Research

National and international policies to mitigate disease threats

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To devise and implement effective health policy, we must define the problem, choose the tools, craft the policy, build consensus, set goals and deadlines, raise funds and take action. Success or failure depends on the perception of risk, the strength of the underlying science, the efficacy of the technology, ownership and intellectual property, the conflict between individual and public health, the choice of weaker (guidelines) and stronger (law) policy instruments, the level of public interest, political opportunity, institutional inertia, mechanisms for enforcement and who foots the bill. All these things considered, this paper is a brief policy-making guide by example, illustrating some achievements and disappointments with reference to cholera, drug-resistant tuberculosis, HIV/AIDS and rabies.

Keywords: cholera; drug resistance; HIV/AIDS; international health regulations; rabies; tuberculosis

1. ORIGINS OF INTERNATIONAL HEALTH POLICY

International health policy began in the middle of Europe in the middle of the nineteenth century. As ‘Asiatic’ cholera swept across Europe in the early 1800s, its containment became a cross-national problem, highlighted by the remarkable death toll in and around theatres of war. During the Crimean conflict of the 1850s, far more people died from disease than from battle injuries. According to Mulhall [1], 51,945 were killed in action and a further 66,397 died of their wounds. But 491,455 died of disease, including tens of thousands from cholera. The death toll from cholera among British and French forces was reportedly around 7000, much of it before troops reached Crimea.

A Europe-wide solution to cholera was needed, and France took the initiative. In 1851, the first of a series of International Sanitary Conferences (ISC) was held in Paris [2]. The goal of the ISC was to agree upon and standardize International Sanitary Regulations (ISR). On the agenda of the early meetings were the cause of cholera, and the relative merits of hygiene, sanitation and quarantine to prevent the spread of disease. Prior to John Snow’s work in the 1850s, linking cholera to contaminated water sources in London’s Soho district, British delegates to the ISC opposed the view that cholera was water-borne, favouring Pettenkoffer’s air-borne (miasma) theory. Without agreement on the cause, there could be no consensus on the remedy, and the British (among other delegations) objected to the various quarantine measures proposed at the ISC.

In the ensuing decades of the nineteenth century, further advances in cholera epidemiology and microbiology established the truth, and cholera was ultimately driven from Britain and Europe during a ‘sanitation revolution’ [3,4].

Six cholera pandemics emerged from Asia in the nineteenth century. The current, seventh pandemic, which began in Asia in the 1950s, has not taken hold in Europe, but remains a major public health problem in the developing world [5]. Displaced by a succession of wars since the 1990s, the people of Burundi, Democratic Republic of the Congo and Rwanda have been exposed to cholera epidemics with the loss of many thousands of lives. And cholera has spread to the neighbouring countries of Angola, Mozambique, South Africa, Zambia and Zimbabwe [6]. In 2010, the disease reappeared in Haiti when an Asian strain was introduced in the aftermath of a major earthquake [7,8].

This short history of the ISC and ISR points to many of the challenges in setting national and international health policy. These include defining the problem, choosing the tools, crafting the policy, building consensus, setting goals and deadlines, raising funds and taking action. Sections 2–4 take a closer look at these challenges with reference to different contemporary disease threats: rabies, drug-resistant tuberculosis (TB) and HIV/AIDS. In the final part of the paper, I return to the modern incarnation of ISR—the World Health Organization’s (WHO) International Health Regulations—and draw some general conclusions about health policy-making today.

The examples in this paper draw on quantitative analysis, especially mathematical modelling. Analysis of this sort rarely plays the deciding role in policy change, but it has a guiding function at every step, from framing the problem to formulating a solution.

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2. QUARANTINE AND RABIES IN GREAT BRITAIN

A change of government is a chance to change health policy. As the British Labour Party took office in 1997, the quarantine laws that helped keep rabies out of Britain presented both a problem and an opportunity. With more frequent travel between European countries and beyond, temporarily for leisure or for longer periods of work, there was mounting pressure to allow freer movement of people with their pets (notably from the organization ‘Passports for Pets’). Six months’ quarantine for dogs and cats was unpopular. At the same time, there was an obvious possible solution: a highly efficacious rabies vaccine, with demonstrable impact in continental Europe where rabies cases had been much reduced through oral vaccination campaigns [9]. How, then, could vaccination, along with other safeguards, be used to relax the quarantine procedures in Britain?

