Figuring out what makes populations sick: unraveling disease mysteries: 2014.10.21

In your great grandparent's time, life expectancy in Canada was less than 40 years; today it is over 80. Some of the improvement is thanks to new treatments for sick people, but a lot of it is due to the efforts of community medicine (and more broadly public health), where the goal is prevention.

I will begin by distinguishing community and clinical medicine. Population-level epidemiological research is one of the activities what advances the knowledge-base for community medicine and public health. There is always a lot riding on this type of research, but as you will see, it is not that easy to figure out what makes populations sick or keeps them healthy. And when researchers did produce new evidence that would convince us today, it was difficult to convince people at the time. Epidemiological research hasn't featured much in past MiniMeds, so I and the other speakers in the series would like to give you a sense of what it it is, and how it is done, and why it matters to everyone. • 177 / 177

Here is one way to look at the differences between community and clinical medicine: doctors see one patient at a time; community medicine (and more broadly pub-

lic health) deals with an entire population at once, and uses somewhat different tools: community nursing, vaccination, community health education, sanitation, food standards, etc. You could say that community medicine is about keeping people in the community from becoming patients. • 67 / 244

Population-level epidemiological research is not easy, for a number of reasons:

It is not like lab research where one can control all the other factors and compare like with like, by using rats or mice from the same mother, fed the same diet, etc.

The timescales can also be much longer; it might not be so difficult to figure out what it was that you ate yesterday, or were exposed to this week, that makes you ill today. Nowadays we are often trying to understand links between what happened to you in utero, or you did your earlier in your life, and your health now.

And there is one other big difference: in clinical medicine, depending on how sick you are, or what the options are, your doctor might be willing to recommend a treatment with a 1/100 or even a 1/10 risk of a serious side effect. But that would not do if we were recommending one vaccine or another for an entire province or country. • 174

/ 418

Two clarifications: I am mainly going to be talking about epidemiology and public health RESEARCHERS.

Today, many of them, like I am, are not MDs, but PhDs. My grandmother was puzzled too. • 35 / 453

Epidemiology researchers try to figure out what causes and spreads DISEASE in populations, and how to avoid it. • 19 / 472

Of the killer diseases on the list, we have eradicated just one.

Vaccination and other public health measures have tamed most of the others in the first 3 columns.

It is easy now to put these diseases into these columns, but it wasn't at the time. People blamed the plague on their enemies, or thought God was angry at them. The scientists blamed atmospheric disturbances. In the Great Plague of London, the Mayor tried to have all the dogs and cats put down. It took until the end of the nineteenth century to figure out that plague is spread by fleas and rats, and yellow fever and malaria by mosquitoes, not by bad air. • 119 / 591

I will leave this mystery one to the end, and spend some time on these 3. For one of them, the method used to avoid it caught on quickly and the disease was already mostly under control in part of the world by the end of the nineteenth century. In another, a researcher used both small and Big Data to figure out the way it is spread, and how it could be stopped. He got the evidence by studying people in their natural habitat, without experimenting on them. But he also used 'outside the box' first principles thinking and a lot of shoe-leather and good luck. It took much longer to turn HIS evidence into knowledge and into public health practice.

I will then move on to some epidemiological history that many of you have lived through, and also show you some of the population research tools we use today. I will close by revisiting a twentieth century triumph of rigour and Big Data over another of the diseases I have circled. • 175 / 766

More than a thousand years ago, people had already realized that they could inoculate susceptible individuals with material taken directly from the pustules. If it did not kill them, it would protect them. But even with the improvements over the centuries, it was quite dangerous for the 'inoculatee' and for susceptibles who would be in

contact with him, and took time and care to get it right. • 68 / 834

In the late 1700s dairy-farming people in the south-west of England noticed something: the milkmaids and other workers who contracted cowpox from handling cows' udders (they got it through breaks in the skin) were afterwards immune to smallpox. Such people were able to nurse smallpox victims without fear of catching the disease themselves. A farmer decided to try to give his wife and two eldest sons immunity by infecting them with cowpox. He took them to an infected cow at a farm six miles away. He used a darning needle to transfer pustular material from the infected cow by scratching their arms. The boys had mild local reactions and quickly recovered but his wife's arm became very inflamed and she got very sick, but she recovered. It gave them protection against the smallpox, but the neighbours were appalled at the idea of introducing an animal disease into a human body, and the practice was not taken up or widely publicized. • 161 / 995

