GRESHAM COLLEGE

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COVID-19

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Good evening. This evening I am going to talk about what is the major medical issue at the moment, the new novel coronavirus: Covid 19. And this is very much an initial view early on in this epidemic.

Epidemics can have very profound medical and social impacts, and Covid 19, caused by the virus SARS-CoV-2, definitely will. Epidemics occur actually more commonly than are popularly imagined, and whilst most of them are localized, some of them are severe enough to have international attention. And this is actually the third time here, as a Gresham professor, that I've talked in the middle of an epidemic: there was the West African Ebola epidemic, another major one subsequently occurred in DRC. There was the Zika epidemic, which affected particularly pregnant women and their offspring in Brazil. And now the largest of them by some distance, the Covid 19 one. And this is certainly the most medically and socially important epidemic since HIV and a lot more indiscriminate than HIV, which tended to be in particular groups or particular parts of the world.

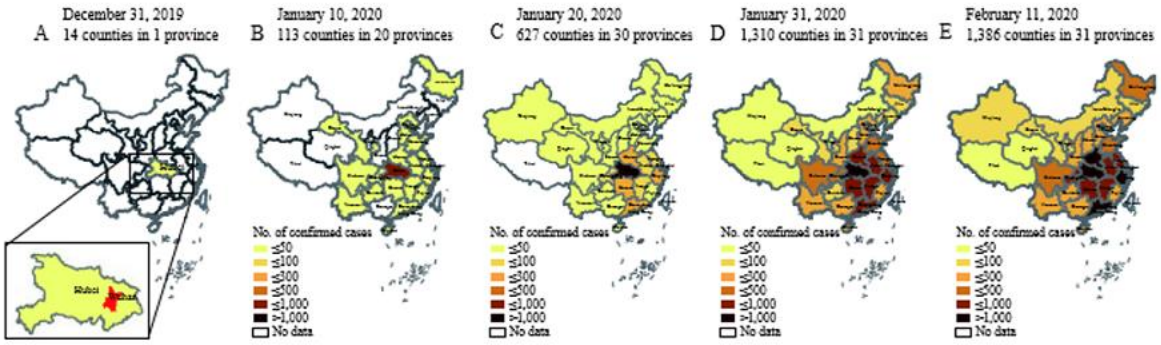
In the last century only flu pandemics have had an impact anywhere near as significant as this pandemic has had already. And we are still, I'm afraid, very much in the early stages and we will know a lot more about this in the next six months, and certainly a lot more in one and in two years. So undoubtedly many of the things in this talk will be superseded over time by science. And some of them, although based on our current understanding of this virus, which emerged and was reported to the W.H.O (World Health Organisation) less than four months ago, will turn out to be wrong because science advances and our understanding, I'm glad to say, will improve.

This talk will cover the epidemiology, including the mortality, the routes of transmission, and the force of transmission, the R or R0. It will then cover the epidemiological public health, societal counter measures we're having to use because we don't have drugs or vaccines or other powerful tools. I'll briefly cover the clinical picture and then talk about how the different potential medical counter measures, including vaccines, drugs, and diagnostics, may be used as we combat this serious threat. And then in a brief section, I'll talk about the global picture.

The early history of this epidemic I think everybody knows, it has dominated the news for the last four months. At some point in late 2019 a new coronavirus jumped species from animals into humans. This is the way that most epidemics and pandemics start, probably in Hubei province in China, and probably Horseshoe Bats with the initial reservoir species. Initial reports suggested Pangolins might be involved but evidence is still weak, and there is still some debate. In a sense, it doesn't really affect what happens now because it rapidly became a human to human infection. And it was able to do this because it is able to use a common receptor in particular the in upper respiratory tract, the ACE-2 receptor, to infect humans and be transmitted efficiently from person to person.

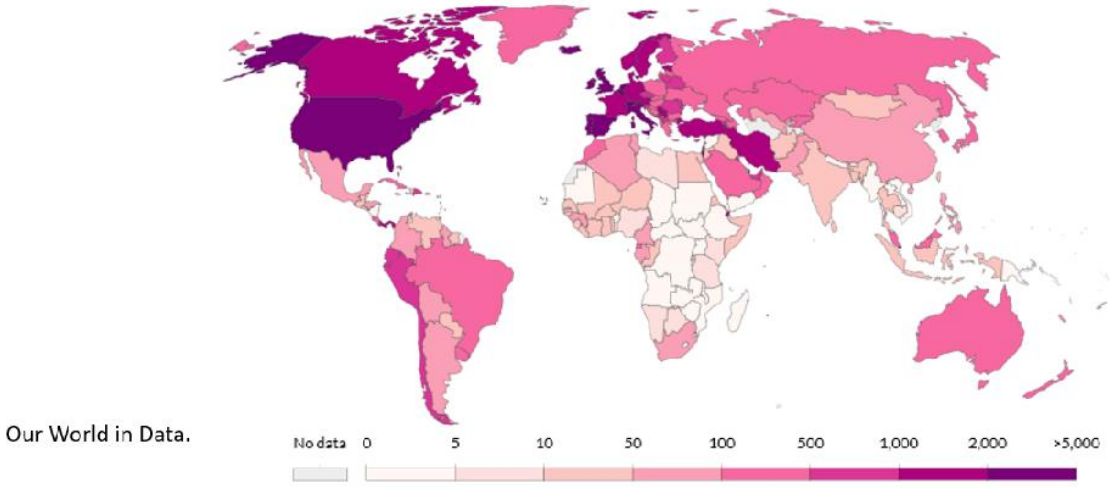
Its initial spread in China was very rapid and if you look at this map this goes from December 31st of last year until February the 11th of this year. And as you can see, the spread was very fast indeed. There was then a period in which there was significant transmission in China: there were spill over cases, cases that were imported from China in many places around the world but relatively little obvious transmission outside China, a few small outbreaks, which appear to be brought under control, but then it began to spread very widely, and the World Health Organization, WHO, declared this as a pandemic on March the 11th of this year. The current situation, I've shown you the numbers here, has very significant transmission here in Europe and also in the USA but also significant transmission around the world, and it's continuing to spread and continuing to increase in numbers in almost every continent other than Antarctica.

Initial spread in China was rapid. China CDC Dec 31st-Feb 11th.



After a short delay, rapid spread around the world.

WHO declared it a pandemic on March 11th. Current Situation.
3,041,777 cases, 211,169 deaths reported. Johns Hopkins.

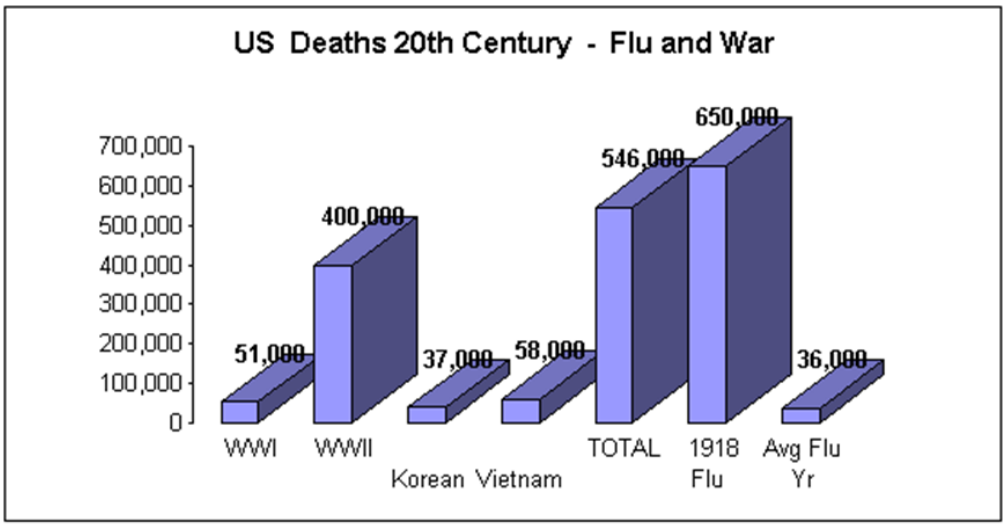


Now it's important when we think about epidemics that they are addressed systematically. And I've taken this slide from a talk I gave two years ago at Gresham College when I laid out how you should think systematically about how to tackle a new epidemic or pandemic. And at that point I said that there were five questions that you needed to have answers to, to work out what the best response was. The first is to think about the mortality or the severity, often sometimes referred to as the virulence, of the virus. How bad is it? How many people is it going to affect? The second, very important for how you tackle it, is the route and the duration of transmission from one person to another. The third is, do we have a treatment available that means we can use that treatment to blunt the effects of this new infection? Or even better potentially, do we have a vaccine available? And the final question is, what is the force of transmission? And these are the questions you need to ask at the beginning of any epidemic.

In the case of COVID-19 unfortunately two of those things we know the answer to, and the answer is we do not have them. We do not have a specific treatment for this virus, and we do not have currently a vaccine available. So, we therefore have to start with the other three questions and I'm going to go through them one after another.

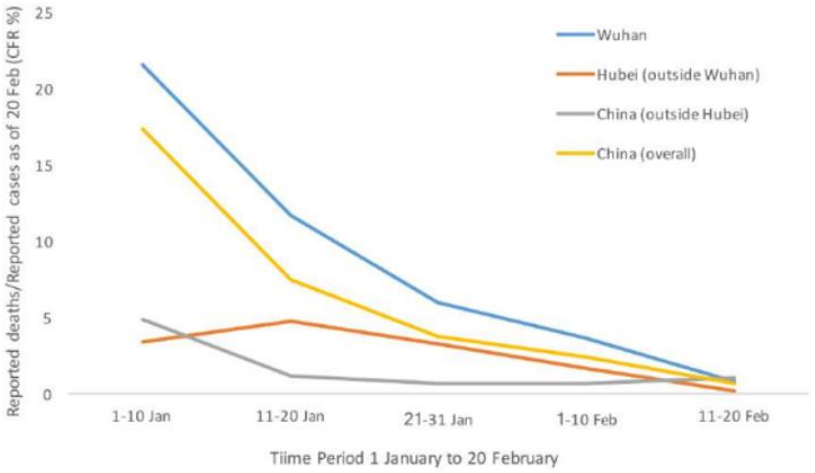
Let us start with mortality. Mortality, chance of dying, is a combination of the fatality and how many people are infected. Now, the infection fatality rate, the probability of dying if you actually have this virus, is probably around or just below 1%. This may change as we understand how many other people have been affected without symptoms.