Part of the work of a UK government commission (the Advisory Group on Quarantine) was to calculate the enhanced risk of a cat or dog developing rabies in Britain, under various modifications to the quarantine arrangements [10]. We compared the existing policy of six months’ quarantine for all immigrant dogs and cats with a mix of alternatives, which included reducing the quarantine period, tagging, vaccination and serological testing, with animal checks carried out at ports of entry or at other designated inspection centres. We first identified all possible routes by which dogs and cats, infected and uninfected, could enter Britain, accounting for all relevant control measures and points of interception (figure 1). Then, compiling all available data, we calculated the likely number of rabies cases that would occur in Britain per year, and per animal entering the country, comparing the existing policy with defined alternatives.

The first finding was that the absolute risk of any immigrant, rabies-infected animal developing rabies at large in the UK varied from extremely low to very low under different policies. Under a policy of six months’ quarantine, it was less than 1 in 50 million prospective immigrants. In the absence of any policy, the risk was about 1 in 10 million. The risks associated with all other policies lay between these two figures.

Weighing costs, practicality and risks, the most satisfactory alternative was to combine vaccination of animals more than three months old at a fixed time (e.g. six months) or during a fixed interval (e.g. 6–12 months) before entry to the UK with serological testing and permanent marking for identification. The rules would apply to all European Union (EU) and rabies-free countries. We calculated that this policy marginally increased the risk of a rabies case in Britain, causing one case in 28–34 years instead of one case in 36 years (figure 2). All other options were more risky, more costly or more difficult to implement.

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At the interface between science and politics, the risk analysis had to be presented in various ways. We were asked, for example, whether the analysis guaranteed that Britain would remain rabies free for at least 2894 C. Dye

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20 years. The chance of a case within 20 years was not zero, but it was very small (figure 2). The political outcome was a discrete decision based on a continuous probability distribution: the quarantine law was swiftly changed, and replaced by the pet travel scheme (PETS). Since 2000 in Britain (and throughout the European Union since 2004), dogs, cats and ferrets have been given freedom of travel, with their owners, to and from listed countries without quarantine provided the animals are vaccinated, tagged, blood tested, and de-ticked and de-wormed. They must also carry a passport and enter via an authorized route. More than a decade on, Britain has had no case of dog or cat rabies outside quarantine.

3. REVERSING THE SPREAD OF DRUG-RESISTANT TUBERCULOSIS

The two principal drugs used to treat human TB in combination chemotherapy are isoniazid and rifampicin. Patients that carry strains of Mycobacterium tuberculosis resistant to both are ‘multi-drug resistant’ (MDR-TB) [11]. Treatment for MDR-TB is long (18 months or more), costly, awkward when it involves injectable drugs, more toxic, and generally less successful than the treatment of drug-sensitive TB. Although MDR-TB emerged (above background mutation rates) when isoniazid and rifampicin began to be used together in the 1970s, drug-resistant TB reached new heights of notoriety during an outbreak of an ‘extensively drug-resistant’ (XDR-TB) strain during 2006 at Tugela Ferry in Kwa-Zulu Natal, South Africa [12,13]. XDR-TB strains are refractory not only to the first-line drugs isoniazid and rifampicin, but also to second-line drugs including fluoroquinolones (e.g. ciprofloxacin) and aminoglycosides (e.g. kanamycin).

As XDR-TB joined the ranks of serious emerging pathogens, several concurrent events put TB on news bulletins worldwide. First, patients who were part of the outbreak at Tugela Ferry suffered a very high mortality rate: 52 of 53 patients died, half of them within 16 days [14]. Second, the chosen name positioned these new strains as ‘X’ rated emerging pathogens, undoubtedly raising the fear factor. From one perspective, this was a stroke of policy-making genius. Third, an incident that began in 2007 in the USA showed that drug-resistant TB is not only a pathogen of remote places and peoples, but an infection that anyone could acquire anywhere. Andrew Speaker, a lawyer from Atlanta, Georgia, was found to be infected with a strain of MDR-TB shortly before his planned wedding and honeymoon in Europe [15]. Believing himself to be non-infectious, he left for Europe against advice not to travel, keeping one step ahead of public health officials en route, before returning, married, by a circuitous route to the USA. The story generated a massive media spike for TB in June 2007, which probably helped fix the problem of resistant TB in the minds of policy-makers and funding agencies.

