Title	Epidemiological and Evolutionary Dynamics of Pathogens in Time and Space
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Language	English
Event title	The 2022 Kyoto Prize Commemorative Lecture
Publisher	Inamori Foundation
Issue Date	01/31/2024
Start page	1
End page	11
URL	https://www.kyotoprize.org/wp-content/uploads/2024/01/2022_grenfell_en.pdf

URL for Japanese translation: https://www.kyotoprize.org/wp-content/uploads/2024/01/2022_grenfell_jp.pdf

The 2022 Kyoto Prize Commemorative Lecture

Bryan T. Grenfell

Epidemiological and Evolutionary Dynamics of Pathogens in Time and Space

The Kyoto Prize is renowned for recognizing contributions to human betterment across a remarkable range of disciplines. I am profoundly honored to have my research considered worthy of this year's Prize in the area of Basic Sciences.

In this lecture, I want to highlight some key findings from my four decades of research on the epidemiological and evolutionary dynamics of pathogens in time and space. I'll begin by painting a simple picture of what drives the dynamic patterns we see in infectious disease epidemics. I'll then explore three major themes that span my research career, focusing on how pathogen evolution is necessary to understand epidemic spread, and vice versa. Finally, I'll summarize some broad lessons that I've learned about the process of doing science.

What is Infectious Disease Modeling?

My research group and I have studied the epidemic dynamics of many infectious diseases, notably measles, influenza, rotavirus, enteroviruses, and latterly SARS-CoV-2. What do we mean by epidemic dynamics? Here is a lovely example. Fig. 1 is a graph of data from the Japanese National Institute of Infectious Diseases. It shows the number of cases of children diagnosed with Hand Foot and Mouth Disease (HFMD) from the early 1980s to the mid 2010s. HFMD is caused by enterovirus infections, and the number of cases oscillates considerably over time. This is an example of a dynamical pattern. My research has centered on using simple mathematical models to understand key aspects of infectious disease dynamics.

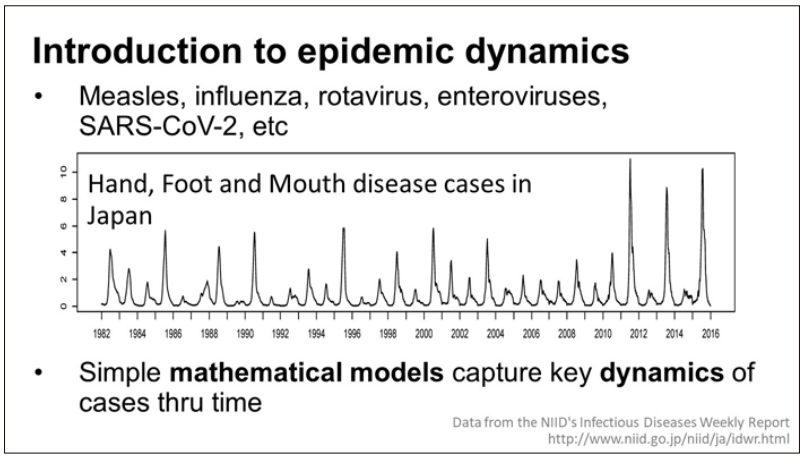

Fig. 1

As in many areas of science, it can be useful to explore a relatively simple system to try to understand some basic principles. For epidemics, measles is arguably such a system, for two reasons: firstly, it has a straightforward natural history of infection, and secondly, particularly rich historical data are available. Measles is an acute infection caused by an RNA virus. It is highly transmissible, mainly via a respiratory route. It mostly affects children. The symptoms are very characteristic which helps the process of surveillance. It causes significant disease, and can be fatal in some circumstances. Interestingly, measles is immunosuppressive, yet elicits a strong immune

response against future measles infection. Once infected, individuals develop strong immunity that is lifelong. This is particularly important for the modeling that I will describe presently. There is an excellent vaccine, which was first developed in 1963. Despite this, there is still a high disease burden in some countries, and vaccine hesitancy is a continuing problem. In many parts of the world, doctors have long been required to report measles cases. For example, in England and Wales, we have records of cases going back to the 1940s. Epidemics waxed and waned, often in regular cycles. The cycles are fairly synchronized geographically. For example, when there's an epidemic in London, there tend to be similar outbreaks nearby. We can also see some evidence of "waves of infection" moving away from London and other large cities. We can explain many of these patterns, using mathematical models.