And if we compare that to other diseases, it is actually a lot lower than many other diseases that have recently emerged. So, for example, Ebola when it first emerged, around 70% of those who were infected and had symptoms died. HIV, it was 100% of people who were infected who died, before we found medical counter measures. Smallpox, before it was eradicated, the major form of smallpox, mortality in most countries is around 30%. But then if we think about the H1N1 2009 flu pandemic, that had a much lower mortality than both those diseases but also than COVID 19, about 0.1% of people are estimated to have died of that. And then consider the other H1N1, the 1918 to 20 Spanish flu pandemic that had a mortality rate of around 3% but because so many people were infected, because the overall rate was quite low, the number of people who actually died of this was absolutely massive. And if we look at this slide, what it shows is that if you combine all the people, for example, in the USA who died as a result of World War 1, 2, Korean and Vietnam Wars, a smaller number of people died of all those wars combined then of this single infection, the 1918-19 flu pandemic. So even a disease with a relatively low mortality, if it affects very large numbers of people, can have a massive impact.



Now this disease, COVID-19, initial reports of the case fatality rates were very high and that's quite common because when a new infection starts, people notice the people who are dying, notice the people who are very sick. But as doctors and scientists in China began to understand the disease more, they started picking up much milder cases of the disease, and therefore the actual fatality rate was found to be a lot lower. And what you can see here is the assumed fatality rate over time as things went on. And this wasn't because the disease changed, but because our understanding of the disease and particularly of milder cases of the disease improved.

Initial reports of the case fatality rate were high. As milder cases were identified it went down. (WHO Joint Mission to China).



What I'll do now is just compare this infection, COVID-19 with six other coronaviruses which affect humans. There are many other coronaviruses in animals but in humans that are six, and there are four, which very commonly effect humans and have done for probably a very long period of time. I've written them out here, I'm not going to give them their names, they're very dull combinations of letters and numbers. But these coronaviruses are human coronaviruses and they cause up to 15% of ordinary colds, which people have generally in the winter season. Very occasionally these can cause more severe disease, pneumonia in adults or children, but that is rare. By contrast, there are two other coronaviruses that emerged over the last 20 years: MERS, and I'll talk about both of these a bit later on, which is a disease that jumped the species barrier primarily from dromedaries and this had a case fatality rate, and still does have a case fatality rate, of around 35%. So 35% of those who have a case of it, symptomatic case, sadly die. And SARS which had a case fatality rate of somewhere between 11 and 15%. So, the current infection COVID-19 is somewhere between these two, the four human coronaviruses and these two, which have recently jumped the species barrier.

COVID-19 (SARS-CoV-2) compared to other 6 coronaviruses that affect humans.

- 4 human coronaviruses have low mortality.
- Mainly common cold (up to 15%), some pneumonia esp. young children and the elderly.

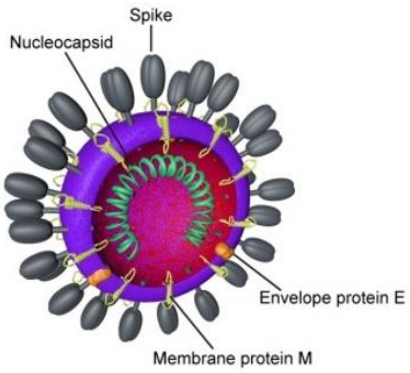
229E (alpha coronavirus)

NL63 (alpha coronavirus)

OC43 (beta coronavirus)

HKU1 (beta coronavirus)

- MERS case fatality around 35%.
- SARS case fatality around 11-15%.



In understanding how this works, it's probably worth thinking about this in terms of this two by two table, that what causes problems is if you have an infection, which causes both significant mortality and has very high transmission. So if you think about the coronaviruses, you have the current human coronaviruses, they have high transmission, there's a lot of them around, but they have incredibly low mortality. And therefore they have a relatively small impact in terms of their burden of disease.

Transmissibility and virulence (mortality) of coronaviruses.

Data approximate.

	Low mortality	**Higher mortality**
High transmission	**Current human coronaviruses 229E, NL63, OC43, HKU1.**	**COVID-19. Around 1% mortality, CFR around 1.5%. Very high transmissibility.**
Low Transmission	**Not worth worrying about.**	**MERS. 2494 cases, 858 deaths. 35% CFR. SARS. 8422 cases 774 deaths. 11-15% CFR.**

The other extreme are MERS and SARS. Both of these have a high fatality rate, if you catch them you have a high chance of dying. But actually the number of people infected was small in both cases, in the low thousands, and in

both cases, at least to date, the number of people who have died from them, at least in terms of people who are recognized or dying from them, is less than a thousand.

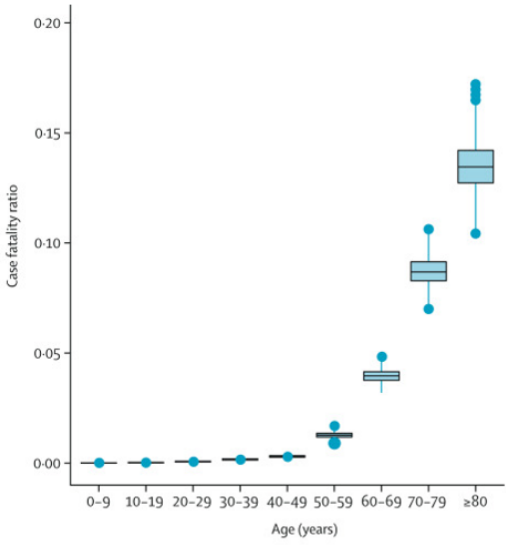
COVID-19 has around a 1% mortality, case fatality rate is a bit higher than that, that's people who've actually got symptoms, but it has very high transmissibility and if you multiply a very small chance of dying by a very large number of people, you can still have a very big impact on society.

Now, at an individual level, the chance of anybody watching this dying of coronavirus are actually low. Over the whole epidemic, even if we have no vaccine, a high proportion of people will not get this. Of those who do get it, a significant proportion, exact number is not yet clear but it's certainly a significant proportion, have no symptoms at all - they get it without even realizing it. Of those who do get symptoms, the great majority, probably around 80%, depends on a number of factors we'll go on to, have a mild or moderate disease, which is sufficient that they would want to go to bed and feel unwell in some cases. Some people can actually just carry on doing their ordinary activities, although we ask them not to, but they don't actually need to go to the doctor or medical services and they make a full recovery. A minority have to go to hospital, but most of these actually the principal thing they need is oxygen and the great majority of those will go on just to survive. And then a minority have very severe disease, may need ventilation, and of those, some sadly die with current treatment. But important to stress, even in the most high risk group, the majority of people who actually get this infection do not die.

Now, the biggest risk factor for dying from this disease is undoubtedly age. Doctors and scientists in China picked this up at an early stage, and what they found was that the case fatality rate, the probability of dying if you actually have symptoms, was extremely low in children, and that's been replicated over time. And then steadily as you go up through the ages, certainly once you get above 60, the mortality rate climbs quite significantly. Now there's a difference between what's called the 'case fatality rate', your chances of dying if you have symptoms, and the 'infection fatality rate', and it's possible the number of people without symptoms, asymptomatic infection, are different in these different ages. We don't yet have those data because we don't yet have a test that can say reliably: has someone previously been infected? But even for those who get symptoms, these are the case fatality rates and even in the oldest group, people over 80, I re-stress the majority of people who catch this will survive.

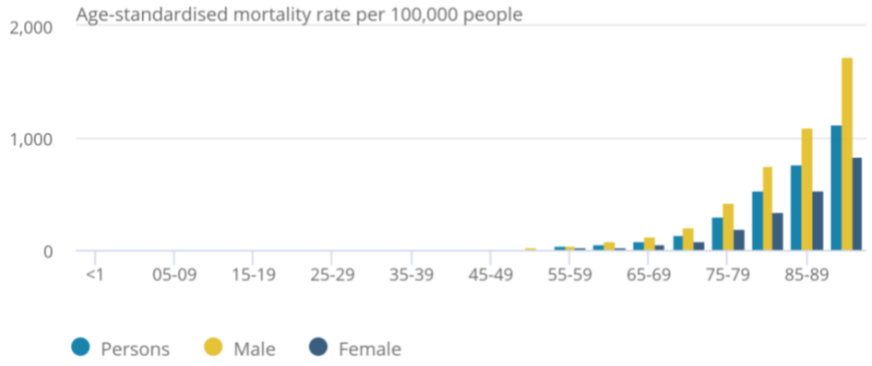
Initial data from China suggested a strong trend of case fatality to increase by age. Infection fatality lower. *Verity R et al Lancet ID 2020*

- 0-9 years CFR 0.003%
- 10-19 years 0.01%
- 20-29 years 0.06%
- 30-39 years 0.15%
- 40-49 years 0.3%
- 50-59 years 1.25%
- 60-69 years 4%
- 70-79 years 8.6%
- 80+ year 13.4% (IFR 7%?)
- We do not currently know asymptomatic infection rate.



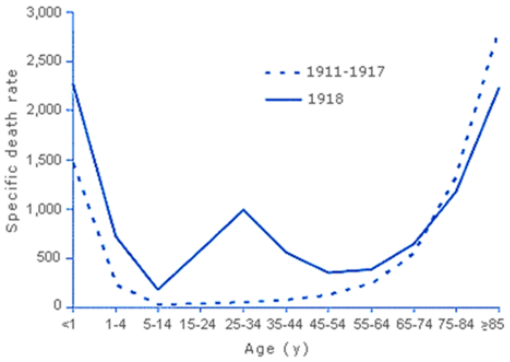
When we look at data from the UK, the same pattern is found and that's true in Italy and Spain and other countries, which have had significant epidemics, that you see very, very few deaths under the age of 50, and then a quite steep climb as you go on in time. But importantly, and I'll come back to this, quite a big difference, and this is the second risk factor, between men and women, a higher mortality rate in men - quite significantly at every age group.

