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Trans-boundary commons in infectious diseases

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Abstract Emerging threats to global health, including drug-resistant pathogens, emerging pandemics, and outbreaks, represent global trans-boundary commons problems where the actions of individual countries have consequences for other countries. Here, we review what economic analysis can offer in countering these problems through the design of interventions that modify the behaviour of institutions and nations in the direction of greatest global good.

Key words: strategic complementarity, economic incentives, global pandemic, surveillance, reporting of disease outbreaks

JEL classification: H4, I1

I. Introduction

The past century has been marked by significant improvements in life expectancy, due to greater child survival and reductions in infectious disease. The greatest victories in global health have come through globally coordinated actions—the eradication of small pox in 1980, the Global Polio Eradication Initiative (still ongoing), and the sharp reductions in malaria through the Global Malaria Eradication Program (GMEP) in the 1960s. Just the first two of these initiatives resulted in roughly 5.65m deaths averted each year (UNICEF, 1996; Ehreth, 2003), and the GMEP was responsible for eliminating malaria in 25 countries (Kouznetsov, 1977).

Largely as a consequence of these efforts and of improvements in wellbeing that have translated into better ability to prevent and treat infectious diseases, these conditions have diminished in importance as a source of ill health across much of the world. According to the 2010 Global Burden of Disease estimates, the percentage of disability-adjusted life years (DALYs) due to prominent infectious diseases (comprised of the following four cause groups: HIV/AIDS and tuberculosis; diarrhoea/lower respiratory infections/other infectious diseases; neglected tropical diseases and malaria; and other communicable diseases) decreased from 54.4 per cent in 1990 to 49.8 per cent in 2010,

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while the percentage of deaths due to prominent infectious diseases decreased from 54 to 51.5 per cent (IHME 2013).

Nevertheless, infectious diseases continue to be a significant source of ill health globally and a number of the world's emerging global health threats involve infectious diseases that can easily cross boundaries. The emergence of a new infectious disease—Ebola being the most recent example—poses a significant risk to other countries, no matter where it arises. The risk is not uniform: countries that are connected by geography or population movement with the country where the disease emerges, and those with weak health systems are particularly vulnerable. But there are counter-examples as well. New Delhi metallo-β-lactamase (NDM) enzymes that cause drug resistance in bacteria, which were first reported in 2008 from one patient hospitalized in Sweden, are now reported globally (Nordmann *et al.*, 2011). Multiple factors including human population growth, land-use changes, and infectious diseases originating from wildlife (also known as zoonoses) are accelerating the frequency with which infectious diseases emerge (Jones *et al.*, 2008).

Even if the direct health toll from these emerging infections does not approach the levels that were observed during the 1918 global flu pandemic, when nearly 50m people died, these infections can nevertheless do serious damage to economies, health, and health systems by virtue of their speed of attack. Ebola has killed roughly 10,000 people in the last year, mostly focused in the west African countries of Guinea, Liberia, and Sierra Leone, and resulted in a 5 per cent loss of GDP in these countries (World Bank, 2015). A recent study projected that after 6–18 months of disruptions, the accumulation of a large connected cluster of children unvaccinated for measles across Guinea, Liberia, and Sierra Leone resulted in between 2,000 and 16,000 additional child deaths due to measles alone (Takahashi *et al.*, 2015). The deaths of healthcare personnel may have ripple effects down the road and could even discourage people seeking to train to be tomorrow's healthcare workers. The overall damage to health systems due to the large numbers of health system professionals lost to Ebola will only become apparent in coming years.

Drug resistance is now a global problem and threatens public health in nations regardless of economic status (Laxminarayan *et al.*, 2013). Antibiotic-resistant gonorrhoea emerged in Vietnam in 1967 (Holmes *et al.*, 1967), before spreading to the Philippines and finally to the United States (Rasnake *et al.*, 2005). NDM enzymes are now in nearly every country, as discussed earlier.

In this paper, we discuss the global health threats that involve 'commons' problems. With such problems, the actions undertaken in one country have consequences for other countries, but these are 'externalities' that are not taken into consideration by decision-makers. For instance, a country may not report a disease outbreak for fear that it would discourage tourism, but the failure to report the outbreak could put other countries at risk. Other examples of country-level actions with global consequences include inadequate vaccination coverage; slow progress on disease elimination; failure to report and contain pandemic flu, antibiotic resistance, and counterfeit drugs; and climate-related health threats. We provide some examples and case studies of such negative externalities across borders. Then, we discuss the need for international cooperation for tackling these global health threats.

The remainder of the paper is organized as follows. Section II describes trans-boundary externalities in tackling infectious diseases. Section III deals with incentives for

surveillance and reporting of disease outbreaks. Section IV addresses incentives for disease elimination and eradication. Section V addresses incentives and financing mechanisms for controlling drug-resistant pathogens. Section VI concludes the paper.