Twenty two years later, a county doctor named Dr Edward Jenner decided to inoculate a young boy with the material taken from the cowpox pustules on this milkmaid's arm (he was also a naturalist and did the drawings himself). He then challenged the boy twice with the

smallpox virus, but the boy did not get smallpox. • 57 / 1052

He vaccinated his own son. • 6 / 1058

The reactions were a lot milder than with the material from smallpox patients. Jenner's paper was rejected by the Royal Society, so he published his method and results in a private pamphlet. The practice was quickly and widely adopted. Jenner's material was used in Newfoundland the very next year (You must be wondering how they sent it). Later, to honour Jenner's work with the cowpox (vaccinia), Pasteur suggested that it be called vaccination, and indeed we have adopted the word now for inoculations with material from other infected sources, not just cows. • 93 / 1151

This sketch relates to trouble in Montreal in 1885, when the disease (and then the public) got out of control. A large segment of the population was afraid of the vaccine (there and been some bad batches of it, and one particular doctor was also very anti-vaccination) and also opposed quarantine and other public health measures. Almost 4000 Montrealers died of smallpox that year – the last urban outbreak in North America. This outbreak is the subject of an excellent NFB movie. I have put the links on my website. • 91 / 1242

Endemic smallpox was eliminated from Europe and North America before you were born. It took a concerted WHO effort in the rest of the world to eradicate smallpox. The last known case anywhere in the world was in late October 1977, some 37 years ago already. • 47 / 1289

I mentioned that Montreal had the last serious smallpox in North America, but Montreal and Quebec City were also the FIRST places in North America that cholera landed, coming by ship from Ireland in June 1832. Cholera is still with us today, and can still kill. In this drawing from the early 1830s, you see why it terrified people. • 60 / 1349

At that time, what did the public, and the public health people, think about how the cholera poison was spread? Until the late 1800s, the less popular theory was that it was by direct person-to-person contact.

The dominant view, especially among public health people, was that it was caused by Miasmas. It was the same for Puerperal fever. Miasma is not a word we hear a lot today. Here are some dictionary definitions: a vapour, emanation, atmosphere, smell. The theory was that disease arises from an invisible emanation from rotting organic matter. • 95 / 1444

Here is the epidemic curve for the biggest of England's cholera epidemics. It killed over 50,000, more than a 1000 a day at its peak [for perspective, England had a smaller population then than Quebec and Ontario combined have today].

You can see the pre-occupation with miasmas: they looked for connections with temperature, rainfall, barometric pressure and wind direction. • 62 / 1506

Before that epidemic had run its course, a London physician used his professional earnings to publish a pamphlet suggesting that it was not from Miasmas or the atmosphere.

No, its not the Jon Snow in the tv series your children and grandchildren watch. He was the British physician who introduced anaesthesia to Britain, made it safe and scientific and practical, and administered it twice to Queen Victoria. The title of this very readable book puts it well: Anaesthetist to a Queen and Epidemiologist to a Nation. His work is often the first piece of epidemiological research we show students. The pamphlet argued that Cholera multiplies in the gut, and is passed on by the fecal-oral route, and though water. Lime was the usual disinfectant used back then. He advised washing

food and hands, boiling soiled cholera clothes, and boiling the drinking water. • 145 / 1651

The Government Statistics Office took two and a half years to make a Big Database of the information from the 50,000+ death certificates, link them to the census data, and produce a huge report full of stunning colour graphs and tables. The bottom line was that the cholera poison SOME CHEMICAL MODIFICATION OF ORGANIC MATTER. In the meantime Snow awaited the next epidemic to get more evidence for his theory.

He knew that in most of London the water companies divided up the territory so they were not in competition (like the cable TV companies today). But he also knew that in South London there were 2 companies that had been in active competition for customers and that in many streets, pipes from these 2 companies went down the same street. But since they both drew their water from downtown London, one here, one just bit further downriver, its didn't help Snow to tease things apart – not until the Government gave the Water companies a deadline to move their intake to above the tidal portion of the river. • 182 / 1833

The Lambeth company was the first to so so, well ahead of the deadline, moving its intake upriver starting in

1852. When Snow leaned this, he saw his chance to take advantage of this natural experiment during the next epidemic. The pipes still served the same people, but now people who were in the same neighbourhood, of the same social class, at the same elevation and population density got different water, some connected to the sewers of London (and the evacuations of cholera victims) and some not. As you will see, he did not have long to wait.