Age and gender. ONS data for England and Wales, March 2020.

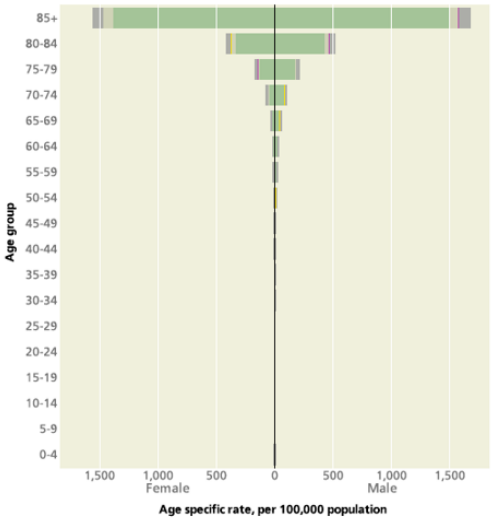


Now, there's a complicated interaction with very many infections between age and mortality. In general overall on the right here (below), the expectation is that people who are older have a higher risk of dying from any infection. There are a few exceptions to this. So this is the mortality rate by age, at the top the biggest bar is people over the age of 85, below that, 80 to 84 and so on, all the way down. And these are all infections in the UK leading to mortality. So it is the case that there are very many infections where if you're an older person, your chance of dying from any infection, it might be a pneumonia, urinary tract infection, other forms of sepsis, your chance of dying are significantly higher.

Age and infections often have complex interactions.
Influenza mortality 1918 USA (L) and UK infectious mortality (R).



Source: CDC Emerging Infectious Diseases · Vol. 12, No. 1, January 2006
Link: http://www.cdc.gov/ncidod/EID/vol12no01/05-0979.htm

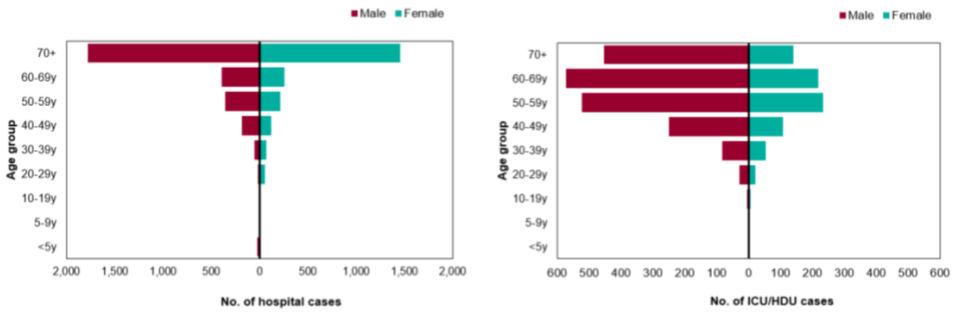


But that isn't always the case. So for example, if you look at pandemic influenza, the 1918-19 pandemic influenza period, what you find is that young children and the elderly, the two groups who normally die of flu and many other infections were badly affected, but so also were young adults. But that has not been seen in this coronavirus epidemic. Mortality is very heavily shunted towards people who are older citizens or who have pre-existing health conditions, which I'll come on to. But you can also look at this a slightly different way. In reality, other than children where the mortality rates are very low under all circumstances, COVID, If you catch it slightly increases your risk of mortality in every age group but in younger people, the chance of dying is incredibly low in the first place, and COVID therefore only slightly increases it.

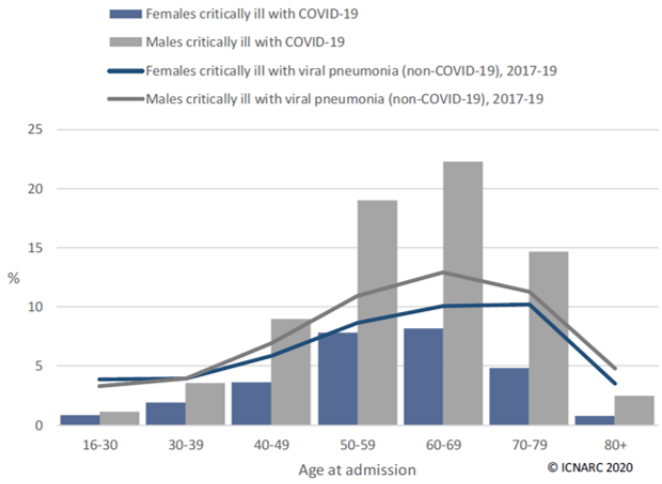
But the main thing is that older people are more likely to be hospitalized, of the people that are hospitalized older people are more likely to get severe disease, which means they have to go to intensive care and sadly, as I've said already, older people are more likely to die.

Now, just moving onto this point about the gender difference, I think this slide shows very clearly, in the UK, the difference between men and women in terms of the severity of this disease. In red are the bars, which are men and in green the bars are women. On the left, what you see is people who go to hospital, there is a very slight increase in hospitalization rate in men compared to women but by the time you get to intensive care, you get to a situation where men are much more likely to have severe disease and therefore need intensive care and then sadly to die. And this is very atypical, we do not know why this has happens. So here, what we've got is a graph of ICU data showing the COVID cases - in the grey and blue bars showing the big difference between men in grey and women in blue, and then underneath that, a line which shows the difference between men and women who are critically ill with other viral pneumonias. And as you can see for those, there is very little difference between men and women, but a very big difference with this disease. So this is a very significant risk factor.

Hospitalised cases (L) and ICU/HDU cases (R).
PHE, data from England.



This sex differential is very atypical. ICNARIC ICU data.



And the third group of risk factors are things which are what are called co-morbidities, which other diseases that people have and these make them more susceptible. The ONS data, the Office of National Statistics here in the UK, show that about 90% of people who died from had at least one other so-called co-morbidity or other disease. These include cardiovascular disease, heart disease, stroke, diabetes, chronic lung disease, people are immunosuppressed either because of infections, because of underlying disease or cause of treatment, people with chronic kidney disease and liver disease and also, there's a significant link with people who are more obese.

There are also probably some ethnic groups who are at greater risk. There's no doubt that there are higher rates of in the UK, people are from a minority backgrounds who have significant severe disease. Some of that is due to comorbidities, some of it may be to do with the job they do, or socioeconomic factors, but there may also be a factor which is genetic and which has to do with their genetic heritage.

So those are the risks for mortality. The next thing to consider is the route of transmission of COVID-19. And this is important because if you understand the route, that tells you what counter measures you can use. And again, in broad terms, infections have five routes, which typically are the route of transmission. There is the respiratory route, which includes COVID-19 SARS, MERS, and flu. There's a sexual route and the last really major pandemic we had, HIV, was a sexual route of transmission or a bloodborne route, a secondary route. Touch is a route and that's a significant route particularly for Ebola. Water or food is a route and that's a major route for example, cholera. And then there are insects transmitted diseases such as Zika or malaria.

The reason that knowing this is important is if, for example, it's a sexually transmitted infection that takes you down one route in terms of how you combat it, if it's an insect borne one or vector-borne one, it takes you down a different one.

Respiratory infections are in fact the most difficult to tackle. And then it additionally has a secondary route, which is maybe quite an important one, which is touch where people touch a contaminated area, which someone has coughed or sneezed or talked over putting droplets onto it and then touch their face. Outside healthcare settings, the main transmission mechanisms all are via the mouth or nose and possibly eyes. And there are, outside healthcare settings, really two ways that people will catch this disease, the first of which is droplets, and these are produced, they're small but they're produced by people coughing, potentially sneezing, although that's much less of a feature of this infection but you can also be talking, singing, even just breathing, and they go direct to people's mouth or nose, to their mucus membranes. And they tend to travel shortish distance, WHO estimates most of them within a meter but it can go

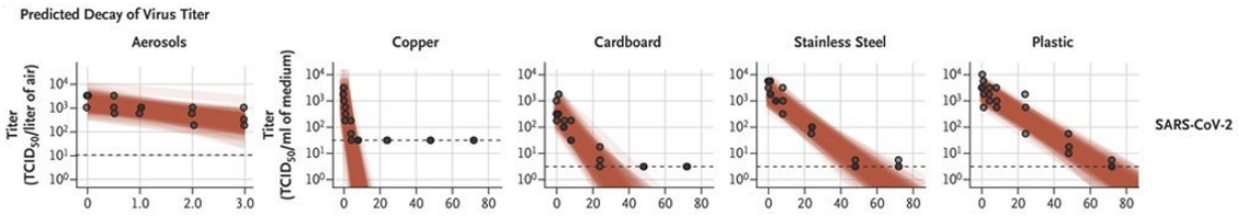
beyond that - in the UK, we say two meters is a safer distance, but they can carry occasionally even beyond that and then they drop to the ground, they're large enough that they actually dropped to the ground. But if you're within that zone, when people cough, you can actually have them deposit it on you.

And then the second route is if someone has coughed on or they have coughed into their hand and then touched a surface and then you touch it and then you touch your face, that's the key bit, and then you touch your face, it gets to your mouth, throat, your nose. Then you can transmit it from an object, a door handle or something like that, onto your face or nose and then catch it that way. And that means that there are two things that really everybody has to do, one of which is to try and make sure that if they sneeze or cough, that they catch it so that it doesn't go any further than it needs to. The second, and very important, is to wash hands because if you touch it and then you wash your hands before you go on to touch your face, then the virus will not be transmitted. Washing your hands with soap and water is highly effective. This is old fashioned, but highly effective in preventing transmission. If you can't get soap and water, an alcohol gel will work. Soap actually damages the lipid around the virus, so it is important you add soap to just rinsing your hands under a tap. And this is a relatively easy virus to get off surfaces, most normal detergents and soap will actually kill the virus so cleaning in the ordinary way will usually get rid of it.