What do I mean by a model? It's an attempt to capture key biological features of a system to explain observed patterns. Ideally, we focus only on absolutely necessary details. Fig. 2 is a picture that captures a very simple model for the natural history of measles infection. When they are born, babies can have immunity from their mothers. This wanes over a few months. They then become susceptible to infection and can acquire the infection by contact with infected people. During infection, they can infect others. After a couple of weeks, most people recover, and cease to be infectious. Their immune systems have learned how to recognize the virus, and they no longer have serious disease or transmit the virus if they are exposed to it again. We can express this progression through stages of disease mathematically in the so-called Susceptible-Infected-Recovered, or SIR model for epidemic spread. A key parameter in this model is the transmission rate, which is often measured by the reproduction ratio, the number of secondary cases caused by an infected person. We can use this simple model to explain the dynamics of cases through time, as shown in Fig. 3. We start off with one infected person, indicated in red, on the left side of the graph, and everyone else in the population is susceptible, shown in black (Fig. 3). The infected person gives the disease to several other people, and they in turn pass it on, which causes a rapid increase in the number of cases. This quickly depletes the susceptible population, and as people recover, they become immune, shown in green (Fig. 3). As the number of susceptible people dwindles, the pace of the epidemic slows, and the number of cases starts to decline. Each infected person passes the disease to fewer and fewer susceptible people, because more and more of the people they come into contact with are immune. Eventually, we end up with most people having contracted the disease and recovered. There are not enough susceptibles to continue the epidemic, so it dies out. This is the simplest possible model. In reality, things can be more complex. For example, births generate new susceptible individuals. When these build up enough, we can have another epidemic.

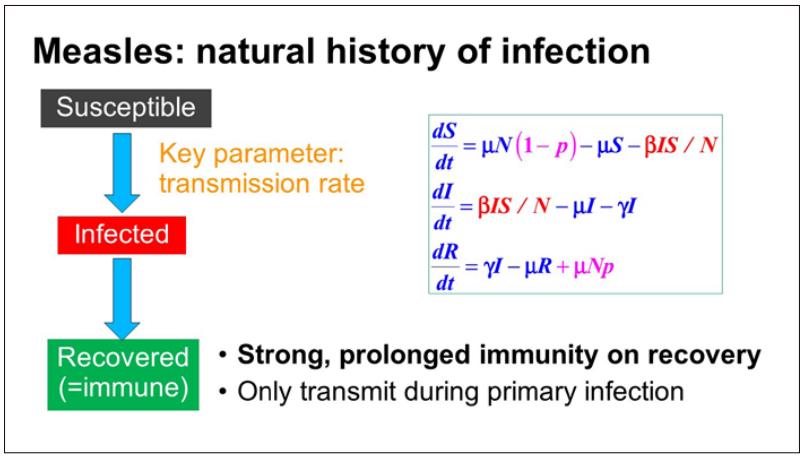

Fig. 2

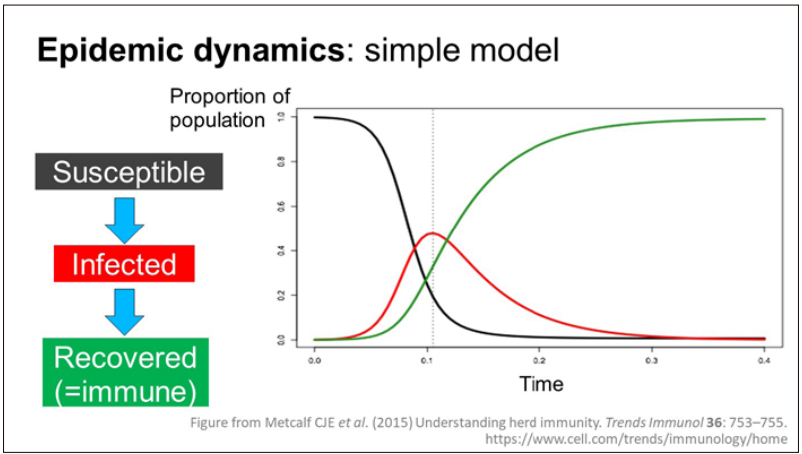

Fig. 3

Time Series Analysis of Infectious Disease Epidemics

With this simple model as background, I now turn to major themes in my research. The first of these is looking at non-linear epidemic dynamics, the determinants of regular and chaotic fluctuations, and disease persistence. I explored these in measles and other childhood infections. We needed, first, to develop statistical methods to analyze epidemiological data, as well as new modeling frameworks. Then we applied these tools to address biological questions.

One of the statistical methods I deployed to describe the dynamics of epidemics was time series analysis. I was encouraged to do this by two gentlemen: my postdoctoral advisor Roy Anderson and his great collaborator, the distinguished theoretical biologist, Robert May (Fig. 4).