But first look under the 1849 column, before the switch. These are the cholera death rates in South London in the 1849 epidemic, when both companies were still taking their water from the Thames downtown. The worst area was that served by both companies, probably because it had the poorest people most crowded together. The southern area, even though it was less densely populated, was served by the Lambeth company and it took its water from a little further downtown than the Southwark company. • 185 / 2018

Now look at the death rates in 1854, when the next epidemic showed up. By this time, the Lambeth company had moved its intake upstream. You see that in the area served only by the company that continued to serve more polluted water, the rate got worse. In the overlap area it improved a bit, and in the area that was now getting its water from way upriver, there was dramatic improve-

ment. • 73 / 2091

A big drawback with these type of comparison is that we don't know where those who died were actually getting their water from. We just know that the MIX is more Lambeth Company water in one AREA, more equal in another, and more Southwark Company in the third. And for all we know the deaths could be in people who are not connected to the water supply at all, but are getting their water from pumps and from ditches and drains. To avoid being fooled, the only way was to find out what water those who died of the cholera had been drinking before they got sick. As I told you, Snow had been waiting his chance; for the deaths in the first 4 weeks, he got their addresses of the dead from the Government office, and personally called on each of the houses in the (salmon coloured) area where the source could be the Lambeth Company, the Southwark Company, or a ditch or drain. He had another doctor visit the (turquoise coloured) area where it could be the Southwark Company, or a ditch or drain.

In the first 4 weeks, a few of those who died had gotten their drinking water from non-company sources, but in the remaining 300, the split was dramatic. So much so that the death rate was 13 times higher among the Southwark Company customers than the Lambeth Company

customers. • 238 / 2329

Snow know that even with those striking data, he would have some trouble from his critics, and you too might have some objections. But then an extremely violent outbreak happened almost in his neighbourhood, in ten days killing more than 600 in an area no bigger than the McGill campus. He interrupted his South London shoe-leather epidemiology.

In this plot of the deaths in the Soho district, each dot represents one cholera death. Not all of the 600 are plotted here, but a good number of them are. It seems to be centred here. And the suspect, for Snow, was this Water Pump, maintained by the Parish. It was not connected to the mains, but drew its water from a well about 25 feet deep. It had very good-tasting water, and was very popular. It tasted OK to Snow on September 3, and he couldn't see much wrong with the water. But he knew that water that had been contaminated by rice water evacuations from cholera patients could still look and taste OK. A large majority of those who died in the first few days has drunk this water. And, even more striking were three exceptional situations that were hard to explain by the miasma theory. Why was this block spared? It was the brewery, and the workers were given free beer and had their own well. This large workhouse

for the poor escaped: it too had its own supply. But the clincher for Snow was the case of the Hampstead widow who moved from Broad Street some years before. She liked the water from the pump, and had it sent to her by cart every few days. She was sent some on the Thursday and she was dead by the Saturday, along with her niece who was visiting her. No one else in Hampstead died of cholera that week. • 313 / 2642

Snow didn't delay. He had finished his book, with the South London data, and the Broad Street pump data as the centrepieces, by early December. 25 / 2667

His critics argued, among other things, that Snow had no proof that the pump water was contaminated. This gap in the evidence was filled the next year thanks to a very sceptical curate of the local church. The story is well told in the book The Ghost Map, so I will only give the punch line. • 57 / 2724

• The index case is the one thought to start the outbreak. The index case in the spread of HIV in North America was called "Patient Zero". 27 / 2751

The pump was just outside the house where an infant died, but it was on day 3 of the epidemic. Normally, patients die within a day or two of onset, so he didn't think

it could have been the first case. until he noticed that this infant had been sick for 4 days. The mother told him that the soiled diapers were steeped in a pail; water from pail was poured into cesspool. The engineer excavated and found the cesspool blocked, and the brickwork defective and leaking contents into the drain. The drain was also defective and leaking material into the well that fed the pump. • 107 / 2858

Twelve years later (when Snow had already been dead for several years) cholera broke out again, and was particularly bad in East London. This was when the government statistician and miasmatist had his epiphany. His weekly reports quickly identified the massive outbreak in East London, and documented that 90% of the deaths were in the area served by one Water Company. He called the water company on it.

By this time, the thinking had turned sufficiently in the direction of the waterborne theory and the authorities were able to minimize the size of the outbreak. • 98 / 2956

This was the last epidemic in England. It was the German microbiologist Koch who got the credit for identifying and isolating the cholera bacterium in 1883. The germ theory was a big factor in cities chlorinating their

water supplies against thyroid and cholera and the results were dramatic. • 49 / 3005

I now turn to some episodes many of you, or your parents, have lived through. I will begin with birth defects, where the time lag between exposures (or deficiencies) during pregnancy and the defects is relatively short. • 38 / 3043

People were panicked by polio, which we now know is a virus spread by the oral-fecal route, like cholera. It was an infection more of the rich, with smaller families. than the poor with bigger ones. I will come back to how the Salk polio vaccine was tested.