If it is on a surface because someone has coughed on it or touched to having coughed into their hand, there is a relatively rapid drop off in the viability of this virus. It does depend a bit on the temperature, on the humidity and importantly on the surface. But even under ideal circumstances to this virus, it's unlikely to be viable beyond about 72 hours. And what you have here at the bottom (data below) are some data that compare the survival of the virus on different materials, showing that, for example, on copper the actual survival is really a matter of a small number of hours. On softer things like cardboard, it survives for less time than if it's on something like stainless steel or plastics. But even under these, the great majority of it will be gone within 48 hours and it's very unlikely to be viable beyond 72 hours.

Preventing transmission via objects and hands.

- Washing hands- soap and water, or alcohol gel.
- Soap damages the lipid around the virus.
- Most normal detergents and soaps will kill the virus.
- Rapid drop off of viability of the virus. May be a few hours depending on temperature, humidity, surface.
- Very unlikely to be viable beyond 72 hours.
- van Doremalen et al, NEJM, 2020



So those are the routes of transmission. It's also important to work out what the duration of transmission is, how long is someone infectious for after they become infected themselves? And for some infections, and we actually initially thought this might be true for this infection, people are only infectious after the time they've had symptoms, but actually increasingly evidence has come out that people are infectious for probably two, or maybe even three days

prior to getting symptoms. And then once people get symptoms, they're probably significant infectious for a few days, and then it drops off quite rapidly to about seven days, although a few people may be infectious a bit beyond that.

We also know that a significant proportion of people get this virus without symptoms. What we don't know is how much that contributes to the epidemic. Now this is important because if it was the case, as it is with some infections, that only people with symptoms significantly transmit, then if you could isolate everybody who's got symptoms, then the epidemic would be significantly reduced. But in this infection, it does look as if people are infectious before they get symptoms, and they may be infectious even if they don't get any symptoms at all.

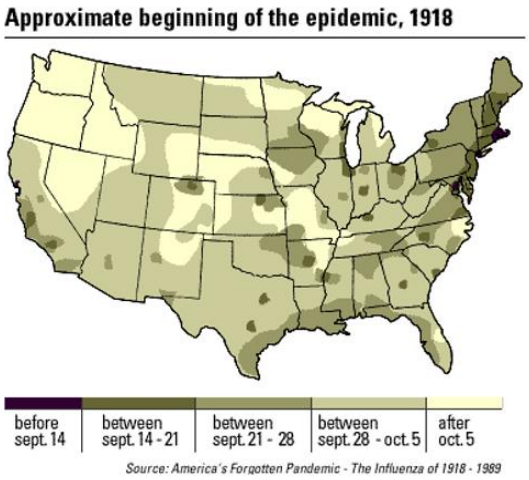
Now in thinking how a pandemic or an epidemic coming from our respiratory virus might go, it's important to think about previous examples where we've had new or emerging respiratory viruses epidemics, and I'm going to start off with the two recent coronaviruses and then move on to the most classic of the respiratory viruses in terms of epidemics, which is influenza. The first of these, the more recent of these, is MERS-CoV: this has as its reservoir dromedaries, and it is transmitted, at least at this stage, dromedary to human mainly in the Arabian Peninsula - and then there is some human to human spread. As I said earlier, if you actually catch this infection, it's difficult to catch but if you do catch it, the chance of dying are high, about a third of people with MERS and symptoms will die. And in this case, what has happened over time is that there have been spikes of transmission of this, there were some significant outbreaks, including in 2015 - a significant outbreak in South Korea where it was transmitted person to person, particularly in healthcare settings, and then brought under control, but it's never taken off as a major epidemic or pandemic around the world.

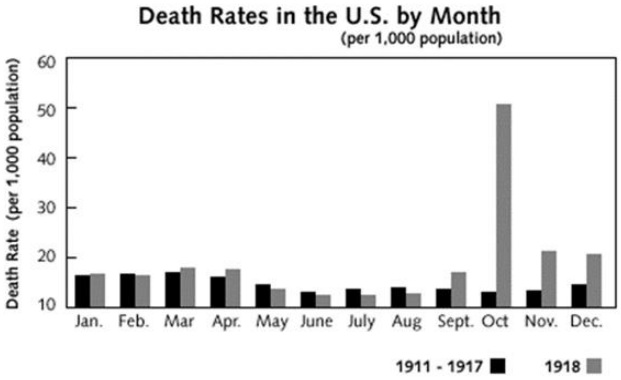
The second one to consider is SARS. SARS is actually a coronavirus that has got some similarities as a virus to the current COVID-19 coronavirus. In 2002-3 it emerged from bats, also in China, it spread widely in China and then spread to a variety of other areas around the world. There were significant outbreaks, for example, in Taiwan, in Canada, and in Singapore. And then around the world, there were what's called 'spill-over cases' where people would fly in with this infection but then they'd be identified early, isolated and it didn't get transmitted on - there were, for example, four cases in the UK. This is a serious disease, between 11% and 15% of people who caught it sadly died, and transmission of this was almost exclusively or probably even exclusively from people who had symptoms. There was a very concerted effort to find all the people who had symptoms of this, based in particular on their geographical travel or where it was. They were isolated, classical public health, and this infection went away in the early stages. It was much less transmissible, we now can see, than the current coronavirus. And so after this initial 2002-3 epidemic and just under 10,000 cases of people getting it, this disease went away and has never re-emerged since that time.

Now, this is an important one to look at, and when this current coronavirus COVID-19, SARS CoV-2 the actual virus itself, first emerged many people thought, well maybe this is going to behave like SARS: there will be a significant outbreak in its initial country of origin, China, some spill-over cases, but we will be able to contain it, it'll be controlled in its country of origin and this will just disappear. But obviously that has not happened in the case of COVID-19.

The other examples that are relevant here are probably the influenza pandemics. And of these, the most important is the 1918-19 influenza pandemic, the worst on record - estimates vary but somewhere between 17 and a hundred million deaths. Three waves occurred over two years, and the second wave was the one that killed the majority of people. And to give you some idea about how fast this spread: this is the USA at a time when travel was less connected than it is now - the dark colours are where it was before September the 14th and the light colours are where it was after October the 5th. This moved incredibly fast, and if you look at mortality rates in the US in October of that year, you can see a really massive spike over the baseline rate of mortality. So, this moved at phenomenal speed and killed very large numbers of people.

The 1918-19 influenza pandemic. Worst on record: 17-100m deaths. 3 waves over 2 years- the second was worst.





Two other significant pandemics of influenza occurred in the last century. In 1957, H2N2, one called the Asian flu, had round about 0.3% mortality, so quite a lot less than the 1918 H1N1, which killed around 1.1 million people in the world and in the US, where there was good data, around 116,000 deaths occurred as a result of this. And then 11 years later another flu pandemic, which again killed around a million people worldwide, had a significant mortality in the USA - around a hundred thousand people but lower in most other countries, including the UK - occurred in two waves again, the second wave killed more than the first. And here, what you can see is the kind of Nightingale hospital equivalent from that era.

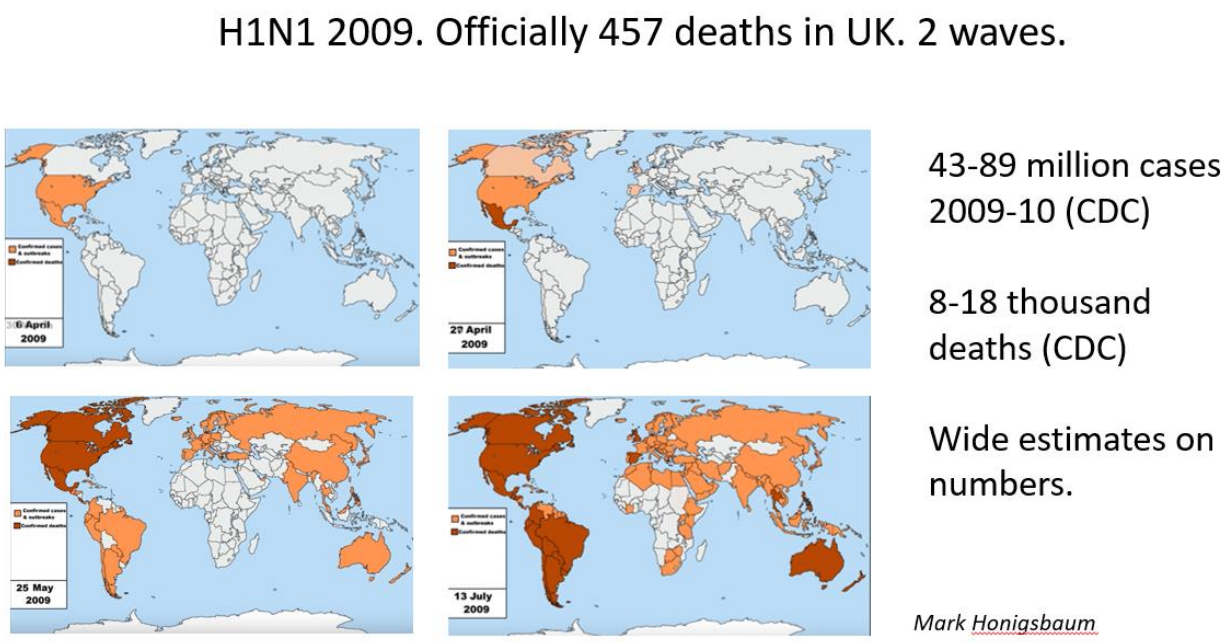
1957 (H2N2 'Asian') and 1968 (H3N2 'Hong Kong') flu pandemics.

- 1957 0.3% mortality. 1.1 million people worldwide, 116,000 USA (CDC).
- 1968 1 million worldwide, 100,000 deaths USA (CDC) but lower mortality in UK. Occurred in 2 waves, second killed more than the first.

Asian flu, Sweden

And then the last flu pandemic, which most people will probably remember although it was relatively mild, was another H1N1 in 2009. This again moved very fast so what you can see here on the left, this emerged in Mexico originally, spreads through the USA initially and then spread around the world. And as you can see on the top left, we have 9th of April and the bottom right, how far it had spread by the 13th of July - it moved incredibly quickly. But fortunately this had a very low mortality, so very high transmission, low mortality, and therefore probably,

although several million cases - probably between 40 and 90 million cases were actually infected - the number of deaths around the world and in individual countries was very low. So, in that pandemic there are only about 460 deaths officially recorded in the UK.



