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SECTION & CHAPTER: Theoretical Perspectives and Approaches: Eight Centuries of Epidemic and Pandemic Control

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Abstract
This paper outlines the historical development of approaches to the geographical control of infectious diseases that have relevance today for interrupting the spatial transmission of COVID-19. Lockdown, isolation, and social distancing have their origins in medieval Italy's attempts to inhibit the spread of bubonic plague, whereas the practice of producing immunity by vaccination finds its early expression in the smallpox experiments of Edward Jenner in the 1790s. Since that time, vaccines have been used as a means of controlling the geographical spread of an expanding list of infectious diseases. Until a vaccine (or an effective treatment) is available, variants of the spatial control strategies that evolved in medieval Italy will remain the only means of controlling the COVID-19 pandemic.

Bios
Matthew Smallman-Raynor is Professor of Analytical Geography at Nottingham University, while Andrew Cliff is Emeritus Professor of Theoretical Geography at Cambridge University and a Fellow of the British Academy. They have worked together for 30 years on the geography of infectious diseases, jointly publishing over 100 papers, monographs and thematic atlases on the subject. They received the British Medical Association (BMA) Medical Book of the Year and Public Health Book of the Year awards in 2013 for their *Atlas of Epidemic Britain: A Twentieth Century Picture* (Oxford University Press).

1 Introduction

Lockdown. Self-isolation. Social distancing. These are intrinsically geographical expressions that have come to evoke the global effort to control the first pandemic wave of COVID-19. Many of the defining characteristics of COVID-19, and the causal virus (SARS-CoV-2), have yet to be confirmed. But, eventually, the disease will be pinned down in its infectivity, its morbidity and mortality to lie somewhere along the lengthening sequence of plagues and pandemics that have swept through human populations over the centuries. Confronted with a disease agent to which the human population has little or no immunity, three approaches to control may be employed: (1) allow the agent to spread so that natural herd immunity is established among the survivors; (2) separate the susceptible and infected components of the population by isolation or quarantine; and (3) develop and deploy safe, effective vaccines and treatments. This chapter examines how these responses to disease control have evolved historically, and how approaches that were first developed and implemented in medieval times have been adapted to a twenty-first century pandemic. Methodologically, the chapter sits in that part of medical geography which has come to be called spatial epidemiology, "studies of disease causation and prevention which adopt a distinctly analytical spatial perspective" (Thomas, 1990, p. 1).

2 The Underpinnings of Disease Control

Figure 1 shows a simple model of the spread of an infectious disease in a human population. The population is divided into three sub-populations: those at risk of infection (susceptibles, *S*); those who are infected (infectives, *I*); and those who have recovered from the infection (recovereds, *R*). Propagation of an epidemic occurs by mixing between the *S* and *I* sub-populations. This generates new cases by the transition $S \Rightarrow I$. Once an epidemic has begun, its continuation is dependent upon the presence of a sufficiently large *S* sub-population for transitions of the type $S \Rightarrow I$ to be uninterrupted and, hence, for community transmission to be maintained. The size of the *I* sub-population falls as those infected either recover, *R*, or die, while the *S* sub-population is renewed by births into the population.

Control of an infection can be undertaken at two points in **Figure 1**. The first approach, labelled (i) in Figure 1, is inherently geographical and involves the breaking of chains of transmission by interrupting the mixing of the *I* and *S* sub-populations through the establishment of protective spatial barriers. Such barriers range from the highly local (social distancing and individual isolation), through community isolation and quarantine, to the imposition of regional or national restrictions on movement via 'buffer zones' or *cordons sanitaires*. As discussed in Section 3, these geographical approaches to disease control can be traced back to medieval times. The second method of interrupting the chains of infection, labelled (ii) in Figure 1, is to short-circuit the route from the *S* to *R* states by creating population immunity through immunization. Immunization is commonly achieved today through the use of vaccines and may, *prima facie*, be viewed as an aspatial control strategy. However, as a means of epidemic control, immunization is usually geographically directed to achieve optimum results. This strategy evolved from the late eighteenth century and is discussed in Section 4.