In mining towns, where they first link was made, they thought the protection against caries was from several years of drinking water with high levels of copper, but they eventually figured out, using observations on rats and then on children in different communities, that the agent was fluoride. Adding it to the water was tested in community trials in New York State, Michigan, and Ontario in the 40s and 50s.

The last one was an even longer hunt into the past, since the women were in their teens and early 20s when this rare cancer showed up. I will come back to this too. •

157 / 3200

I won't even go into the reasons for the long list of illnesses adults get. Except for some drugs with immediate effects, the trail is even longer and more complex. • 31 / 3231

What tools do population-level epidemiological researchers use? • 8 / 3239

The first, I would say, is the case report, or the report on a set of cases, like here: some were his own, some from colleagues. By itself, if these was the first data on this, would you say it was an open and shut case? At first some did did not, but some more very imaginative work by an Australian doctor, statistician, and epidemiological researcher did convince people. • 70 / 3309

What kind of comparison was this ob/gyn making? Would this have convinced you? The makers said initially that the evidence from these reports was 'circumstantial' but they felt they had 'no alternative but to withdraw the drug from the market immediately pending further further investigation' • 46 / 3355

Would a finding of defective folate metabolism in 2/3rd of the mothers of babies with severe malformations (prin-

cipally of the central nervous system) have convinced you that folate was somehow implicated? No, you would want to know how common this defective metabolism is generally? For that you would need a sample of mothers from the general population. They got one and they found it was defective in 1/6 (17%) of them. Today, this sample is often called a control series, but a clearer term would be a denominator series. If I have time, I will show you a clearer example of missing denominators. The authors cautioned that a positive FIGLU test may indicate defective absorption or metabolism rather than deficient intake of folate. So it took some years of randomized trials to convince people that it was safe to give high risk women folic acid to try to prevent neural tube defects, and many more years before safe dosing levels could be established and the folic acid put into the white flour that we buy. The result is another seldom-told success story for community medicine and public health. • 189 / 3544

In this example, the young women were diagnosed between 1966 and 1969, and their mothers had been pregnant with them between '46 and '51 – 14-22 years before. • 29 / 3573

If you only got histories from the cases, you would have found that 7/8 mothers smoked (at least 10 cigarettes

a day) before the child was born. Would this be striking? You need to know what was happening back then. The controls (4 per case) were mothers of daughters born within five days and on the same type of service (ward or private) as the cases. You see from the controls how common smoking was at the time • 79 / 3652

how common X-rays during pregnancy were at the time, and how uncommon breast feeding was; DES was even less common, but clearly very very harmful. Even if we had very good medical records, in this type of design we would still be up against against time and the limits of people's memory for many of these factors, and the ones I have not shown you (birth weight, age at menarche, complications of pregnancy, other meds, childhood diseases, tonsillectomy, pets, cosmetic use, alcohol, parents' occupation etc..) So there is a limit to this type of after the fact rely-on-memory study design. And of course, if this were something where we needed blood levels, it is unlikely that stored bloods would be available. And it is hard to get people in general to be interested and equally attentive and thorough. • 139 / 3791

So this issue of time lag and needing to be there at the beginning to record the data is one of the reasons why we have those kinds of studies. They are often called cohort studies or prospective or longitudinal studies. They

usually involve large numbers of initially well people: we don't know ahead of time who is going to get sick, or or what. We document the information of interest at the beginning and also as they all march ahead together, with some coming down with various illnesses. Very few of the first Framingham cohort are now alive, but researchers are now following their children and their children's children. • 111 / 3902

Here is another follow-up study that is often in the news. It was originally set up to study oral contraceptives, but has expanded to many other topics. • 28 / 3930

It found that that postmenopausal hormone use appears to DECREASE risk for major coronary events in women without previous heart disease. Other non-experimental studies had also found this, but they had relied on information they got after the fact, so the findings from the much larger prospective Nurses study were taken as much stronger evidence – until it was overturned in a randomized trial conducted by the Women's Health Initiative. This overturning gave epidemiology research a bit of a black eye: As this author argues, some researchers had fooled themselves into thinking that by measuring enough variables on large numbers of people, they can tell us what decreases risk. They may be better able to tell us what increases risk (and Samy Suissa will do

so, in his studies of the UNINTENDED consequences of medications) but figuring out what decreases risk (the INTENDED consequences) is typically more challenging. • 149 / 4079