Fig. 4 Right: Roy Anderson, left: Robert May

Specifically, I taught myself Fourier analysis and used it to explore how the cyclicity of epidemics changed due to the impact of vaccination. It's always great fun to have a new method, and learn a new method and apply it. At that time, I was based at Imperial College London, and had access to summary measles data for England and Wales. But when I moved to the University of Cambridge, some years later, I discovered, much to my delight, that the England and Wales measles data was available in its entirety in the University Library there. The full dataset, which I and my research group digitized, was a great resource for subsequent modeling. Once we had these detailed data, we were able to adapt more sophisticated time series methods, notably wavelet spectra, to describe changes in epidemic cyclicity in space and time. This is also a great example of serendipity in research. I was browsing through a journal looking for something else, and came

across a meteorological paper that used wavelet analysis. I realized that the analytical techniques used in that paper, from quite a different academic field, could be adapted to quantify changes in epidemic cyclicity not only through time, but also across space.

From Epidemiological Patterns to Infection Dynamics

So far in this research theme, I've been showing examples applying statistical methods to describe what happens in epidemics. But we don't just want to describe the patterns we see, we want to understand "why" we are seeing them. What underlying processes could be causing the fluctuations we see? To answer this, we need to develop mechanistic models. I have already shown the simplest of these models, the SIR model, in measles. We made a lot of progress on this following my move to the University of Cambridge and digitization of the detailed datasets. I won't go through this in detail, but I touch on some of the mechanisms that I and my research group have shown to affect patterns of disease across space and time. Firstly, seasonality can be an important driver of disease transmission. We see this in measles in England and Wales, as epidemics coincide with the start of the school year, when susceptible children gather. Secondly, how big does a population need to be before disease ceases to vanish from an area in the troughs between epidemics? This is the idea of critical community size and stochastic persistence. Thirdly, when particular age classes of people, such as children, are important for transmission, how does the age structure of populations combine with seasonality to drive the epidemic? Fourthly, how do changes in the supply of susceptible individuals, whether increased through births, or removed by vaccination, affect epidemic dynamics? We didn't only look at measles for these questions, we were also lucky enough to get data for other diseases such as whooping cough, that's pertussis. Much of this work was done in my early period in the University of Cambridge, in collaboration with a wonderful set of students and postdocs.

In order to more efficiently tackle the very large amounts of spatio-temporal data available to us, we also had to develop new methods to fit models statistically to epidemiological time series. We therefore developed the Time Series SIR (TSIR) model, aided by my then-postdoc Barbel Finkenstadt's great statistical intuition. This model captures the impact of birth rates and seasonality on epidemic dynamics, as summarized in Fig. 5. In this graph, the open circles show data for London, and the red curve shows what's projected by our model. As you can see, the model captures much of the variation in the data. In particular, there were annual cycles immediately after the Second World War, when birth rates were high. There's then a transition to biennial epidemics as birth rates drop. Since this work was published, my colleagues Ottar Bjørnstad and Jessica Metcalf have applied the TSIR model much more broadly, to other diseases and contexts.

Not all the epidemic series we see in measles are regular cycles as we saw in Fig. 5. Models had suggested that increasing seasonal forcing of transmission could make the cycles irregular, or even chaotic. We used rich data sets from contrasting epidemiological settings, together with the TSIR model, to show that epidemics can indeed be very irregular, with a signature of chaos, in highly seasonal environments. For example, Fig. 6 shows measles epidemics in Niamey in Niger. The data were collected as part of a great collaboration with Médecins Sans Frontières and the Niger Ministry of Health. Our models showed that the pattern was driven by highly seasonal movement of a large portion of the population: people moved from farming areas to cities in the dry season and back for the wet season.