So, this is a range of different ways in which respiratory pandemics and respiratory epidemics of known coronaviruses can behave.

How they are going to impact on people will be a combination, as I said, of their mortality and how far and fast they spread. And this brings us on to the force of transmission, the R_0 or R. This is a key concept, probably the key concept, in understanding both how epidemics propagate and also how you have to control them once the rote of transmission is known.

The force that transmission is the number of people, the average person with an infection, goes on to infect. And the R_0 is what happens if you put this into a population who have no immunity. By definition, to get an epidemic, you've got to have an R of greater than one, so the average person has got to pass it on to more than one other person. If you can get the R to below one if, let's say, you've got a hundred people infected and they infect, let's say the R is 0.5, 50 people who then infect 25 people, this epidemic is going down. But if it's anything above one, this is going to increase. For COVID, the R is somewhere, in the UK, when it first arrived in the UK with an R around three maybe slightly lower, but in that order of magnitude. So on average, one person was giving it to maybe roughly three people who give it to nine people and so on. And just to put this in context, the Ebola epidemic in West Africa had an R of somewhere between 1.2 and 2.5. It's spread really quite fast in West Africa. The 1918 flu pandemic probably had an R slightly lower in fact than the one we've got at the moment. In the expansion phase of HIV the R was somewhere in the two to five range, depending on which country we're talking about. It can of course go a lot higher than this. So if you think about measles, a very highly infectious disease, that can have an R of greater than 10 and malaria in parts of Africa has an R of greater than a hundred. But for most epidemics, the kind we are talking about for this disease is quite sufficient to lead to a significant onward transmission and propagation.

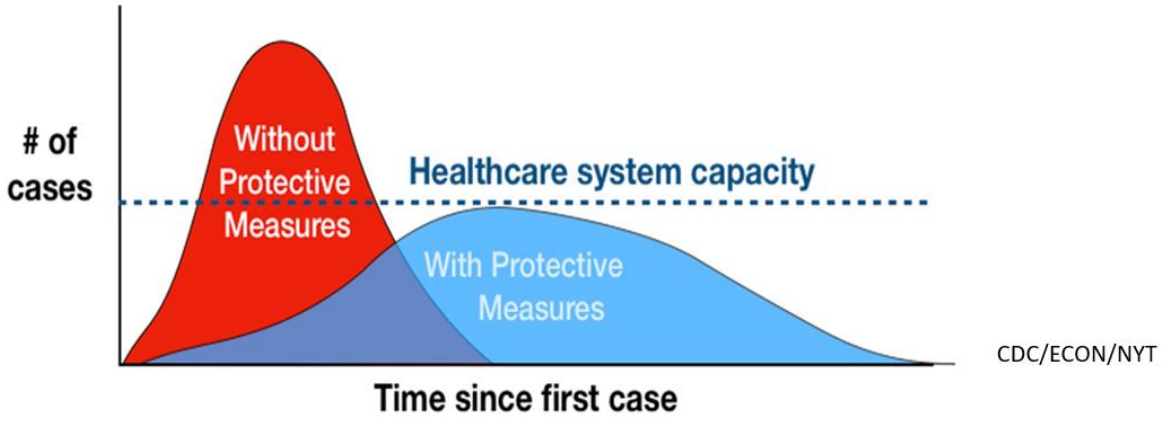
And if R is above one, even by a small amount, you'll go on to get exponential growth in this epidemic. It may be slower if the R is low, and if it's high, it'll go faster. It depends on a number of things, including how fast the generation

time is but in the case of COVID, it was fast. And when it came to the UK the initial doubling times, depending on where you were, were between three and five days. So every three days, in for example London, every three days the number of people who actually had this disease was doubling. And this means that without interventions, you get from very low numbers to very high numbers extraordinarily fast, because it goes up an exponential curve. So you've got two and four and eight, initially they seem small numbers, but when you're turning from 2,000 to 4,000 to 8,000 over a six day period, for example, you're clearly then starting to move into very, very large numbers extremely quickly. And the results of that, if you've got a disease which has got significant mortality and a significant severe disease as COVID-19 has, is in addition to large numbers of people being infected and a significant proportion of those going to hospital and potentially sadly dying, you also get the health service likely to be overwhelmed extremely quickly.

So what can you then do? In the absence of a vaccine or an effective drug, which is clearly the way we want to get out of this, and I'll come onto that in the third section of this talk, we then have to move on to relying on social and public health measures to try to control this very rapidly spreading virus with a significant mortality which was doubling every three days.

And the concept, which I think most people are now very aware of, is the idea of flattening the curve. Because what you have is you have an exponential curve if the R is uncontrolled and mitigated, this goes up very sharply, very quickly. So you get extremely large numbers in a very short time. Health service becomes overwhelmed, and if you can slow this down, pull the R right down, you can both slow it down so you get much lower peak and also if you can get the R below one the number of cases starts to fall. Simultaneously with that, you then look at the healthcare system and you try and increase the capacity of the healthcare system to cope. And in most countries that have had significant COVID epidemics, that is what we've done. We've collectively as society done social measures to flatten the curve, to pull down the force of transmission and pull the R below one. Then we've raised the bar in terms of expanding the health service capacity, and my colleagues in the NHS in the UK have done an absolutely heroic job in doing that over the last six weeks.

In the absence of a vaccine or effective drug we have to rely on social and public health measures. 'Flattening the curve'.
And raising the bar (expand capacity).
Keeps within healthcare capacity. Prevents overshoot of COVID-19 cases.



The third thing that this achieves, however, is that if you have an epidemic that runs without any check, more people get infected. You get what's called overshoot, and more people get infected then you actually would do if you can flatten the curve right down. So what you're trying to do is three things: pull the curve down below the ability of the

healthcare system to cope, stop this overshoot where more people get infected than you can avoid, and increase the capacity of the NHS or other healthcare systems. And those are the three things we've been doing so far this year.

And if you don't have a vaccine or drugs, there are broadly four things you can do. The first of which is at an individual level to reduce the chances of infection - these are the respiratory hygiene things and hand-washing, as we've talked about before, really effective interventions, in fact, at an individual level.

The second thing, classical public health, is you isolate the cases. If someone's got the symptoms, you stay at home. Because this is something which can infect people early and with minimal symptoms, we also say their close household contacts also have to stay at home over the period of potential infectivity. And if possible, you also want to isolate all their contacts, what's called contact tracing and isolation. So isolate cases, isolate households, and ideally isolate their contacts. There are a variety of ways this can be done, and different countries have taken slightly different approaches to this, but the idea of isolating cases so they don't go on to infect is common to everybody's response.

The third thing, and this is where the concept of social distancing comes in, is the idea of reducing links between individuals and above all between households. So if individual household members normally wouldn't meet but their children meet in school or they meet at the school gate or they meet at work or they meet on public transport or in shops, these are in situations where one household can pass on infection to another household. And the social distancing measures are a way of reducing the links between these households. And this helps to pull the R down for any infection, particularly respiratory one where this is the most relevant thing we can use.

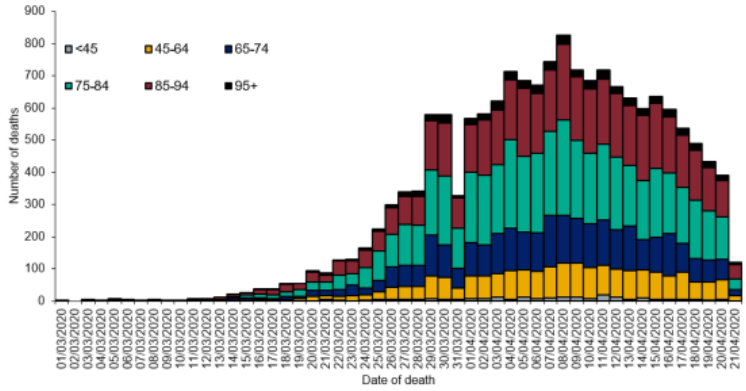
And finally, in an infection like this where we know which group of people are the most likely to die of this disease, you try and make sure that that group, older people, people with co-morbidities are particularly unlikely to come into contact with infection and you ask them to take particular caution not to come into contact with people unnecessarily and in the most severe cases to do what we've called 'shielding', which is absolutely minimize their contact with anyone else to reduce the chance that they are one of the people who gets infected because they could go on to have severe disease and to die.

One of the troubles with Covid-19 is because it had this significant force of transmission, one measure, or even two or three measures, were not sufficient to pull the R – the force of transmission – below 1 and therefore flatten the curve, and eventually get the number of deaths to reduce.

Modelling exercises were done here in the UK and in other countries and what they showed was that you have to use a combination, quite a large combination of different measures to have enough force to push the R down by isolating as many cases as possible and breaking the contact between households; by closing schools, closing workplaces, reducing all unnecessary contact between people who are in different households.

Now, that has worked. It has worked in every country that has used it and what you are seeing in the UK for example, these are hospital death rates (the curve is slightly different in social care settings) but what we are now seeing is that the number of deaths, the number of cases, the number of intensive care cases has now started to reduce. The R, the force of transmission, has gone down.

Hospital deaths by date of death and agegroup. 1/3 to 21/4.
Public Health England.
But note that total all-cause age-adjusted mortality is the key metric.



I should put a caution on this: these data are hospital Covid proven cases. We know that there will be people outside that setting who will have died in care homes or at home and we also know that some people may have had Covid who are not recognised as having Covid. So it is important when we start looking eventually, at the number of people who have died of this, that we don't just look at people who have been identified as having Covid, but we also look at the all-cause age-adjusted mortality, looking at actually how many people died in total. This is the key metric. However, it is clear by all the metrics under, or in almost all the settings in the UK, in most European countries, (and previously in China for example) that the curve has reduced as a result of these aggressive social distancing measures and isolation by a variety of different means.