II. Trans-boundary externalities in disease control

Early examples of international medical cooperation in the modern age were based on the idea that because infectious diseases do not respect national boundaries, meaningful control necessarily transcends national programmes. The first International Sanitary Conference was convened in Paris in 1851 to discuss the quarantine of ships to contain plague, yellow fever, and cholera; it predated the first Geneva conventions on treatment of war casualties by 13 years (Stern and Markel, 2004). More recently, campaigns to eliminate smallpox and eradicate malaria have been built on the idea that infectious disease control depends not just on national priorities but also on the priorities of one's neighbours and trading partners. An understanding of transnational disease transmission was deeply rooted in the GMEP, which was launched in 1955. Funding from the top 12 contributors to the special account for malaria by member countries during 1956–79 accounted for 93 per cent of overall contributions over this period (Table 1). Of these 12 contributors, only Saudi Arabia had any significant malaria. Malaria-control investments in the current era are also likely to be largely externally funded, but contributions are not likely to continue indefinitely. Therefore, the gains made from control have to be sufficiently large not just in the focal country but also in neighbouring countries so that malaria control will continue to be a priority for national planners even after the donors have exited.

Malaria control benefits the country in which it occurs, of course, but in the longer term, its neighbours benefit as well because they face fewer cases of imported malaria. The spatial coordination problems introduced by trans-boundary malaria are also relevant for the problem of regional elimination within large countries, especially those with frequent in-country movement, such as India. In contrast, China has managed to eliminate malaria from most of the interior of the country, but

Table 1: Top 12 contributors to special account for malaria by member countries during 1956– 1979 (in US$ in cash or in kind)

USA	18,874,995
Sweden	4,105,710
Netherlands	1,808,594
Kuwait	1,410,900
Saudi Arabia	1,214,500
Germany, F.R.	765,002
USSR	554,722
Denmark	400,920
Norway	378,583
Switzerland	376,540

Note: These are not indexed on a single year but are just the arithmetic total of nominal values over the period of time indicated.
Source: Gramiccia and Beales (1988).

imported malaria remains a problem on its southern border. The extent of the 'external' benefit (to a neighbour) depends on malaria prevalence in that neighbour and the frequency and direction of overland migration. If malaria is common, then the benefit of fewer imported cases is minimal. However, the benefits can be large if the neighbour has eliminated malaria but still has to deal with cases imported from the focal country.

Barrett describes four equilibria in interactions between two countries that share an infectious disease (Barrett, 2006). In the first equilibrium, neither country engages in control, irrespective of what the other country does. In the second, each country eliminates the disease, irrespective of what its neighbour decides to do. In the third, each country eliminates the disease only if the other can be relied upon to do so. In the fourth, one country does not eliminate the disease, irrespective of what the other does.

When countries are not identical in either epidemiological conditions or economic prosperity, it may be in the interest of some countries to eliminate malaria but for others not to, even if all others have eliminated malaria. Yet elimination may be the optimal outcome for the two countries as whole. This is the case in which richer adjacent countries have financed elimination in poorer countries, as we observe in the Lubombo Spatial Development Initiative (LSDI).

Lubombo Spatial Development Initiative

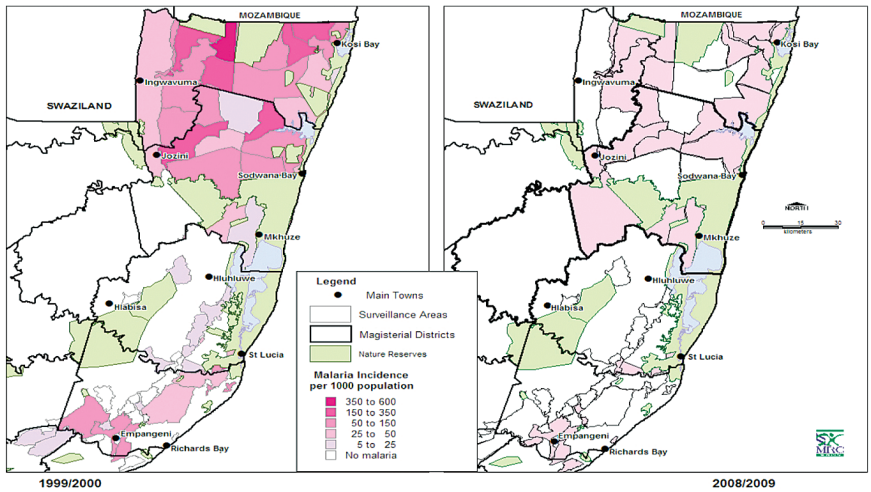
LSDI offers a recent example of trans-boundary control of infectious disease (Sharp *et al.*, 2007). Malaria control was seen as an essential element of economic development in the Lubombo region of eastern Swaziland, southern Mozambique (Maputo), and north-eastern Kwazulu Natal province in South Africa. Malaria prevalence in these three regions was closely intertwined because of the frequent migration of people (Sharp and le Sueur, 1996). Most malaria cases in Swaziland and Kwazulu Natal were imported from Mozambique: for instance, nearly 70 per cent of the malaria cases in Kwazulu were in the district adjoining Mozambique. Between November 2000 and February 2004, indoor residual spraying with bendiocarb insecticide was carried out twice a year in Mozambique. Spraying started in zone 1 (Figure 1) and proceeded incrementally, eventually covering seven districts and a population of roughly 800,000 people.