Some of you may be aware of or participating in this Canada-wide longitudinal study. Dr. Christina Wolfson in our department is a Co-Principal Investigator. 24 / 4103

This longitudinal is being carried out by a multi-disciplinary team that includes researchers from 6 Quebec universities including ours. Dr Paradis is one of the McGill researchers. It started with children when they were age 8. 36 / 4139

I will fast-forward now to the next April, when the new Hospital will open. The planners decided it would have all private rooms. Some reasons had to do with patient comfort and privacy, and some with reducing the spread of infections. Indeed when someone asked why Montreal needed 2 super hospitals, one response was that, if nothing else, having two separate one rather than one super-super one would reduce the sizes of outbreaks of hospital infections. • 77 / 4216

But let's ask: what evidence do we have that single

rooms will reduce the spread? One would have a hard time studying that in lab animals, and it would cost a lot to have a randomized trial of human patients that simulated real-life. So we have to make the best of the opportunities that arise naturalistically. One of these arose when the MGH ICU changed to single rooms; before that it had 2 large rooms of 12 beds, 2 private rooms within each larger room, and a total of 4 sinks to all single-bed rooms. • 96 / 4312

That was the title the journal insisted on. Here is how I would have put it. • 17 / 4329

Can we just compare rates before and after the switch? No. Lots of other factors (such as the arrival of C-difficile) could affect the comparison. Fortunately, during the 6 years from 2000-2005, the ICU of the RVH hospital remained unchanged and had rooms with 2, 5, or 6 beds and 8 single rooms. The hospitals have a single, common infection control service with 1 director, and they share infection control policies and practices. The patient-nurse ratio was the same in both hospitals and remained constant during the study period, even when a temporary shortage in nursing staff meant intermittent bed closures. The same alcohol-based hand gels were available in the same ratio of 1 per 2 beds in each hospital. 120 / 4449

Our study was large: over 19,000 admissions and 86,000 patient-days at risk • 13 / 4462

One of the constraints is that we came into these data after the fact. We were not there at the beginning in 2000, so we couldn't measure all the variables we might have wished to. We were also worried that there could be other factors that could artificially make the switch look good. So, one of the things we did was to make a number of before-after comparisons. I am interested to know what you see in the 3 different before-after comparisons in this graph. I showed this to several colleagues. They all wanted to know what X Y and Z were, but I would not tell them until after they had given me their impressions. I didn't want our conclusions to be based only on statistical tests carried out by computer software: I wanted the data to pass what statisticians call the inter-ocular traumatic test: it should hit you between the eyes. And they, like the MUHC planners who had already committed our taxes, and had the hospital half-built, should not be influenced by what they were hoping for. • 181 / 4643

OK. So, here is what they are. X, especially the first 3, are the bugs that were the focus of infection control efforts and that SHOULD be affected by the change. The bugs in the Y group were a negative comparison; NO

CHANGE in their rate of acquisition was expected as a result of the switch. And Z is the length of stay in the ICU. • 67 / 4710

The graph that appeared in the article makes it a bit easier to see the average changes. • 18 / 4728

Some of my colleagues don't like the journals' insistence on 'conclusions', but this is how we summarized the evidence. We did not want to dwell on a specific percentage, but we called it a substantial reduction. We will never know for sure, but no doubt the MUHC will be keen to track the infection rates once the new patients move in, and to claim that their all-single-rooms choice was a wise one. Now that you have a taste of how epidemiology researchers think, you too might be a bit more skeptical as to why the rates will be lower. • 100 / 4828

Earlier I mentioned the Polio Trial of 1954. I Showed the video before the lecture. Whenever you get depressed about Ebola, I suggest you watch it again. • 28 / 4856

This is why it was so scary. • 8 / 4864

This is how big it was. The children received their shots before school got out in June, and were followed up until December. The report was completed over the next few

months, and the results announced on April 12, 1955. • 41 / 4905

Those who had received the placebo were immediately offered the real vaccine. And the March of Dimes people had several million batches ready so as to be able to vaccinate all American children before the next polio season began. • 40 / 4945

So what is the bottom line? Epidemiological research is vital. We cannot experiment like the lab scientists do, but we must also be careful not to be fooled by Big Data. We need brains that can work and think and see outside the box. And even today it may still take several decades to convince the public health people and the public themselves. But if a nation or the world puts its mind to it, things can be done relatively quickly. • 82 / 5027