Unfortunately, however, we have a situation where the R could very easily go back above 1. Since we are sure that a significant proportion of the population and probably the great majority have no immunity to this disease, if R went back above 1 we would certainly get a second wave. If it went back to exponential growth through any length of time, the NHS or any other health service would go back to being threatened and potentially overwhelmed. So we must be aware of the fact that we are going to have to keep in place measures to keep R below 1 for the foreseeable future until we get effective medical countermeasures such as a vaccine or clear demonstration that large numbers of people have been infected asymptomatically without any symptoms.

Although we tend to think about the direct causes of mortality from this disease, there are also four ways this epidemic will cause excess mortality and morbidity - morbidity being people who get severely ill, but maybe not to the point of dying.

-There are the direct causes of deaths from the coronavirus assuming that the health service is functioning optimally. So these are people who die of the disease despite the fact that health service is working fine because this can be a dangerous disease, particularly for older people or people with coexisting health conditions.

-The second cause of death, which has occurred in some areas, but has not to date occurred in the UK I'm glad to say, is indirect deaths because the health service becomes overwhelmed and therefore unable both to treat people with Covid-19, and also potentially overwhelmed and unable to treat other emergencies. A lot of the activities that countries around the world in Europe, in the US, in China and elsewhere have done, have been to make sure that health services are not overwhelmed and therefore this cause of indirect deaths does not occur.

-The third cause of mortality or morbidity is indirect deaths because the health service has had to cancel things to make space for the surge of people who had Covid coming into the NHS. We had to cancel, or postpone, a lot of

non-urgent but important things for example, elective surgery or screening. There may also be indirect deaths because people are afraid to come into hospital or do not want to overwhelm the system and stay at home despite the fact that they have heart attacks, strokes, or other severe causes of mortality. And it is very important, and we stress this throughout this whole epidemic in the UK to date, the NHS has always had capacity for emergencies. We really, really want to stress to people that if they have a medical emergency that is life threatening or serious then they should still go to use the NHS.

-The final cause of mortality, and this is a much longer term one, the interventions that we have had to put in place for this have a very big social and economic impact. This is a complex area; there is a very complex interaction in the short term, between economic and health outcomes but in the long term, if you increase deprivation for the people who are already more socioeconomically deprived, we know that there is a very strong link to ill health. There is a very clear correlation in every country in the world between deprivation or being relatively socioeconomically deprived and having long term health problems.

So these are all the ways in which this epidemic can have an impact. That is important when we're thinking about the next phase in every country as it comes out of a lockdown, because every country has now got an extremely difficult balancing act, and we all need to be honest about the fact that there are no easy solutions here.

There are certain things which are absolutely clear. The first of which is if we allow the R to go above 1 for any sustained period, it will lead back to exponential growth again and the risk that many people will get the infection and the health service will be overwhelmed. But at the other end of the spectrum, Covid-19 is a very long way from finished, and eradication is technically impossible for this disease [for those who want more information on eradication I have done a previous Gresham lecture on this].

There is also the complication that just narrowly, from a health perspective, the optimal answer about how you start to remove some of the things involved in lockdowns and other social distancing, may have different impacts depending on whether you are talking about the direct deaths from Covid or indirect deaths through some of the other mechanisms through other impacts on the health service or the long term socioeconomic effects on individuals. In addition to health impacts, there are of course, important social and economic considerations. So this is going to be a very difficult decision for every society – how they balance the relative impacts of different things. But all societies, I think, would agree that we need to make sure that the R does not go back above 1, because if not, we will go back to a second wave. And the point I made with the flu pandemics is it is entirely plausible for a second wave to actually be more severe than the first if it is not mitigated.

One other slightly gloomy point before I move on to clinical things, it is not just in Game of Thrones that winter is always coming, it is also true in any health service. You have to think about winter and there are several ways in which this may have an effect on this virus. So despite the fact we are in early spring now, I and my colleagues are having to think about this at this point. There may be a seasonal element to this, we don't know as it's too early with this virus, but if so, for most respiratory viruses, there's a higher likelihood of transmission in the winter. Secondly, in a period when other infectious diseases that look very like Covid are there, a syndromic approach where you say, "if you've got these symptoms, stay at home" becomes much less easy because people will have potentially repeated infections with things that are not Covid, but look like Covid. At this point in the year, if someone has got something that looks like Covid, there is a high chance it is Covid but in the winter, that is less true. Thirdly, is that the NHS and all other health services around the world are more under pressure during this period through a combination of different reasons; it is an observable fact everywhere.

On the other side of the equation, the fact that there will have to be some social distancing is likely to reduce or even significantly to reduce flu and other respiratory tract infections. Nevertheless, the winter is always worse than the summer, spring and autumn for health services. So we need to think about this at this point, and we need to think about this in terms of how we come out for the next phase.

Now, a short section on the clinical aspects of Covid. The symptoms of mild and early Covid are often very nonspecific. The majority of people who have symptoms, and as I said, some people do not have any symptoms at all, have a fever or cough. That is the reason why in the UK, we say if you have a fever or cough, you should stay at home, even before we started to have the other social distancing measures, and this will need to continue to be the case. And also stay at home with your household if you are living with others.

Additionally, there can be muscle aches, headaches, shortness of breath, chills, or sore throat, all things which are common for many other respiratory infections. Something which seems to be particularly prominent in this infection, and we are still looking at this, but I think it looks likely this is true, is there seems to be an association with losing taste or sense of smell. Now, for most people who have mild symptoms, they do not actually need to seek medical advice; they'll have a mild or moderate disease, and they only need to call for help if they deteriorate. Most of them will recover, either after a very mild illness or maybe after two or three days in bed with a 'flu-like' – as people normally call it – symptoms and then people improve. But they must, and we really must stress this, self-isolate immediately even with minor symptoms.

Most people will recover within about seven days. They may have a persistent cough, which goes on for quite a lot longer than that. It can be a bit annoying for some weeks but other than that, people with mild disease tend to make a relatively quick and full recovery. But a minority fail to settle and are still unwell at a week and may start to deteriorate. People can deteriorate before that, but it tends to be after a bit of a delay. And they may go on to get respiratory failure requiring, in most cases, oxygen, not an absolutely all cases. And in more severe cases, they can have other organ failure.

And it does look as if this deterioration which occurs maybe a week after the first symptoms, is actually in part at least an immunological reaction, so it is not necessarily directly from the virus, but is an immune response to the virus and that's important for possible treatment. And then some of those will go on to have severe or critical disease requiring intensive care or at least high dependency levels of care. It can have a very rapid deterioration. This is still a very early period of understanding of this disease we are still evolving on the basis of clinical studies and people looking and working out what works, how best to manage this. The mortality rates are probably in the UK and most other countries beginning to come down as doctors get better at managing this just from the normal way in which doctors learn how to manage a new disease. There is quite a lot of debate about things like mechanical ventilation; who are the right people to have mechanical ventilation? One thing that is very striking from this disease, is that it seems to have a significant increased risk of blood clots, like pulmonary emboli in the lungs, or indeed strokes and other kinds of clotting. Initially we thought the majority of the severe disease, would be just in the lungs but a significant number of people who have ventilation, also for example, have kidney problems and need renal support. So this can be really a very severe disease and at the extreme end people can be very sick indeed and for the sickest patients there is a significant mortality rate.

So now I am going to move on to the next section of my talk which is asking the question, "will technology dig us out of the hole?". Currently, we are having to use relatively crude social interventions because we do not have a technological solution to this virus, and my optimistic answer, and I am reasonably confident about this, is undoubtedly that we will- eventually.

Infectious diseases are something which humans have proved incredibly effective at combating. If you had gone back to the period when this College was founded, medicine was very heavily dominated by infectious disease. It has gradually improved over time. A hundred years ago, infectious diseases were still killing more people than cancer, and were pretty similar, but not quite at the same rates as cardiovascular disease. Over the 50 years that followed that, infectious diseases have really gone down to very low levels as a cause of mortality. And that is because through a combination of public health measures and interventions, medical interventions, we have got incredibly effective at preventing and treating infections. However, with a new infection it can take some time. With HIV, for example, it

took several years before we started to have the highly effective drugs which now control it and reduce the number of people who catch it. With Ebola, it took a while to get vaccines and more recently drugs, and the same is likely to be true here. So the question is, what medical interventions will we have and how quickly, and these include better diagnostics (which help both with medical management and also public health interventions), vaccines, and often overlooked, but very important – drugs.

Start off with what we currently have. We already have, from early on, because scientists from China and elsewhere released the data very early, the genome of this virus. It allowed people to develop a PCR test for this virus very early on. They can be done and these tests are for current viral infections. So if someone has got an infection generally with symptoms, and we are increasingly finding if they do not have symptoms, you can do a throat or nasal swab and you can then test the virus directly. Tests are very good already and steadily improving, but they are already extremely accurate once they reach the lab. The difficult questions with the current test are who to test and at what stage. For example, what kind of people would you test who do not have any symptoms? So the questions in science at this point are primarily around the 'who to test'. We definitely do need faster tests because we do have a problem in every country, we certainly do in the UK, with some transmission in a hospital setting, and being in a situation you can screen people as they come into hospital and almost immediately say, 'you have got the virus' and they need to be isolated. This would help us significantly in terms of reducing onward transmission in hospitals and other institutions. We need a good strategy for the tests and we need faster tests. We already have tests for this virus however, which given the time since this virus emerged, I think is extremely impressive on the science front.

The second form of tests that we need (and we have already got early ones but these will improve) is serology tests or antibody tests. Serology tests are not testing for the disease now, what they are testing for is the fact that someone has had disease in the past. This is important for several reasons, but the most important at this point in time is it will tell us what we do not currently know – what proportion of people have been infected but without having any symptoms at all.

When you have an infection, several different antibodies are produced. The first ones are IgM tests. Tests for these are usually not very accurate and that's true for this infection as well, at this least at this point in time although that may change. But later on, you develop other antibodies, particularly, something called IgG, and this tends to give much more accurate tests. They tend to only become accurate three or four weeks after someone has been infected. Currently, the tests that we have for this are probably about 70%, maybe 80% sensitive. They are not really adequate for individual case management, but they are already adequate to give us a feel for what proportion of people have been infected without having symptoms and what proportion of the population currently have antibodies. Studies around like this are going on around the world at the moment, and we will have the results of those very shortly. We do not currently know, if you have antibodies, does that show you cannot get this infection again? There are some reports now of people who appear to have either continued to have the virus for a prolonged period, or possibly been re-infected having recently been infected. So we do not know how long people remain immune to this infection. This is a critical question both for the epidemiology of this infection and also potentially for vaccines.