FIGURE 1 NEAR HERE

3 Spatial Strategies

Intrinsically spatial approaches to epidemic control can be traced back to medieval times and the repeated waves of plague activity that followed on from the great pandemic of Black Death (1346–53) in Europe. The first landmark moves against the disease were taken by the republic of Ragusa (modern-day Dubrovnik, Croatia). On July 27, 1377, the city's Major Council passed a law which stipulated that "those who come from plague-infested areas shall not enter [Ragusa] or its district unless they spend a month on the islet of Mrkan or in the town of Cavtat, for the purpose of disinfection" (Tomic and Blazina, 2015, pp. 106–7).

3.1 Italy and the Plague Centuries

The subsequent fight against plague was led by a group of states in northern Italy (Venice, Milan and Genoa). Venice itself became the focus of developments, establishing in 1423 an island hospital (Lazzaretto Vecchia) in the centre of the lagoon – the first in the world – for the treatment of plague-infected people and the decontamination of goods. The hospital was designed so that each patient had a separate cell; adjacent gardens were used for food production to complete the isolation. The system became overwhelmed during major epidemics, but the basic ideas of isolation, on site food production, and overwhelmed facilities in plague years have their echo today in the approach of many countries to the COVID-19 pandemic. In the UK, for example, isolation finds its parallel in shielding and 14-day self-isolation, while the slogan "stay at home, protect the NHS, save lives" speaks to preventing the overburdening of the National Health Service's facilities and resources.

From thereon, Italy's northern states gradually evolved a system of public health which, by the mid-1600s, had reached a high degree of sophistication. First, echoing Ragusa, ships arriving in their ports from infected areas were required to sit at anchor for 40 days (*quaranta giorni*, a practice from which the term 'quarantine' is derived) before landing. Second, the states devised a system of Health Magistracies which had, as their prime focus, the prevention of plague. Underpinning the system was surveillance and inter-state communication. During the sixteenth and seventeenth centuries, these states established the custom of regularly informing each other of all news they had gathered on health conditions prevailing in various parts of Italy, the rest of Europe, North Africa and the Middle East (Cipolla, 1981).

To assist in surveillance at the local level, there emerged the ubiquitous plague doctor who, COVID-like, wore his own Personal Protective Equipment (PPE). Introduced in 1630, the protective suit consisted of a light, waxed fabric overcoat, a mask with glass eye openings and a beak-shaped nose, typically stuffed with herbs, straw, and spices. Social distancing was facilitated by a cane that permitted the plague doctor to examine patients without the need for direct contact, while detailed records of plague-infected individuals, their dwellings and contacts were maintained in a medieval version of 'track and trace'.

3.2 International Sanitary and Health Regulations: The 'Quarantine Diseases'

The modern international development of the Italian ideas of quarantine began with the International Sanitary Conferences which took place from 1851. Their work came to fruition at the World Health Organization's (WHO's) First World Health Assembly in 1948. The Assembly devised a single code (WHO Regulations No. 2, 1951) based on modern epidemiological principles which provided an adaptable international instrument to deal with the sanitary conditions to be maintained and measures to be taken against the so-called 'quarantine diseases' (cholera, plague, smallpox, typhus fever, yellow fever, and subsequently, relapsing fever) at seaports and airports open to international traffic.

3.2.1 The International Health Regulations (2005) and Covid-19

Faced with the global health challenges posed by new and re-emerging infectious diseases in the late twentieth and early twenty-first centuries, including contemporary concerns over SARS and the highly pathogenic H5N1 avian influenza, the WHO issued a fully revised set of International Health Regulations (IHR) in 2005. These ushered in a new global public health surveillance regime that requires member states to notify the WHO of *all events which may constitute a public health emergency of international concern* (Article 6.1) – whether naturally occurring, intentionally created, or unintentionally caused (World Health Organization, 2008, p. 1). It was on the basis of these regulations that, on January 30, 2020, the Director-General of the WHO declared the COVID-19 event to be a public health emergency of international concern – an event that constituted a public health risk to member states and which required a coordinated international response. At this time, the WHO deemed it:

> …still possible to interrupt virus spread, provided that countries put in place strong measures to detect disease early, isolate and treat cases, trace contacts, and promote social distancing measures commensurate with the risk (World Health Organization, 2020, unpaginated).