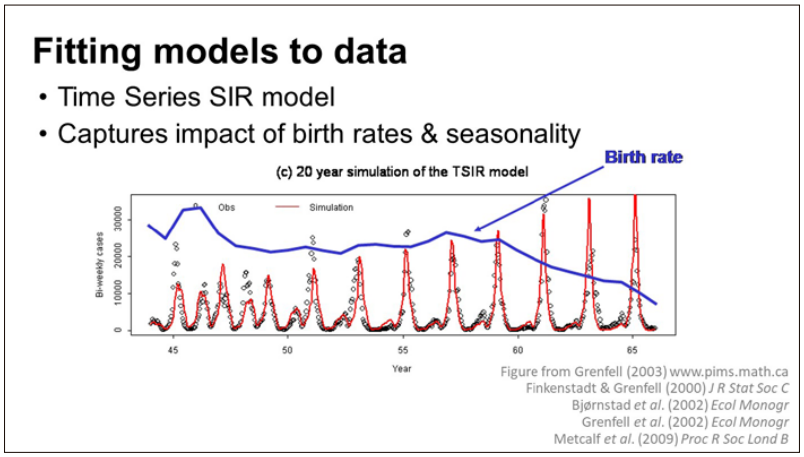

Fig. 5

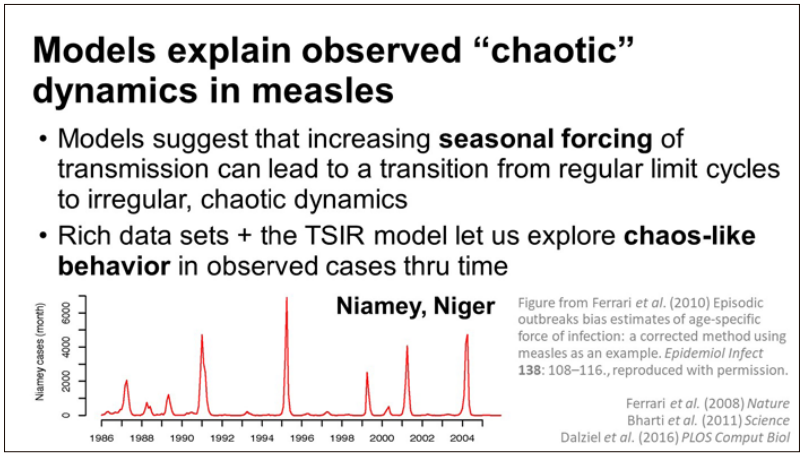

Fig. 6

Spatial Dynamics of Infection

So far, we've been looking at patterns of cases through time. But as I mentioned earlier, there are also rich and important spatial patterns in epidemics. That is, infections spread from place to place, and epidemics can become locally extinct for a while, especially in small populations.

We explored the spatio-temporal dynamics of measles by extending the SIR model to metapopulations. This allowed us to capture how the flow of infection between towns and cities affects the pattern of cases. Specifically, we adapted a technique known as "gravity modeling" from spatial geography. We used these gravity models along with a novel competing risks framework to quantify epidemiological linkages between towns and cities, based on distance and population size. We showed that large cities are very important for driving epidemics across the whole country. You can see in Fig. 7, where each circle depicts a town, and the size of the circle is related to the town's population size. If we look at the yellow circles, we see that London has considerable influence in seeding measles epidemics in the whole south-east of England.

Looking at how vaccination affects this spatial spread, we showed that the influence of large cities is strong in the pre-vaccination era, before the late 1960s. In Fig. 8, this is indicated by the blue symbols on the maps. However, as vaccination reduces cases, local stochastic transmission and long-distance seeding come to dominate transmission. This is shown in black symbols on the later maps in Fig. 8. These dynamics have significant implications for the efforts to eliminate measles regionally.

