sharing the data to use for analysis, which is quite extraordinary.

I can show you one Excel spreadsheet of our one Ebola collection plan template that was sent out to my group, and it's very interesting. We wanted to include data that we absolutely need but they may not be able to get, so we have that marker in here. It includes indicators that are health related, that may be related to the security of the country (or of that neighborhood or village), and items that deal with human rights, food security, economic stability, and public awareness. This is a pretty informative data set. Details that we're looking at for those areas in Africa are the governance units, the tribes by county, and what the administrative structure is of the census data (how many people).

We also looked at critical infrastructure. Remember in the beginning I described the investigative plan about looking at the environment, cultural aspects, different things that come into play? We're going to look at water pumps; we're going to look at helicopter landing sites. We're going to look at the airports, bridges, and seaports. These are all typical things when you think about a disease like this and the spread of the disease.

Communications and those main public supply routes are vital, and I can tell you, just to digress off of Ebola right now, that when we study HIV and AIDS, one of the first things that we'll look at when we're going into a new country that doesn't have a surveillance system is the infrastructure. We'll look at trucking routes and accessibility because a lot of times when you start seeing the appearance of HIV/AIDS into a particular country, or an area of that country, it comes from somewhere. So for a lot of our studies we will actually survey truck drivers. We'll look at the ports they've gone to and their hubs for deliveries and pickups. One of our studies looked at HIV rates through prostitution and the truck drivers, and then bringing the disease home to their wives and their community that way. We could actually follow the transition rate of HIV/AIDS from one country into the other from the trucking routes. When we're thinking about that kind of outbreak, the infrastructure is a huge part of it, and patterns of people, commerce, water, and so forth related to the infrastructure. That's why you will see those things on a data collection template.

Medical response is another important area: what treatment units, what is the bed capacity, what is our lab testing capacity? We must know if there are Ebola response centers, medical team deployment locations, or plans. And then of course we're going to start going into contact tracing team deployments. Contact tracing team deployment means going house to house, village to village, and starting to do that census of people and who is sick and who is not sick. Then we'll look if there have been any quarantines, if the village has been quarantined, if there are any actual security lockdowns as well, and any other type of health report of items that have come up from that particular government or Ministry of Health.

Security is another factor, especially in Liberia and Sierra Leone, so we actually monitor checkpoints and collect data. We'll have data on some of the patrols. The Liberian national police will release some of their information as well for data. There are many different sources for the information we gain.

Normally when we're studying an outbreak, a disease spread in an area, we're going to look at all the economic and social aspects of it as well. We'll see sometimes that there's going to be a correlation with crime reporting and different elements that they track. This is why we track if there are any protests or riots. There will be human rights organizations that will collect their own data, especially over land disputes, border issues, or related tensions between villages, countries, or whatever they may be. Logistics, transportation, and human factors will all be considered: political, social, religious, and so

forth. The focus for this one is for Liberia, which has an ex pat sentiment of other people coming into the country. Then all of our imagery data will be shared with street map data, world geography, any rivers, land use, and other things that will come into play.

As you can see, getting down to the root of health problems and outbreaks in a population or community is both fun and important. It requires learning about the scientific method of investigation, problem solving, and being a disease detective. Perhaps your passion for epidemiology will be sparked tonight as mine was sparked at Juniata College when I was a student.

NOTES

1. Department of Health and Human Services (DHHS) and the Centers for Disease Control (CDC), *Principles of Epidemiology in Public Health Practice - An Introduction to Applied Epidemiology and Biostatistics,* third ed. (Atlanta, GA: DHHS/CDC, 2012), pp. 1-2.