These measures have formed the backbone of control responses by the WHO member states.

4 Vaccination: The Evolution of a Control Paradigm

A safe and effective vaccine is one of the holy grails of the current global COVID-19 research effort. In the absence of such a vaccine, Figure 1 indicates that the world will remain largely reliant on spatial control methods to limit the geographical spread of COVID-19. Vaccination has been used as a means of controlling an expanding list of infectious diseases since the late eighteenth century. While practices analogous to the process of conferring increased resistance to infection ('immunization') can be traced to antiquity, the modern history of vaccines dates to the late eighteenth century and local knowledge from the southwest of England that dairy farm workers who contracted cowpox were immune to smallpox. It was the English physician, Edward Jenner, who studied and promoted the prophylactic powers of cowpox. On May 14, 1796, Jenner vaccinated James Phipps with material obtained from a pustule on the hand of a milkmaid. Six weeks later he attempted, without success, to infect Phipps with pus from a smallpox patient. After 12 more successful vaccinations, he privately published a report of his findings and a new epoch in disease control dawned (**Figure 2**).

FIGURE 2 NEAR HERE

4.1 Vaccination, Critical Community Size and Disease Control

As noted in Section 2, once an epidemic has begun, its continuation is dependent upon the presence of a sufficiently large S sub-population for transitions of the type $S \Rightarrow I$ to be uninterrupted (Figure 1). This gives rise to the notion of critical community size (CCS) – the proportion of the population which must be immune to a disease for community transmission to cease. Individuals who are immune act as a barrier to spread, slowing or preventing the transmission of disease to others. Immunity can be acquired after infection with a disease agent or by vaccination. Once the CCS is reached, community circulation of the disease agent stops, the disease ceases to be present and can only recur by reintroduction from other reservoir areas. It follows that vaccines can be used to reduce the S sub-population, raise the R sub-population and effectively force an infectious disease out of a community or geographical area.

4.1.1 Vaccine-preventable diseases and the WHO-EPI

The global eradication of smallpox, formally announced by the WHO in December 1979, was one of the outstanding successes in the control of vaccine-preventable diseases. Then, policy advisors to the WHO looked for a successor to the smallpox eradication campaign. Representatives from industrialised countries, particularly those from Europe, were now seeing the results from their own immunization programs against a variety of vaccine-preventable childhood diseases and urged that these diseases be made the new WHO target area. The resolution creating the Expanded Programme on Immunization (EPI) was adopted by the World Health Assembly in 1974, with the initial aim of targeting six vaccine-preventable diseases (diphtheria, measles, pertussis, poliomyelitis, tetanus and tuberculosis) for a substantial reduction in global incidence. Program policies of the EPI were formalised by the World Health Assembly in 1977. It was at this time that the twin goals were set of (1) providing immunisation services for all children of the world by 1990 and (2) giving priority to developing countries.

When the *EPI* began, vaccine coverage for the initial six EPI target diseases was around five percent. From this low baseline, immunisation services in developing countries were extended to almost 80 percent of children (aged < 1 year) by the mid-1990s. Nevertheless, some 34 million children were being born each year in the poorest areas of the world which lacked adequate immunization programs. In response, new programs have been developed to increase vaccine coverage – including the Global Alliance for Vaccines and Immunization (GAVI) and the Global Immunization Vision and Strategy (GIVS) – as a contribution to achieving the United Nation's goal to reduce childhood mortality. A number of remarkable developments have followed, including the substantial global retreat of wild polioviruses under the Global Poliomyelitis Eradication Initiative (GPEI) and the elimination of indigenous measles in the Americas (Doherty, et al., 2016).