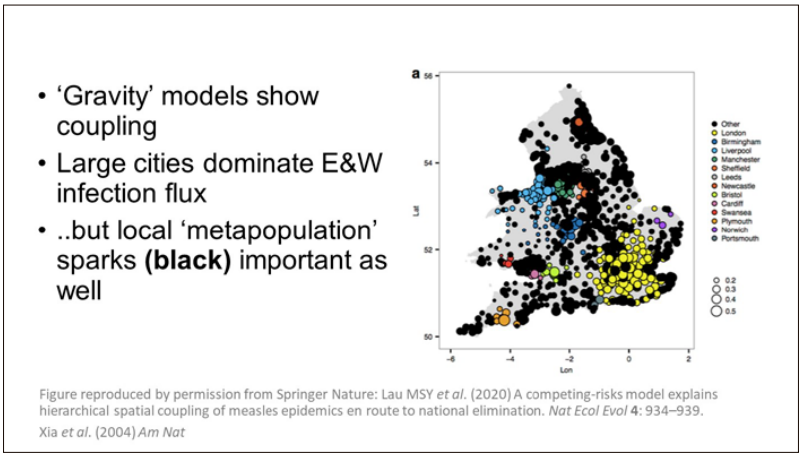

Fig. 7

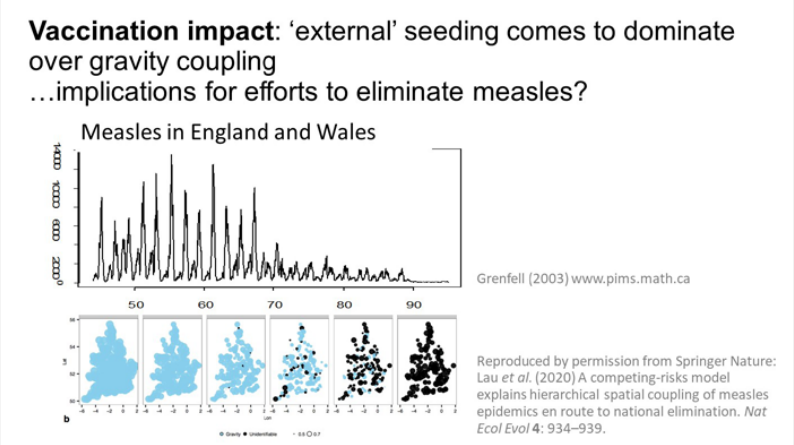

Fig. 8

Phylodynamics

Thus far, we have mainly considered infections, like measles, where people who recover from infection have strong lifelong immunity. But, for many diseases, notably influenza and COVID-19, immunity is weaker and more short-lived. This partial immunity often arises because of viral evolution. Some viruses can be strongly selected to evolve to escape prevailing immunity in the host population. I’ll illustrate this with a comparison of the evolutionary dynamics of measles and influenza.

Both measles and influenza are RNA viruses with error-prone replication. This means the offspring viruses are often slightly different from their parents. Depending on where mutation occurs, offspring viruses can have the same surface molecules as their parents, or different ones. In measles, the surface molecules are highly stable through time, so once the host immune system has encountered the virus, it can recognize subsequent variants. But in influenza, the surface molecules are much more variable, allowing the potential for immune escape. That is, host immunity developed in response to the parent virus is not as effective at protecting from new variants. This leads to sharply different evolutionary trees for the two viruses (Fig. 9). Measles doesn’t show any directional evolution to avoid immunity. By contrast, seasonal influenza has a highly characteristic “ladder-like” phylogeny, as new escape variants are progressively selected to avoid prevailing population immunity. In our model, this means that people who were in the “recovered” group regain susceptibility to the next variant. You’ve probably become somewhat familiar with this concept over the last few years as the world has seen the spread of successive

variants of the SARS-CoV-2 virus. To understand these patterns, we need a model that captures not just the impact of host immunity on pathogen phylogenies, but also how this interaction affects the epidemiology of the infection.

I coined the term "phylodynamics" as shorthand for the interaction between viral evolution, host immunity, and epidemiological dynamics. The extent of pathogen immune escape is a balance between opposing forces (Fig. 10). On one hand, selection for new variants increases as host immunity strengthens. On the other hand, viral abundance in hosts, and hence transmission to new hosts, declines with the strength of immunity. The more offspring a parent virus produces, the more opportunities for onward transmission of the virus to new hosts. One of the main concepts of phylodynamics is that selection for pathogen immune escape is strongest at intermediate levels of host immunity (Fig. 10). Since my colleagues and I first proposed this set of ideas in 2004, they have been refined and widely applied by us and other groups.

