GRESHAM COLLEGE

10 OCTOBER 2018

EPIDEMICS, PANDEMICS AND HOW TO CONTROL THEM

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This academic year begins the 500 year centenary of the birth of Sir Thomas Gresham. In his lifetime (circa 1519 to 1579) infectious diseases dominated medicine. Many were a constant presence (endemic disease) but many serious epidemics occurred. These included epidemics of plague, syphilis, smallpox, typhus and the English sweating sickness. Plague is an example of the power of infectious diseases to shape human history and human capacity to respond. Current estimates suggest plague reduced the world's population from an estimated 450 million down to around 375 million in the 14th century. Somewhere between 30 and 60% of Europe's population died. The risk of a plague pandemic now is considered by the World Health Organisation (WHO) to be zero.

October 2018 is also the 100 years centenary of the peak of the 1918-20 H1N1 influenza pandemic, also known as the Spanish 'flu, which probably killed between 50 and 100 million people worldwide. Taking the USA as an example, more people died in that pandemic than all the wars of the 20th century combined. The onset, even in a period of very restricted travel was very sudden with a massive increase mortality in October of that year, demonstrating the speed at which serious pandemics can hit humankind. It is easy to make a case we are increasingly vulnerable to serious epidemics due to much more integrated travel since that pandemic hit. This is wrong, but we do remain vulnerable. There is non-specific hardening societies get richer against epidemics which include inputs from agriculture and engineering such as better nutrition, housing, sanitation, clean and plentiful water and clean heating. The global spread of epidemics can be rapid and even in preindustrial times when transport was very slow diseases such as plague and syphilis moved very rapidly across continents.

Epidemics are certainly not something of the past. Localised outbreaks happen every year; some become epidemics and occasionally we are affected by more serious pandemics. Just taking 2018 as an example there are currently outbreaks/epidemics of drug resistant typhoid in Pakistan, cholera in Zimbabwe and Yemen and plague in Madagascar (all of which would be well-known in Sir Thomas Gresham's time). Alongside these are diseases that would not have been known to Londoners in that period including monkeypox in Nigeria (which they would have mistaken for smallpox), MERS in Saudi Arabia and Ebola, of which there have been two epidemics this year both in the Democratic Republic of Congo.

The societal impact of epidemics depends on how many people are affected but also which occupations and age groups. For example, healthcare workers are regularly more affected than other occupations in epidemics that involve touch or close proximity, and the pandemic H1N1 influenza that hit the world a century ago particularly affected young working-age adults. Predicting or trying to prevent epidemics is hard. Most new and emerging infections come from animals (although we often blame foreigners). Epidemics cause panic and can have substantial societal and economic impact even if the epidemic itself is limited. For example, between November 2002 and July 2003 SARS caused under 10,000 cases and less than 1000 deaths - a tragic loss for the families involved but in global terms a minor heath risk. It wiped around $40 billion off the global economy. A major influenza pandemic or similar epidemic would have massive societal and economic impact.

Although the first reaction is usually panic, epidemics should be addressed systematically. Panic kills. How to respond to any given new epidemic or pandemic depends on factors all of which are predictable as being important. These are: mortality/severity, available treatment, available vaccines, force of transmission and above all route of transmission.

Throughout this talk I will be using three medical terms so I need to define them. The first is endemic disease. This is the background rate of an infectious disease which may well be zero or maybe very high but is the local normal. It often varies by season. If there is a significant uptick above that, it is termed either an outbreak or epidemic. This is a spike in cases significantly above seasonal background. Outbreak is often used to mean limited in geography and that is the way I would use it on this occasion. Pandemic is an epidemic going worldwide over a very wide area across international boundaries.

Two variables, which may well be independent of one another are important. The first is transmissibility, the ability of an infection to spread rapidly through the population. The second is virulence, how dangerous it is, with the ultimate risk being mortality. Some diseases may have very high mortality rates but have very limited ability to transmit. Others may be very low mortality but high transmissibility. The epidemics or pandemics which matter to us are those which are both highly transmissible and highly virulent. Mortality (case fatality ratio) varies widely in epidemics. Some recent examples include Ebola where the epidemic was around 60 to 70% fatal, smallpox where fatality was around 30%, the 1918 H1 N1 influenza pandemic at 3% mortality and new variant CJD at 100% mortality. The 1918 flu pandemic was therefore much less virulent than some of the other epidemics but because it was so transmissible, very large numbers of people died. Epidemics can also vary by issues such as nutritional status or age: for example, in epidemics in malnourished people, mortality from measles can be between 5 and 10% (up to 30%) but in the UK mortality from measles is around 1:5000 children.