4.2 Opposition to Vaccination

Social and political opposition to vaccination (and immunization more generally) emerged soon after the development and standardization of smallpox vaccination practices and protocols (Smallman-Raynor and Cliff, 2012). In England and Wales, the Vaccination Act of 1853 and associated legislation mandated the compulsory vaccination of children against smallpox. This prompted the rise of opposition movements such as the Anti-Compulsory Vaccination League (later, the National Anti-Vaccination League) that objected to vaccination on political, medical and religious grounds. Although the laws on compulsory vaccination in England and Wales were relaxed at the end of the nineteenth century, anti-vaccinationist sentiment continued to cast a shadow over smallpox control in the decades that followed (Rafferty, et al., 2018).

Unfounded or unproven health concerns have occasionally prompted public anxiety over vaccines, as illustrated by the controversy over the combined measles, mumps and rubella (MMR) vaccine in recent decades (Cliff and Smallman-Raynor, 2013). In anticipation of the development of SARS-CoV-2 vaccines, a number of anti-vaccinationist narratives have already begun to develop around such issues as vaccine safety, conspiracy theories, alternative medicines and cures (Johnson, et al., 2020). Such developments have the potential to hamper efforts to exert effective control of the virus as an when a safe and effective vaccine is rolled out.

5 COVID-19 control

The epidemic model in Figure 1 has led to the frequent use of two terms in the UK Government's daily briefings on the COVID-19 pandemic:

(i) **the basic reproduction number, R_0**. This is defined as the average number of new infections caused by a single infected individual in an entirely susceptible, infinite population. In the terms of Figure 1, this number is estimated from the rate at which new cases, *I*, occur and the rate at which patients, *R*, recover. If this ratio exceeds unity, the occurrence of new cases exceeds the recovery rate and the epidemic will burgeon. On the basis of the international experience of COVID-19, the new virus appears somewhat more infectious than pandemic influenza, but substantially less infectious than common childhood viruses like measles and mumps;

(ii) **herd immunity**. This occurs when the proportion of individuals in the population that have acquired immunity to an infectious agent (either through natural exposure or vaccination) is sufficiently large that transitions of the type $S \Rightarrow I$ are interrupted and community transmission ceases.

A multinational study by Kwok, et al. (2020) suggests that 60–80 percent protective immunity is needed to establish herd immunity to SARS-CoV-2 in a population. The achievement of such levels of herd immunity by natural means would have major ramifications in terms of morbidity and mortality and is deemed to be politically untenable in most countries. Under these circumstances, the best hope rests with a safe and effective vaccine. Vaccine development is a slow process, and it is possible that no efficacious vaccine can be found. All this implies that SARS-CoV-2 will remain a significant public health threat for some considerable time, even for the foreseeable future. Until a vaccine (or an effective treatment) is available, variants of the spatial strategies that evolved in medieval times – including social distancing, isolation, quarantine and lockdown – will remain the major means of COVID-19 control. These strategies will be supplemented by enhanced surveillance regimes, including contact tracing as exemplified by the 'Test and Trace' program in the United Kingdom.

As discussed in Section 3, the IHR (2005) are the principal legal instrument for international disease response by the WHO. The extent to which the Chinese government followed the requirements of the Regulations, and provided the WHO with timely notification of the initial outbreak in Wuhan in late 2019, will be one focus of the forthcoming independent international evaluation of the WHO's handling of the pandemic. Similarly, the reaction time of the WHO and the delay in characterising the COVID-19 event as a 'pandemic' (11 March 2020), will also be examined. By the time that COVID-19 had been declared to be a pandemic, the disease had been documented in 114 countries, territories and areas, and the associated case count had exceeded 118,000. Given that community circulation had already been established in many countries, the apparent lack of a coordinated global response will also be under close scrutiny.

COVID-19 is now deeply embedded in the global population. Even with a highly effective vaccine and a determined roll-out, it is unlikely that it would be biologically plausible to eradicate SARS-CoV-2. Even if the virus could be eliminated in the human population, the threat would always remain of a reintroduction from its putative animal reservoir. On this basis, the world will have to face the prospect of controlling COVID-19, by whatever measures are available, in the decades to come. By defining our examination in terms of a spatial epidemic model, we hope that a clearer picture of what can and cannot be achieved, and how, has emerged.