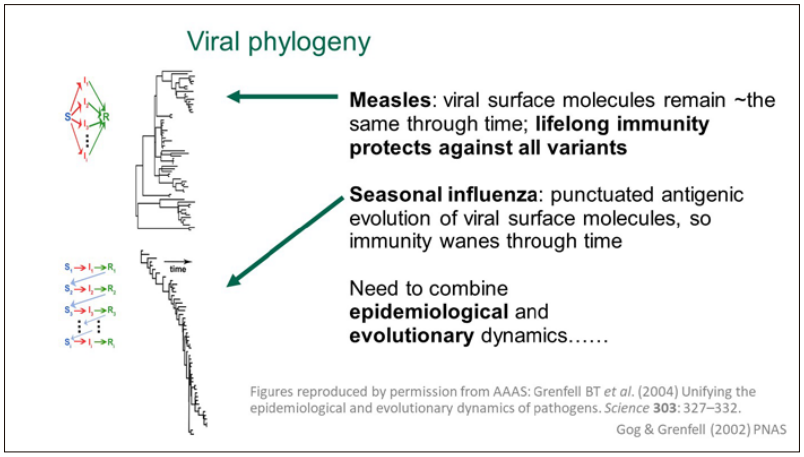

Fig. 9

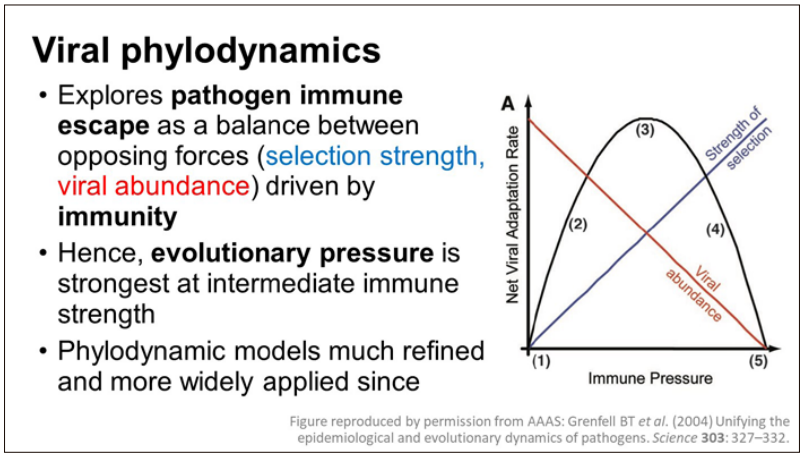

Fig. 10

For example, we need to account for pathogen evolution when looking at the spatial spread of many diseases, such as influenza. In measles, spatio-temporal patterns we see, especially in the pre-vaccination era, are largely driven by transmission between children, often in school settings. This is because of lifelong immunity across variants. In sharp contrast, the spread of seasonal influenza in the U.S.A. appears to be largely driven by the commuting patterns of adults, with some long-distance spread (Fig. 11). This is because of immune escape. Immunity is only partial, so adults can be repeatedly infected by successive influenza variants.

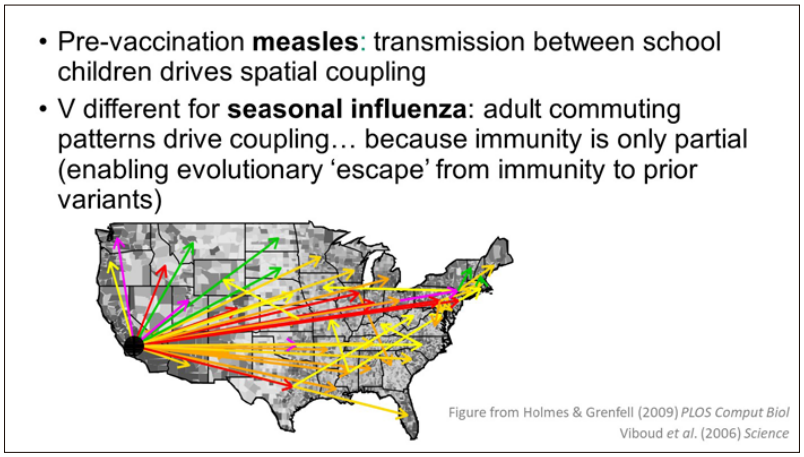

Fig. 11

We have also shown that the relationship between immune escape and strength of immunity can be complex. For example, it can depend on the details of pathogen life history. This is illustrated by rotavirus, a major cause of infant diarrhea. Rotavirus is only imperfectly immunizing, so we would not expect to see strong evidence of herd immunity. But in fact, rotavirus does show evidence of herd immunity in response to highly efficacious vaccines. This is illustrated in Fig. 12. The left-hand figure shows the observed cases, and the right-hand figure shows model predictions. Pre-vaccination epidemics in the U.S.A. are shown with blue curves. Epidemics in the early era of vaccination are indicated by the red curves. Comparing these, we see that epidemics in the mass vaccination era are delayed as well as being smaller. This provides strong evidence for herd immunity, essentially because the vaccine prevents highly transmissible primary infections of rotavirus.