Meanwhile, it was becoming clear that the South African XDR-TB epidemic was not as it first seemed. The deaths at Tugela Ferry were not due, so far as is known, to an especially virulent strain spreading rapidly through a population. The case fatality rate was high because all patients were infected with HIV, and most acquired their XDR-TB infection in hospital owing to a failure of basic diagnostic procedures and infection control [16]. In short, the outbreak could have been prevented.

Unsurprisingly, XDR-TB has now been found in almost every country where second-line drugs are used. Improved surveillance and advanced laboratory
cases, including earlier diagnosis and higher cure rates, then control measures directed specifically at resistant transmission cycles of resistant cases are self-sustaining, simply as a by-product of poor practice in drug perspective, we need to know whether resistant strains are for all strains, then TB will eventually be eliminated, albeit transmission cycles (severe epidemic, test to fixation in the TB, TDR-TB [17]. But will these drug-resistant classes of second-line TB drugs—’totally drug-resistant’ procedures are now uncovering strains resistant to all classes of second-line TB drugs—’totally drug-resistant’ TB, TDR-TB [17]. But will these drug-resistant strains of TB spread to fixation in the Mycobacterium tuberculosis population?

While the emergence of exotic strains of M. tuberculosis presents enormous clinical challenges, the public health strategy for containing the spread of resistance depends on their evolutionary fitness, measured by the number of secondary cases generated by each primary case. At the start of an epidemic, this is the basic case reproduction number, $R_0$ [18]. If $R_0$ can be held permanently below 1 for all strains, then TB will eventually be eliminated, albeit on a time scale of many decades. From an epidemiological perspective, we need to know whether resistant strains are generated simply as a by-product of poor practice in drug therapy leading to treatment failure (benign epidemic, $R_0 < 1$), or whether they can reproduce in self-sustaining transmission cycles (severe epidemic, $R_0 > 1$; figure 3). If transmission cycles of resistant cases are self-sustaining, then control measures directed specifically at resistant cases, including earlier diagnosis and higher cure rates, are needed to ensure that $R_0 < 1$. If they are not self-sustaining, then drug-resistant strains can be eliminated along with drug-sensitive strains.

In a recent analysis of MDR-TB dynamics, we found that in nine out of ten settings, all strains of TB, including MDR-TB, were on a slow path to elimination (figure 4) [19]. This was true even in the Baltic states of Estonia and Latvia, which have had exceptionally high prevalence rates of MDR-TB. The single exception was Russia (four provinces), which may have had severe MDR-TB epidemics up to 2006. The reversal of MDR-TB epidemics in the Baltic states has apparently coincided with the introduction of systematic drug sensitivity testing (DST), coupled with the appropriate mix of first- and second-line drug regimens. The latest data from the four Russian provinces suggest that here, too, the spread of MDR-TB has been reversed.

There are several implications for policy. In general, although drug resistance is a grave threat to TB control, it can be contained by correctly applying the present set of tools. More specifically, treatment of drug sensitive cases with cheap and effective first-line regimens, following WHO guidelines, will markedly slow the emergence and transmission of drug-resistant strains. However, even when the spread of MDR-TB has been reversed, the time to elimination will be many decades if we have to rely on present methods.

Triangulating between evidence, need and pragmatism, WHO’s current recommendation is DST for all patients with recurrent TB, plus new patients judged to be at high risk of MDR-TB (about 20% of all new patients). All patients with a confirmed diagnosis of MDR-TB should be given appropriate combinations of first- and second-line drugs. The implication of this policy is that 270 000 patients should be treated for MDR-TB in 2015, among the 400 000 estimated to arise each year [20]. Given that only 5000 received the recommended treatment in 2008, this target for 2015 looks ambitious. The challenge resides not just in the weaknesses of clinical and laboratory facilities in affected countries, but also in the debate about how best to provide medical services. For example, the goals of public health are not always consistent with opinion about civil liberties: during an outbreak of a lethal infectious pathogen, under what circumstances does the protection of uninfected people justify the detention of uncooperative patients [21,22]?