So moving on to vaccines themselves. Vaccine strategies in epidemics come in various different forms. I am going to divide them broadly into **epidemic modifying vaccine strategies**, and **disease modifying vaccine strategies**. An epidemic modifying vaccine strategy which is the one that most people think of, is where you have a vaccine that is highly effective at preventing infection which you can give to the whole population. What that means is that everybody who is vaccinated is protected against infection. Then if there are a few people who have not been vaccinated they are surrounded by people who have been vaccinated or have had infection and are immune, and therefore they are very unlikely to come into contact directly or indirectly with someone who can pass on the infection they are protected by this and and there is this population immunity, which leads eventually to the epidemic going away. This use of a vaccine incidentally is the only situation where you would ever aim for herd immunity – population immunity- as a policy aim.

You can also as an epidemic modifying vaccine strategy use vaccines to target very high transmitting people – fairly unlikely to be useful in this particular infection where many people who transmit effectively have few risk factors and often few symptoms. There is a strategy which won't work in my view for this particular infection called ring vaccination, but is effective for example in Ebola and was effective in smallpox. It is where you find someone with a disease and you vaccinate around them, but these are unlikely to be relevant for Covid-19. The idea however, of the whole population vaccine strategy is certainly very relevant, and we are clearly - in the UK and every other country - trying to find vaccines which can do this.

Even if you can't find a vaccine which is sufficiently effective and sufficiently safe you can give it to the whole population, you may get a vaccine which is a disease modifying vaccine. It may be a less good vaccine, partially effective, or it may have enough side effects that you wouldn't want to give it to everybody, but you would give it to people who are at high risk. This could have a very important role, particularly if it reduces the severity of disease, even if it can't stop infections. With some vaccines you can give someone the vaccine, it won't necessarily stop them getting infected, but it can reduce the risks of them getting complications. An example: most people listening to this will probably at some point, certainly in the UK, have had a BCG vaccination, or at least a significant proportion would have had a BCG vaccination. This may not stop them from getting infected with TB, but it's very likely to stop them getting a TB meningitis for example. So some vaccines can protect against disease without being fully effective in terms of stopping infection. This could be very useful for high risk groups. So we know who is at high risk of getting Covid; we can vaccinate all of them. We could vaccinate, for example, healthcare workers (occupational exposure) or older people (high risk) and that would significantly reduce the chance that people die of this infection, even if the infection was still circulating in the population. Clearly less of a satisfactory solution than a whole population one but it may be what we would need to use if the first vaccines are less effective, or have side effects, or are in short supply.

Drug treatments, however, can also be highly effective. Just going back to the example of HIV, most of the way in which we have dealt with the HIV pandemic is by using drugs rather than by using a vaccine. An HIV vaccine has been looked for, for a long time and we have not yet got an effective one. We have got highly effective drugs and this is the way in which we deal with this, and many bacterial infections. And for this infection Covid, we could use them in several different ways but the key ones are treatment and then possibly for prophylaxis, which I'll come on to.

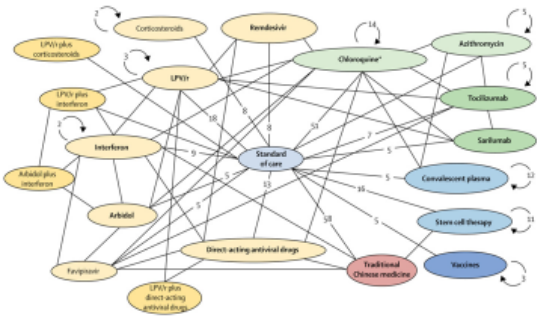
If we're talking about treatment, there are two things we could try to do. A treatment is when someone has symptoms and you give them a drug to prevent them becoming severely ill or dying. You can give them early with mild cases to prevent people who have got mild disease going on to get severe disease. Or- with people becoming severe - we can give them treatment to stop them going on to intensive care for prolonged periods, or dying.

At this point in time there are probably three groups of drugs that we're looking at.

Drug treatments.

- Treatments can be:
- to prevent mild cases becoming severe, shorten duration
- or to treat severe.

- Antivirals.
- Anti-inflammatory.
- Antibodies against virus.



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The network on the right is showing just some of the multiple clinical trials that are already going on with this new infection as we try to find out what drugs can help to stop people dying from this infection, even if they become infected. The first group, the most obvious in a sense, are antivirals – drugs, which actually suppress or stop the virus in its tracks. The second group, important in this disease because if you remember, most people who get severely ill, it is an initial infection and then they seem to deteriorate at about a week, are immune modulating drugs. And the third one, which we are examining in the UK and elsewhere and how we can get these into trials, are antibodies against the virus.

Let's go through those in turn. Antivirals are especially effective in early disease and they may be effective in prophylaxis. A virus has a complicated life cycle and these drugs can act anywhere along that pathway. Now antiviral drugs are less well developed than antibiotics for bacteria, but we do have many highly effective antivirals, particularly for example, for HIV where they suppress the disease, they do not completely cure it, or Hepatitis C where they do cure it completely in most cases – both of these are chronic diseases. We have some moderately good antivirals for things like influenza, herpes simplex virus, and for that matter epidemic diseases like Ebola more recently.

There certainly are diseases for which we have effective or moderately effective antivirals. So the idea of an antiviral is a perfectly plausible one. What we are doing at the moment is trialling several existing antivirals or other drugs that appear to have activity against this virus when you look at them in a laboratory. My expectation is that at best, these will have a moderate effect and we'll probably have to wait until we've got a highly effective antiviral designed for this virus before we have an effect so large that we feel that we actually can manage this epidemic with drugs alone.

The second group of drugs are immune modulating drugs. Now, the immune system is extremely complicated. It has large numbers of feedback loops and very often when you use a drug, it can have an impact that you were not expecting. But we already have many powerful drugs that can suppress different bits of the immune system. They come from various areas, the longest standing and the most widely known and used are steroids which suppress quite large bits of the immune system. There are also drugs, for example, from rheumatology, from things like rheumatic diseases and in other inflammatory diseases such as the Interleukin-6 antagonist group. There are also drugs which suppress the immune system from transplantation, for example. So there are a lot of potential drugs which can interfere with or suppress different bits of immune system. And if this is mainly an immune disease that leads to people getting very sick and dying, it may be that one or some combination of these drugs may actually prevent

progression of the disease and therefore mean people get disease, get moderately severe disease, but don't go onto the critical path that leads to some people are dying or having very prolonged illness.

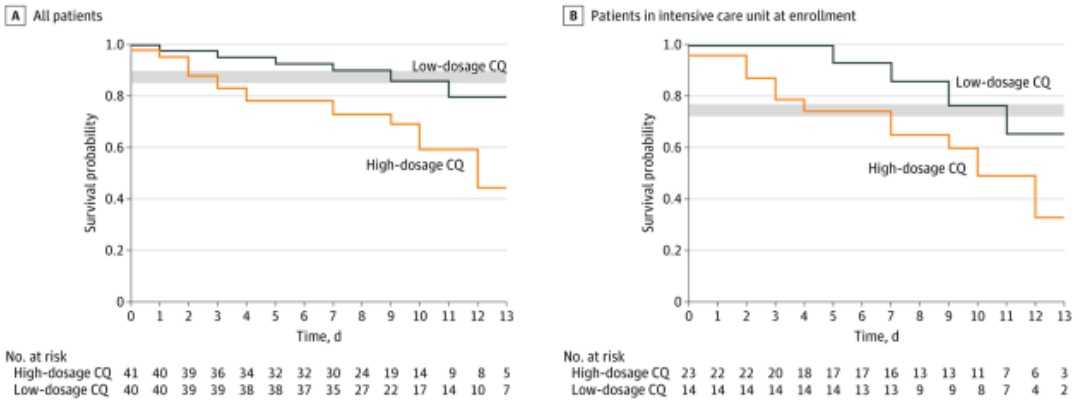
I have to say though, that it is important to remember that anti-inflammatory drugs have been tried in many infections. Sometimes they help, for example steroids are useful in some forms of tuberculosis. Many occasions they make no difference, and in a few occasions they have actually made things worse. So I think we need to be aware that this has a mixed record and we need to trial these very carefully.

It is, however likely that the severe disease is due to some kind of immune immunological reaction. People think it is at this point in time early in this disease, we may well change our view. We think it may well be something called a cytokine storm, where what we get is the white cells, the immune cells of the body are highly activated, they push out some, chemicals – interleukins, interferon – and these lead to more cells being activated and you get a really bad inflammatory response particularly in the lungs. We have quite a large number of drugs, which interfere with bits of this system, this cascade that can occur and it may be that if we try these drugs, we will find that they lead to better outcomes in people who are beginning to move from moderate disease to more severe disease.

And finally on treatment, this is an old concept – conceptually very simple. You take the blood of someone who has had severe disease or even mild disease, and they've recovered, and you assume that they've got antibodies in that blood which are effective, at least in the short term, in fighting the disease. You remove the plasma, which has got the antibodies in it, and then you inject that into someone who is ill and you hope that those antibodies will fight the disease and lead to the disease not progressing. There has recently been progress on looking at this in the UK as with elsewhere. If this works, we could potentially find out what the antibodies are and manufacture them artificially.

Finally on drugs, the idea of drugs for prevention, for prophylaxis. Because we know who the people are who are the most at risk (because of their existing conditions, because they are older for example) we might be able to give some people drugs that actually prevent this in the same way that we give people statins to reduce their risk of heart disease. Or we give people who are going into an area with malaria and are non-immune, antimalarials as prophylaxis. These can be given lifelong, or you could give them for a short period of time for example, If someone was doing a particularly high risk encounter (e.g. a very frail, older person was meeting their grandchildren, you might want to cover it for a short period of time). There are a variety of ways you can consider prophylaxis. It needs to be a drug with low side effects, ideally long lasting and would almost certainly be an antiviral, but prophylaxis is the third way, in addition to antivirals for treatment and the immune modulating drugs.