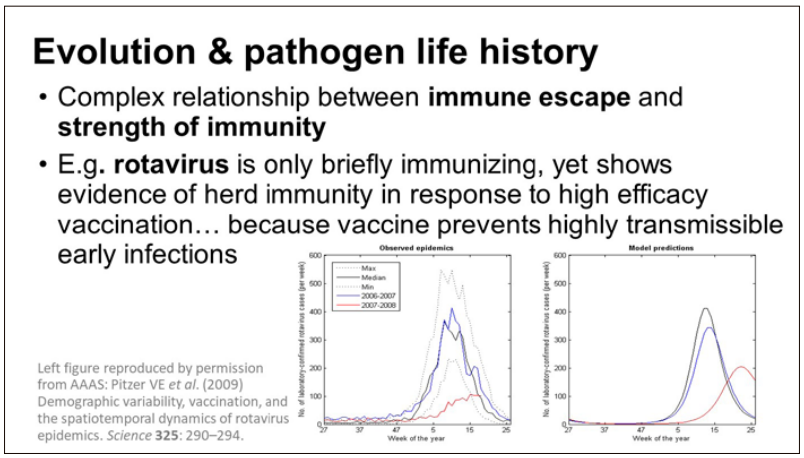

Fig. 12

We can also apply phylodynamic ideas to look at epidemic spread of a disease with which we have all become very familiar over the last few years, COVID-19. We began early in the pandemic by developing a series of simple models to project how the strength of natural and vaccine immunity to the virus might affect the medium-term dynamics of the epidemic. We showed that imperfect immunity would lead to much more pessimistic outcomes, though effective vaccines would mitigate these impacts somewhat. As we now all know, this has largely come to pass. We then explored how vaccine dosing regimes and inequities in vaccine distribution between countries might affect the evolution and spread of new variants. Our results underline the importance of global equity in vaccine distribution. If vaccines are inequitably distributed, the probability of new

variants that can escape immunity increases.

Of course, there are many other complexities that may need to be taken into account in understanding the dynamics of the COVID-19 pandemic. For example, some individual hosts spread the disease to a huge number of other people: so-called superspreading. Some people who become infected develop "long COVID," and so on. In our group, we have focused on two other important issues. First, the impact of COVID-19 non-pharmaceutical interventions on the incidence of other pathogens. For example, transmission of influenza and respiratory syncytial virus dropped considerably because people were staying at home and masking, but both diseases are now rebounding. Second, we have been exploring the impact of climatic drivers, such as humidity, on viral transmission. To cut a long story short, when there are a large number of susceptible people, we expect to see a relatively small impact of climate. So, we didn't expect to see large seasonal fluctuations in the very early stages of the pandemic.

Broad Lessons from My Career

In the last part of the talk, I'd like to mention a few broader lessons that I have learned over the last several decades. First, biology is often extremely complex, but sometimes, simple models can explain some of the complexity. For example, our TSIR model could explain very different patterns of measles epidemics in different parts of the world, from regular cycles to chaos-like behavior. But emergent simplicity doesn't always happen. For example, humans can sometimes respond to epidemics by changing their behavior, and so affect transmission and other key drivers of epidemic dynamics in complex ways.

Secondly, comparative studies can be extremely valuable, as can collaboration across disciplines. We can often draw lessons from particular systems and apply them more broadly. Fig. 13 shows just a few examples from my four decades of research. It was while I was looking at epidemics of influenza in horses that I really started developing some of the ideas that would become central to the theories in phylodynamics. Thinking about spread of morbilliviruses in seals and dolphins informed useful analyses of invasion and persistence in human diseases. Work on the 2001 foot and mouth disease outbreak in cattle and sheep in the U.K. helped shape my thinking about spatial dynamics of other diseases, and the impact of non-pharmaceutical interventions. A great collaboration on filariasis in southern India made me think about the immuno-epidemiology of chronic infections. In an even bigger leap between systems, analyzing sheep population cycles on the island of Hirta, St Kilda, provided interesting comparisons to my work on measles oscillations.

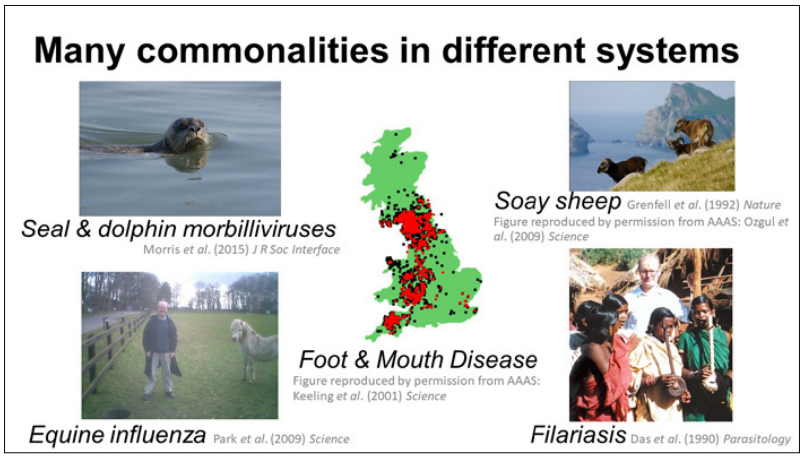

Fig. 13

The third broad lesson I want to highlight is that it is very important to understand how dynamics at different biological scales interact. We have a great illustration of this in the phylodynamics of important human diseases like influenza and SARS-CoV-2 (Fig. 14). In these systems we see that changes in the virus at the molecular level can affect disease dynamics at all larger scales, which then feed back to processes at the molecular level. This is illustrated in the simple chart (Fig. 14). The details aren't important, just notice that there are feedbacks from the molecular level, through the level of individual hosts, host populations, and more globally. To complete the circle, evolution of new variants at the global level affects what happens at the molecular level. For example, a new variant can have different surface molecules that interact with host cell receptors. What's more, heterogeneity and hysteresis at each of these levels can further affect the picture.