4. ANTIRETROVIRAL THERAPY TO PREVENT HIV TRANSMISSION

In 1995, David Ho argued that is was ‘time to hit HIV, early and hard’ [23]. In those early days of antiretroviral therapy (ART; then with nucleoside inhibitors of reverse transcriptase such as zidovudine) he was thinking mainly about the clinical benefits. The aim, said Ho, should be to attack the virus during the initial phase of infection, when it is most antigenically homogeneous. Though a cure for HIV infection is still elusive, the advances in ART since 1995 have been miraculous, and some now anticipate that the latest antiretroviral drugs will restore life expectancy to normal [24]. Now, the debate about using ART is not only about healthy life expectancy, but also about the role

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of ART in preventing HIV transmission. The control of HIV epidemics certainly requires more than clinically effective treatment. For although HIV incidence has been falling in many countries since the late 1990s, an estimated 2.6 million people acquired infection in 2009 and 1.9 million people died of AIDS-related illnesses [25].

The argument for preventing transmission was first set out by Montaner et al. [26], and elaborated by Granich et al. [27]. In simple terms, the logic of elimination is as follows. From the early growth in prevalence of HIV infection, we can calculate the initial doubling time of the epidemic. This is the time taken for each HIV-positive person to infect one other person. In high-incidence South Africa, it was about 1.5 years, based on data from ante-natal clinics. Without ART, the life expectancy from the point of infection is roughly 10 years, and over this period each HIV-positive person infects 10/1.5 = 7 other people on average. Thus, the basic case reproduction number in this setting, \( R_0 \approx 7 \). To put HIV on a path to elimination requires \( R_0 \), that is, we must reduce transmission by a factor of more than 7. A programme of annual testing for HIV infection followed by immediate ART would reduce transmission by a factor of 10, assuming that ART prevents transmission completely.

More specifically, HIV infection will eventually be eliminated in South Africa when everyone is tested for HIV at least once a year on average, and when ART begins at a CD4 cell count of 1000 \( \mu \text{L}^{-1} \) or more (figure 5) [27]. Beginning in 2010, a programme of annual testing with immediate treatment for all HIV-positives, rolled out over 5 years, would cut HIV incidence dramatically by 2020 (figure 6). After

![Figure 4](image_url)  
Figure 4. Case reproduction numbers for drug-sensitive (isoniazid (INH) sensitive, mid-grey bars), INH-resistant (light grey bars) and MDR-TB cases (dark grey bars) in 10 settings. Data were obtained by fitting a dynamical model to the time trends in each of the three strain types. Error bars are 95% CL. Countries are ranked from left to right in order of decreasing \( R_0 \) (INH sensitive). Estimates of \( R_0 \) are less than unity for all strains bar one (MDR-TB in Russia), indicating that most epidemics of drug-resistant TB are benign and in slow decline. Adapted from [19].

![Figure 5](image_url)  
Figure 5. Area plot of \( R_0 \) (contours) against the CD4 cell count at which ART for HIV/AIDS starts (horizontal axis) and the average time between random HIV testing of individuals (vertical axis). Numbers in circles give values of \( R_0 \) on different contours, e.g. solid black line, \( R_0 = 1 \). Solid white line marks CD4 = 350 \( \mu \text{L}^{-1} \), the current WHO-recommended threshold below which patients should start ART. HIV infection will be eliminated in the upper right zone (\( R_0 < 1 \)), which requires everyone to be tested for HIV at least once a year on average, and that HIV-positives begin ART when CD4 counts are 1000 \( \mu \text{L}^{-1} \) or more. Adapted from [27].

2020, few people would acquire new infections, but mass testing and treatment would give millions of HIV-infected South Africans long and healthy lives.
So HIV infection would not be eliminated from the population for a further 30–50 years. Regular HIV testing coupled with early ART would also markedly reduce the incidence of TB, the principal AIDS-related illness in Africa [28,29].

These findings are enticing, but they are not yet part of HIV control policy. For policy to embrace early ART, there must be greater certainty that it will bring net clinical benefits, that intensive treatment will not lead to widespread drug resistance, that there is popular acceptance of, and demand for, HIV testing, and that regular testing and treatment is affordable and logistically feasible. The last of these (on the supply side) is perhaps the greatest obstacle: by the end of 2009, only 36 per cent of all HIV-positive patients with CD4 count less than 350 μl⁻¹, as under current policy; dark grey, annual universal voluntary HIV testing and immediate ART. (a)(i) HIV incidence, (ii) HIV prevalence and (iii) mortality under the three scenarios. In (a)(ii) data points with error bars give estimated prevalence of infection in adults derived from South African antenatal clinic data. (b)(i) Incidence of ART (rate at which people start ART), (ii) the proportion of people receiving ART and (iii) the mortality in those receiving ART. Data are proportions of people aged 15 years and older. Adapted from [27].