Even if controlling the epidemic is not possible, stopping people dying or other serious harm may be. This is the role of treatment. Specific treatments are those which kill or stop the infection. These include antibiotics: most new bacterial infections will be antibiotic sensitive if they come from wild animals. Antivirals currently tend to be virus-specific and which means they may have a role in known viruses but are less likely to be useful in new infections. Antiparasitic drugs are also available- it is unlikely we will have significant outbreaks of a previously unknown parasite. There are also disease specific drugs which will not kill the disease but may prevent harm such Vitamin A with measles which can reduce both mortality and serious complications. The best use of fluids and ventilation is often a significant treatment question for any epidemic.

The core aim however of dealing with any epidemic is to control it, meaning to reduce it and eventually stop in its tracks. Ever since Jenner the automatic reaction of policymakers has been to say ‘get a vaccine’. This may in certain situations be the correct answer. For known epidemic diseases, effective vaccines are available and can have a big impact on the disease; examples include for yellow fever, measles, polio and smallpox all of which have highly effective vaccines. The second scenario is where a variant of a known disease causes an epidemic, of which the most common is influenza. The lead time to get a ‘flu vaccine is at least four months and vaccine efficacy will vary considerably. For a completely new disease however a vaccine will usually take years even it is technically possible. Many diseases have proved biologically incredibly hard to get vaccines for even where well-funded attempts were made over decades including HIV, malaria and cholera.

Where vaccine is available three possible strategies occur. The first is where a vaccine is given to the whole population. This, if the vaccine is effective (such as yellow fever) can terminate an epidemic. It depends on the vaccine being safe with low side effects, easy to give and generally cheap. A second approach is to give the vaccine to high-risk groups who are the ones most likely to get an infection. An example might be commercial sex workers for a sexual infection, or doctors and nurses for one passed on in hospital. The final approach to vaccination is ring vaccination where a case is identified and then a vaccine is given to everybody you had contact with them and all of their contacts as well. This was used in smallpox and subsequently tried in the control of Ebola; it depends on the vaccine being fast acting.

The third major concept is a force of transmission R0 (or R). By definition, an epidemic must have an R over 1. An R=1 means that on average one person gives the disease to one person and so on and the disease is stable in the population. If R is greater than 1 the disease will expand so for example if R is 2 one person gives it two who give it four and the disease is increasing exponentially. If R is below one the disease will die out. Getting R below 1 is a central objective in controlling an epidemic.

Above all however, the route of transmission is key to control, and getting R below 1. Broadly there are five routes of transmission. These are: airborne (influenza); food or waterborne (cholera, typhoid, BSE/CJD); touch (Ebola, Lassa); vectorborne (Zika, dengue, bubonic plague, malaria) and sexual or blood-borne (HIV, syphilis). Usually one route will be strongly dominant although often there are secondary routes; for example, plague can be transmitted both by fleas (vectors- bubonic) and by the respiratory route (pneumonic).

The importance of considering routes of transmission which can cause epidemics of significant proportions means it is worth giving more detailed examples. The West African Ebola epidemic in 2014-15 was transmitted almost exclusively by touch (minor sexual and blood-borne spread). There was high mortality and medical countermeasures were limited with no vaccine. R was between 1.5 and 2.5. Despite touching being the only major route the potential for it to expand very rapidly was modelled and found to be substantial. Therefore a number of interventions were designed to get the R below 1. These included reducing transmission in hospital and other healthcare settings, reducing transmission around death and introducing safe burial, reducing transmission in the community and increasing social distancing. The combined effect of these meant that the R began to come down but the number of cases continue to increase for a while until R had crossed 1. This epidemic also demonstrated one of the major ethical and operational problems with some infections which is that healthcare workers were very heavily affected with significant mortality. There was therefore a trade-off between early intervention which would keep the epidemic under control, and protecting the health care workers from West Africa and internationally. There is now an ongoing Ebola epidemic in DRC; the positive difference is we now have a vaccine which can be used for ring vaccination. Social interventions are however more difficult due to armed groups, politics, distrust of the government and this demonstrates that epidemic responses do not occur in a social and political vacuum.

The HIV/AIDS pandemic was a largely driven by the sexual route although there was also significant intravenous drug transmission; once infected, people were infectious for life. Initially there were no drugs, no vaccine, high mortality and long periods when people remained well but were infectious. Initially responses had to depend on behaviour change. There were many approaches to changing sexual behaviour not all of which worked. An important part of this was getting people to know their HIV status. The intravenous drug route was a separate control challenge: an important subgroup marginalised in society where behaviour change and needle exchange were key. For HIV, the most important biomedical intervention ended up being developing drugs to treat people with HIV and AIDS. It took over a decade for effective antiretroviral combinations to be available and longer still for them to be affordable. Now although the epidemic is a very long way from being over, the great majority of people who were on effective treatment will live as far as can be told at this stage a normal lifespan; unfortunately, many are not on treatment. HIV new cases are gradually drifting down in most countries but it is slow. There has been huge investment and great science to develop a deployable HIV vaccine over several decades but we still do not have one. There is however evidence of people on effective drug treatment are much less infectious and this is likely to have an impact on epidemiology in the medium term. Drugs can also be used for prophylaxis for high-risk encounters. Although the HIV pandemic dropped out of the news because deaths are much rarer, around 1.8 million people became newly infected with HIV in 2017. HIV will probably need either a vaccine or a curative drug to terminate the epidemic completely, although it is very slow retreat.