Whatever we do, however, we need to do trials. The reason for this, I think is illustrated well with this:



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There was a lot of talk early on about a drug called chloroquine (still an important drug for us to be studying at the moment) but there is a slight tendency when there is no treatment to think 'let's just treat with high doses of drugs that look plausible'. Here is the first trial that has come out looking at high dose chloroquine and low dose chloroquine in this infection. What it suggested was that people who were given the high dose chloroquine (a treatment that was supposed to help them) actually died at a higher rate than those who were given the low dose chloroquine. It is really critical if we are going to try new drugs in people, we must do so in proper trials so that we learn and then for the future we can improve on this. I am enormously proud of the fact that we have got really good trials going on in the UK and very much thank the people who volunteer to be part of them because that really is how we will end up improving our knowledge and be able to treat this much more effectively.

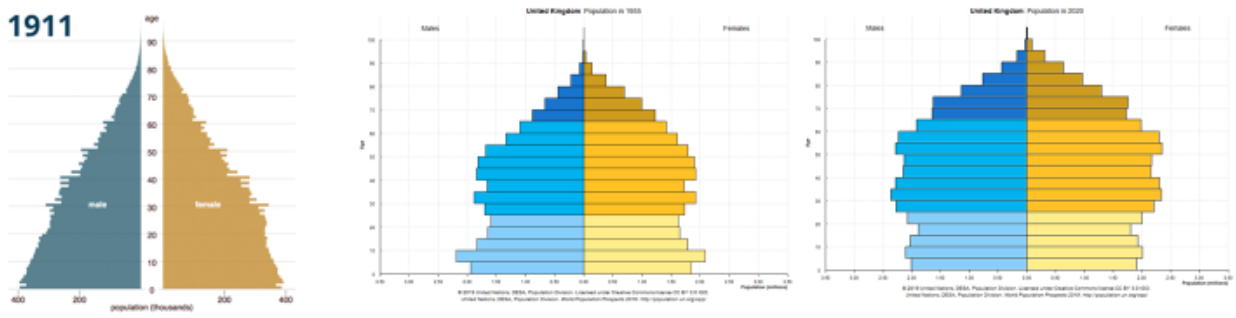
Finally, just some comments about this infection around the world. How different is this going to be in different countries? And I think the answer is very different, but we do not know how. For most infections, poverty and particularly malnutrition are associated with a poor outcome. So it may be that as it starts to spread around the world, we will see a pattern where the mortality rate is higher in places where there is significant poverty.

These also tend to be areas where there are much weaker health systems, which could more easily be overwhelmed if there was a big spike in infections and may not have the capacity for critical care like there is in most industrialized countries. On the other hand, many middle and indeed lower income countries often have better public health systems than you would expect and often very good ones, and they may be able to mount a significant public health response.

We do not know whether climate has a significant impact on this disease. We know countries where it has transmitted but there's a lot we do not know about transmission in, for example, much of Africa. There does appear to be a genetic element, potentially in severity and we are still trying to tease that apart in the UK, the US and other countries. This might have an important impact in terms of people's likelihood of getting an infection or likelihood of dying from it.

But finally and importantly, the demographic structure of different countries is very different and this may have a significant impact. I am going to illustrate this first of all, with the UK facing three pandemics:

UK before 1918 pandemic (L), 1957 pandemic, now. *ONS, UNPD.*

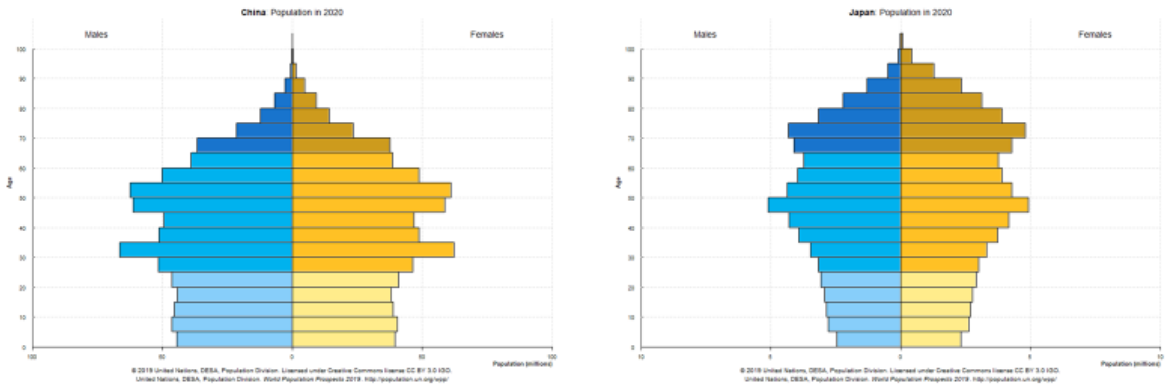


On the left, the best population pyramid I managed to find from near the time around the 1918 flu pandemic. The population pyramid of the UK, elderly people right in the top bar here – very small numbers of elderly people. So although this flu pandemic killed older people there was a much, much smaller proportion of the population who were older than there was in the 1957 flu pandemic in the middle here, and now on the right, a much higher proportion again.

When facing these three pandemics, which have a propensity to kill older people, the proportion of the population potentially affected has steadily gone up in this country. And most other countries, for example, in Europe.

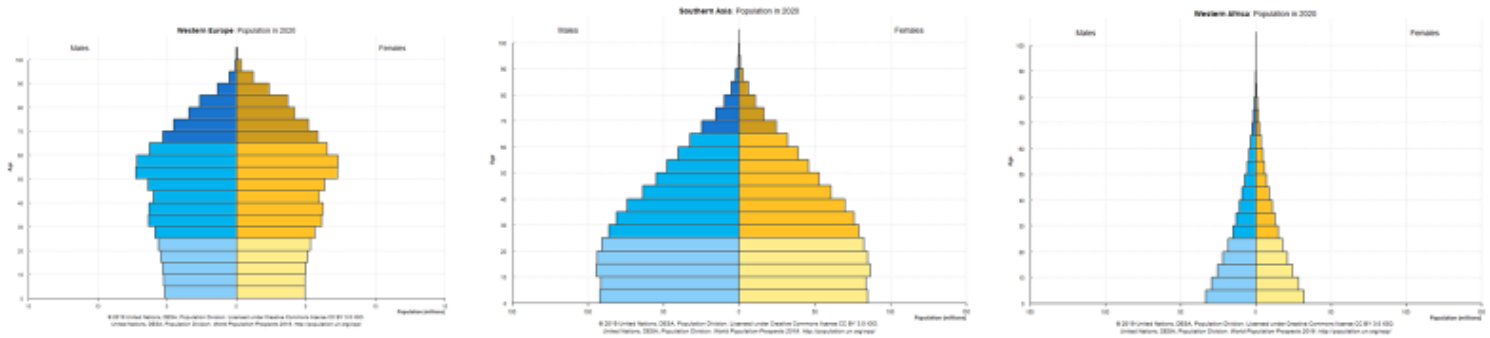
Different countries, neighbouring countries, have very different proportions of their population in the older age group who are much the most at risk of this infection.

China, Japan.



On the left, is China, and on the right is Japan. If the same proportion of the population at all ages got infected, the translation into severe disease and the translation into deaths would be different between these two countries.

Western Europe, Southern Asia, West Africa.



If you compare the population structure of, for example, Western Europe, Southern Asia, and West Africa, again, the proportion of people who are older in these is very different. So if it appears that in or around the world, those at highest risk are people over the age of 70, particularly over the age of 80, they may have very different impacts, on the different countries because of these different populations structures. But there may be other things, like poverty, that are more important and outweigh that.

Finally, before I round out, just to highlight some of the many things we do not know about this virus. We do not know the proportion of the population that is infected asymptomatically (without symptoms), although we think at the moment it is actually quite low in terms of the overall population.

We do not know how long immunity to this infection lasts, and if it does not last very long, this has important implications for the epidemic, and it also potentially has implications for whether we are likely to get a vaccine because there are many diseases for which we have never managed to get an effective vaccine.

We do not know whether blood tests currently correlate with immunity. We do not know how much children contribute to transmitting the virus, and this is very important for example, in deciding on how school closures are a part of our long-term response.

We do not know whether this is affected by seasons. Is this going to get worse again in winter just because of the fact that many respiratory viruses do?

We do not understand why people deteriorate after a week and we do not understand why men are significantly more likely to die than women.

These are important for understanding how we can then find countermeasures, and that is in addition to our need to develop vaccines drugs and diagnostics. There is an absolutely massive international scientific effort now to try and find countermeasures to this in the UK, funded by, among others, the National Institute of Health Research, Medical Research Council, and the Wellcome Trust. That means that in six months, in a year, we will be much further forward

than we are. But we cannot guarantee when we are going to find the drugs or the vaccines that actually allow us a path out of this infection, which means that we can actually release some of the more problematic social measures.

To summarise, this talk has covered the epidemiology, including the mortality, the routes of transmission, and the fact that respiratory infection is much the most difficult to control, and the force of transmission of this infection. We have talked about the epidemiological countermeasures, which include social distancing, but also the need to isolate cases, and the old-fashioned things: coughing and sneezing etiquette and above all, washing hands.

I have talked for a brief period about the clinical picture: our understanding there is evolving quite quickly. Then about the different ways in which we can use medical countermeasures including vaccines, drugs and diagnostics. And finally, we have covered a short section on what may happen in the global picture.

If you want to know more about some of the details of these, three other talks I have given at Gresham might be a useful background:
https://www.youtube.com/playlist?list=PLU3TaPgchJtSMvG23UOtp86Uzu9TFOVp-

One on broad principles of controlling an epidemic and pandemic. One on eradication of diseases and why it is so difficult – why have we only actually managed to eradicate, to date, one disease – smallpox, and one on the interaction between age and infection which is quite complex, and they will give more details if you are interested in those areas.

This is a disease where we are in the foothills of our understanding and undoubtedly I - or someone else - will need in a year or two to come back and talk in a much more knowledgeable way about this virus for which we are really still only beginning to understand how we are going to combat it.

Thank you very much.