5. EMERGING INFECTIONS AND THE INTERNATIONAL HEALTH REGULATIONS

The goal of the International Health Regulations (IHR), the successor to the International Sanitary Regulations, is ‘to prevent, protect against, control and provide a public health response to the international spread of disease’. In 1969, IHR covered only cholera, plague and yellow fever. From the examples mentioned earlier, and from the panoply of emerging and dispersing diseases now permanently in the news—pandemic influenza, severe acute respiratory syndrome, dengue, chikungunya, West Nile virus and others—it is clear that international health policy needs a broader base.

To this end, the 2005 revision of IHR became an instrument of international law that entered into force in 2007 with 194 countries as ‘States Parties’ [31]. The IHR are no longer limited to specific diseases, but apply more generally to health risks, such as those linked to chemical spills and nuclear accidents. The States Parties to the IHR are obliged to strengthen and maintain the capacity to detect, report and respond rapidly to public health risks of international concern; to respond to requests for verification of information about potential public health emergencies; to assess international health risks and notify WHO promptly of these risks; to carry out inspections and control activities at points of entry; and to implement appropriate measures recommended by WHO. Although the IHR are legally binding, the primary intention is not to enforce and regulate, but rather to provide support to governments that promptly report emerging international health risks.

As a broad framework for action, the IHR leave open various questions of detail. How, for example,
can resources be fairly allocated during a pandemic when donor countries control limited funds and recipient countries retain sovereignty over capabilities on the ground [32]? Is it possible to implement a coherent international policy when the legal status of pandemic plans varies among neighbouring countries? A century and a half after the ISC debated cholera, similar questions apply to influenza control in Europe [33]. And how can resources and materials be shared while at the same time preserving intellectual property [34]? There are fears, for example, that pathogen samples taken from the source of an outbreak (e.g. countries in Asia) will be quickly exploited for profit by well-funded laboratories in the rich world.

6. CONCLUSIONS: FROM SCIENCE TO POLICY

Health policy-making blends the art of the soluble (science) with the art of the possible (politics), to rephrase Peter Medawar. With all forces aligned, success can rapidly follow. But if any of the key elements is missing—a precisely defined problem, a clear policy, the right technology, consensus borne on common interest, a trained workforce, laboratories or funding—the route to effective policy might be long. This review of selected examples yields a checklist of essentials, but success in any setting is contingent on circumstances—the devils in the details.

An unsurprising general conclusion is that health policy is usually easier to formulate and implement nationally than internationally. After a review of Britain’s rabies quarantine laws, the new PETS was in place as a legal instrument within 3 years (though lobbyists will recall many years of protest before the right moment arrived). But success in changing the quarantine laws had two other key elements: a simple, affordable and effective technology (vaccine), and a system with which to implement it (a law, adherence to which could be monitored and enforced).

The policies for the containment of drug-resistant TB and reversal of the HIV/AIDS epidemic are weaker in both areas. For drug-resistant TB, there is an agreed international approach to DST and treatment. But the policy is presented as a set of international guidelines, not a legal framework. Diagnosis and treatment is lengthy and costly. And the worst-affected countries have under-funded and weak health systems, lacking trained staff and well-equipped laboratories.

The incidence of HIV infection could be reduced to very low levels if a large enough fraction of infected people could begin treatment soon after acquiring infection. WHO policy on treatment has not yet advanced that far because there is not yet a consensus that early ART is beneficial on aggregate, and it is generally recognized that programmes of regular HIV testing will be hard to implement. While lifelong ART is becoming cheaper and more accessible, African countries with high HIV prevalence are struggling to meet present WHO guidelines (ART when CD4 count falls to 350 μl⁻¹). For both TB and HIV/AIDS, the problem of building affordable and effective systems for diagnosis and treatment underpins the hope for an easily administered, high-efficacy vaccine, like that for rabies [35–37].

WHO might be ‘the nearest thing we have to a ministry of health at the global level’ [38] but it is operating, like all international agencies, in an environment of growing financial and political complexity. One recent count of international health players found 40 bilateral donors, 26 UN agencies, 20 global and regional funds and 90 global health initiatives [38]. The number and diversity of organizations underlines the need for coordination and, at the same time, the difficulty in achieving it. In this context, the strengthened IHR are a step forward, enhancing the opportunities to successfully implement health policy beyond national boundaries.

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