Vectorborne epidemics are now rare in the UK but remain a significant global risk. They were common in England when this College was founded including epidemic typhus, plague (both passed on by fleas) and probably malaria. The UK currently has few vectors that have epidemic potential: midges and ticks are the main ones, although this could alter with climate change. Globally however vectorborne epidemics are very common. Mosquitoes are the main culprit. Sandflies, fleas, biting flies, ticks and mites are however all capable of transmitting disease. An example of a recent vectorborne epidemic is Zika. Although it has been known since 1947 it hitchhiked through to the Americas where it took root because the key mosquito which transmits it, *Aedes aegypti*, is well adapted to periurban living. It was first noticed to be associated with a large spike in cases of microcephaly (small heads in babies) which is likely to be in the long term associated with neurological damage. At the stage the epidemic started around 12% pregnancies where the mother was infected in the first trimester had fetal abnormalities. There was no vaccine, no drugs and the route of transmission by Aedes was difficult to control. The cases in Brazil went down through a combination of herd immunity and the vector decreasing with the end of the rainy season. There is now the potential to spread to any part of the world where *Aedes aegypti* are common, and possibly *Aedes albopictus*. In Europe changes in climate may make this possible in several countries.

Historically, food and water were major routes of transmission. We still have epidemics associated with both of them. Currently there is a major epidemic of cholera in the Yemen which has caused over 1.2 million suspected cases and over 2000 deaths. This is now largely associated with war and social disruption. Cholera was one of the first epidemiologically investigated diseases and in the absence of conflict we know what to do. The key is sanitation and plentiful clean water; if these are provided cholera epidemics do not occur, and rapidly die out once started. Food can occasionally still cause significant epidemics. In the UK probably the most important recent one was the BSE/nvCJD epidemic. This caused 178 tragic cases to date but to get the epidemic under control required mass killings of animals, removal for a neurological tissue from the food chain and changes of feed for animals. It is possible to interrupt food epidemics; at the extremes this means removing the food causing risk from the food chain altogether.

We return however to the most important infection with epidemic potential that is in any way predictable. There is a reason pandemic influenza remains the highest risk in the UK National Risk Register. All other things being equal airborne diseases are indiscriminate and much more difficult to interrupt than other transmission routes. The speed of an influenza pandemic is rapid, and a high proportion of the population be affected over a very short time. The last pandemic we had, H1N1 in 2009, was relatively low virulence but very substantial numbers. It spread very quickly with somewhere between 40 and 90 million cases. The peak of transmission in the UK came on fast. Officially there were only 457 domestic deaths in two waves although this is likely to be an underestimate. A vaccine was available but well after the peak of the epidemic and this is likely to be the same for any future pandemic. Anti-viral drugs against influenza were controversial. They are most useful if taken early and a single mutation can render them largely ineffective. There were interventions called for in the popular press including screening at airports and banning travel which have limited or no effect; more difficult to be sure is whether and when to close schools. Realistically we can put the building blocks in place for pandemic influenza response, but no plan survives contact with the enemy. In advance we can construct mathematical models which predict global and national course from any early data, global virus edification networks, optimise vaccine production and stockpile antivirals. We can pre-decide which bits of the UK health system to turn off most rapidly. The reality however is that we will need to respond to the epidemic we are confronted with and that is inherently unpredictable.

The key point from this talk is that although the first reaction is usually panic, epidemic should be addressed systematically. Above all, the most important response to unknown epidemics is to discover their route of transmission; once we know that, even if we do not know what they are, we can begin to plan countermeasures. Often behaviour change in society is as important as medical interventions and high-end science. Examples given in this talk demonstrate the range of skills we will need. For Ebola we needed behaviour change, isolation and now a vaccine. HIV also required behaviour change and subsequently drugs. For Zika we need vector control; a vaccine is probably achievable. In cholera and nvCJD, safe water and safe food were important. For influenza pandemic's, we will require vaccines and drugs, but above all societal organisation. Epidemics and pandemics will always occur but the reason why infectious diseases are much less important than they were even a hundred years ago and certainly than when Sir Thomas Gresham founded this College is that richer countries are hardened against infections and therefore epidemics. Arguably it is those who bring peace and prosperity to society who do most to prevent epidemics, something Sir Thomas Gresham would have strongly approved of.