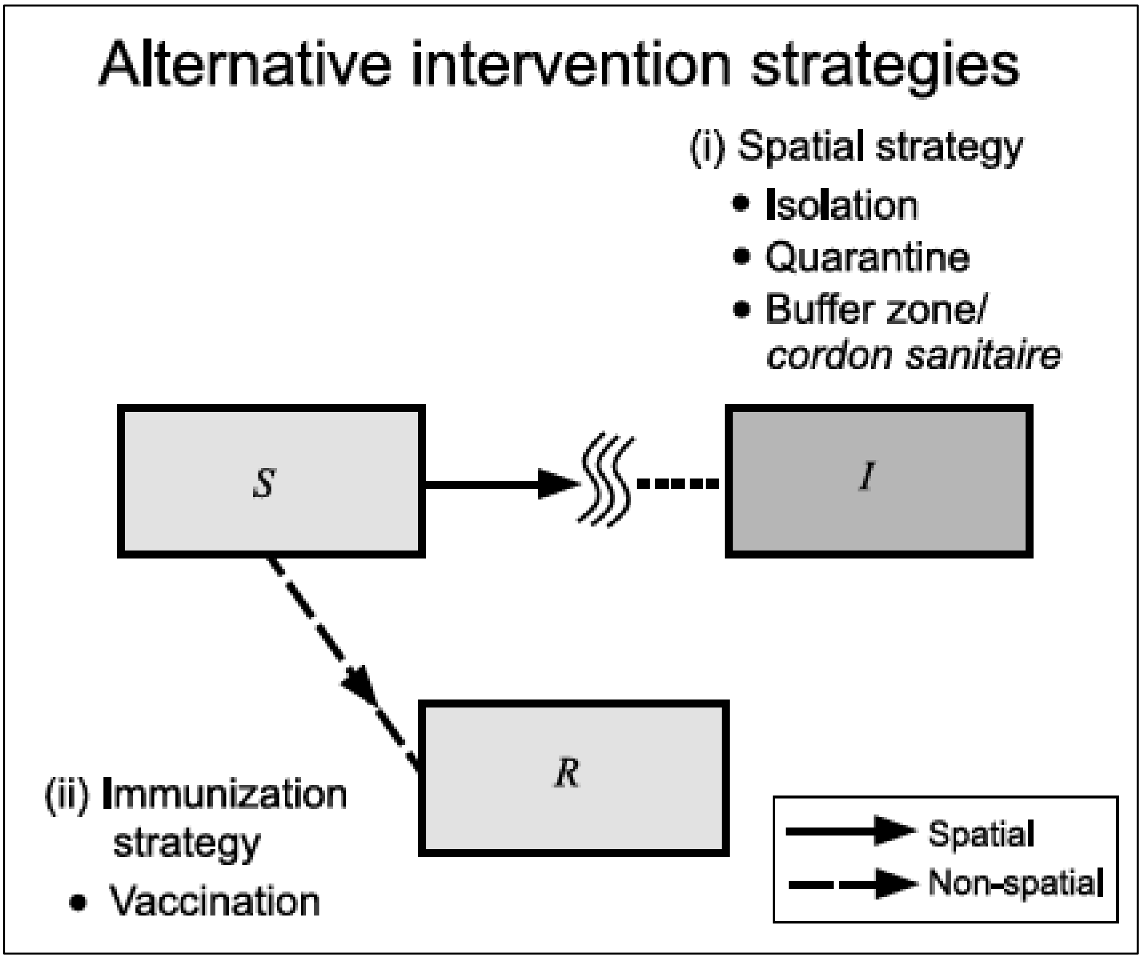

Fig. 1 Interrupting chains of infection. Alternative intervention strategies based on (i) a *spatial strategy*, blocking links by isolation and quarantine between susceptibles and infectives and (ii) a generally *aspatial strategy*, opening of new direct pathways from susceptible to recovered status through immunisation. This outflanks the infectives (*I*) box. *Source*: Cliff and Smallman-Raynor (2013, Figure 1.19, p. 15).