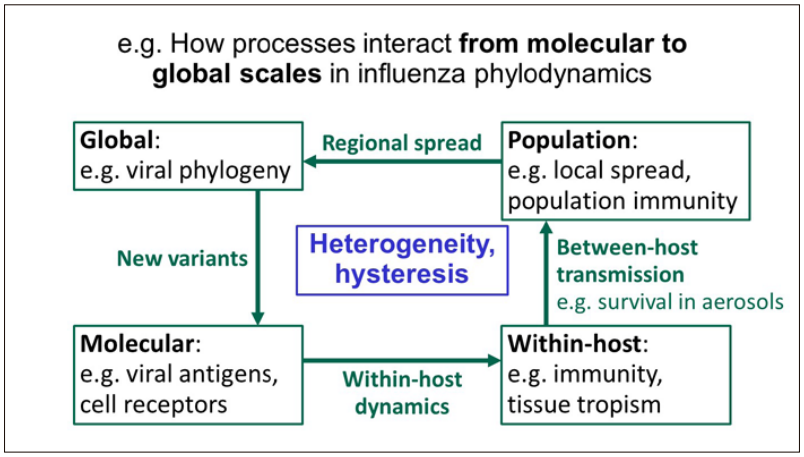

Fig. 14

A major gap in our understanding of cross-scale dynamics is the impact of host immunity at different scales. How host immunity affects pathogen evolution and vice versa is particularly important to understand. Historically, disease surveillance has focused on the dynamics of cases, and, latterly, changes in viral genomes. But going forward, we really should also look at the dynamics of immunity much more systematically. My colleagues Jessica Metcalf, Michael Mina and I have proposed one way to do this. A "global immunological observatory" would use serology and other methods to gauge population immunity to a range of pathogens across the world.

My final broad point is that much of science is a team sport. Collaboration can be extremely fruitful and enjoyable, especially collaborations with people from different disciplines. In four decades of research, I have had the huge pleasure of working with many wonderful people, from biologists, physicists and mathematicians, to clinicians and social scientists. I want to thank them all for their inspiration, dedication, and friendship.

Little did I know as a child that my interests in biology and mathematics at school would eventually lead to working with such a talented set of people. I was born just outside Swansea in South Wales. My mother was a school cook and my father worked in a steelworks, and then as a clerk. I went to the local primary school, where I contracted measles, aged 6. At that point in time, there were no vaccines available. Consequently, many children became infected with measles during their first year or two at school, if they hadn't already been infected by an older sibling bringing the disease home from school. I was an only child, and was probably infected by contact with a classmate, like so many others in that era. When I was eleven, I went to the local grammar school. I became especially interested in biology, but also remember being thrilled when introduced to limits and differential calculus in mathematics. No one in my family had gone to university before. But they valued education highly and were very supportive of my decision to

study zoology at Imperial College London. At the age of 18, I went from my small village to the biggest city in the U.K. for my undergraduate studies. At the time in Imperial College, there was a very strong group working on theoretical ecology, led by an inspiring early mentor, Sir Richard Southwood. I'm extremely shortsighted, and wasn't at all accomplished at laboratory science dissection and other practical assignments, so I gravitated towards theory. I discovered in my second year that I was reasonably adept at computer programming. This was the era of punchcard machines, and I became increasingly fascinated by the use of mathematics to describe biological patterns and processes.

Based on this, I decided to undertake graduate studies, and moved to the University of York. Under the supervision of John Beddington, I did doctoral work characterizing whale population dynamics in the Southern Ocean. It may seem a bit of a leap from cetaceans to infectious diseases, but the link here is the use of mathematics as a tool to address important biological problems. I began studying infectious disease dynamics during a postdoc at Imperial College, and was lucky enough to be able to go on to run my own research groups in universities on both sides of the Atlantic. It is now a tremendous privilege to have my research considered worthy of this year's Kyoto Prize in Basic Sciences, and I am deeply grateful to the Inamori Foundation.