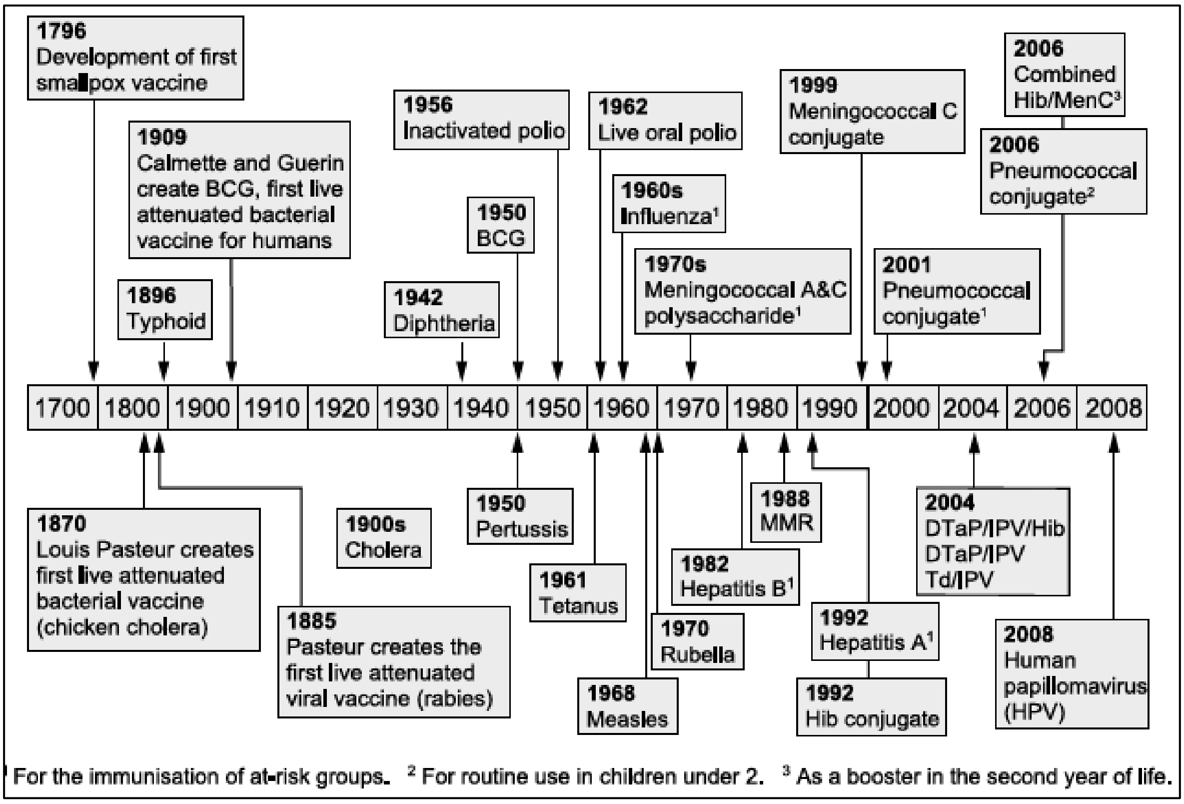

Fig. 2 Timeline of vaccine developments and the introduction of vaccines in the United Kingdom. BCG (Bacillus-Calmette Guérin) tuberculosis vaccine. Hib (*Haemophilus influenzae* type b) vaccine. MMR (measles, mumps and rubella) combined vaccine. DTaP (diphtheria and tetanus toxoids, and acellular pertussis) vaccine. IPV (inactivated poliovirus vaccine). Td (tetanus and diphtheria toxoids) vaccine for adults. DTaP/IPV, DTaP/IPV/Hib and Td/IPV are combined preparations. Source: Cliff and Smallman-Raynor (2013, Figure 4.4, p. 104).

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