In Swaziland, where there were no other changes in malaria control efforts over the same time period, new malaria cases declined by 95 per cent (Table 2). Malaria cases declined by 78 per cent in Mpumalanga province, probably because during this period, indoor residual spraying and artemisinin-combination treatment were introduced on the South Africa side of the border. Nevertheless, the sharp decline in malaria in Swaziland and South Africa was attributable at least in part to efforts in Mozambique, which were largely paid for by South Africa and, to a lesser extent, by the Global Fund to Fight AIDS, Tuberculosis and Malaria.

West African river blindness programme

Coordinated financing, specifically with reference to multi-lateral financing to more than one country, is essential to permit a coordinated approach to disease control. However, such coordination has rarely been accomplished outside of global disease eradication programmes. There are a few examples of regionally coordinated financing such as against river blindness. The Onchocerciasis Control Programme (OCP),

Figure 1: Malaria incidence in LSDI malaria control zones in 1999 and 2009



Source: Moonen *et al.* (2010), reprinted from *The Lancet* with permission from Elsevier.

Table 2: Decline in malaria cases under Lubombo Spatial Development Initiative

	Swaziland		Kwazulu-Natal		Mpumalanga	
Malaria season	Cases	Percentage change	Cases	Percentage change	Cases	Percentage change
1999/2000	4,005		41,077		13,856	
2000/1	1,395	–56	16,985	–59	12,799	–8
2001/2	756	–81	2,818	–93	9,391	–32
2002/3	343	–91	1,709	–96	4,068	–71
2003/4	614	–85	4,200	–90	4,738	–66
2004/5	200	–95	1,778	–96	3,099	–78

Notes: Notified confirmed malaria case totals for Swaziland and the two adjacent malaria-endemic provinces in South Africa for the period July 1999 to June 2005 and the percentage change in case numbers per malaria season in comparison with the baseline year of 1999/2000. A malaria season is the period from 1 July of one year to 30 June of the next.
Source: Sharp *et al.* (2007).

which was launched in 1974, covered major portions of seven western African countries (Burkina Faso, Benin, Ghana, Côte d'Ivoire, Mali, Niger, and Togo). Because the initial set of countries did not cover the limits of the breeding sites of the main vector, the savannah blackfly, the programme was expanded in 1986 to also include Guinea, Guinea-Bissau, Senegal, and Sierra Leone.

A rare example of a transnational disease control effort launched by the World Bank (Kim and Benton, 1995), OCP relied on regionally coordinated larvicide spraying along the Niger river to control black fly populations, and, at its peak, the programme covered 30m people in 11 countries. This coordinated funding was in recognition of the fact that controlling black fly populations in a single country would be infeasible and required the cooperation of all seven countries on the Niger river. Through the Mectizan donation programme, which was initiated in 1988, onchocerciasis was eliminated as a public

health problem in west Africa. Over the period 1974–94, the programme prevented 600,000 cases of blindness, and brought about 25m hectares of arable land—enough to feed an additional 17m people a year—back into productive use.

III. Surveillance and reporting

The earliest efforts in global cooperation in the context of sanitary conventions, which required countries to report cholera outbreaks, subsequently led to the establishment of the Pan American Health Organization, a pre-cursor to the World Health Organization (WHO) in the twentieth century. Despite the benefits of warnings and reports on infectious disease outbreaks, there are few incentives for countries to report disease outbreaks that occur within their borders. Current International Health Regulations, which were first enacted in 1951 and most recently revised in 2005, require countries to report disease outbreaks. However, as there are no penalties for non-reporting, reporting depends on the goodwill of nations (Baker and Fidler, 2006). This may not be entirely true since 'the consequences of non-compliance may include a tarnished international image, increased morbidity/mortality of affected populations, unilateral travel and trade restrictions, economic and social disruption and public outrage' (WHO, 2009). Specifically, if countries do not report promptly, other countries may take actions to moderate their trade and travel relations with the target country for fear that a future outbreak may also not be reported. We have discussed this in detail below as *ex ante* sanctions that precede an actual future outbreak.

From a practical standpoint, countries face conflicting incentives as to whether or not to report an outbreak. On the one hand, reporting brings the near certainty of trade sanctions that can impose large costs. For example, when Peru reported an outbreak of cholera in 1991, its South American neighbours imposed an immediate ban on Peruvian food products. The $700m cost of these sanctions and the additional $90m lost from reduced tourist activity far exceeded the domestic health and productivity costs of the epidemic (Panisset, 2000). On the other hand, countries may report an outbreak in the belief that the information will be reported anyway through the media or informal channels. Furthermore, reporting an outbreak may result in international assistance for containing the outbreak. For instance, in the same Peruvian outbreak, foreign aid in the form of rehydration salts, saline solution, and antibiotics, while unable to prevent an epidemic, helped to significantly reduce the death rate (Brooke, 1991; Suárez and Bradford, 1993).

The appearance of new infections is determined by a number of factors, but generally is mediated by large growing populations that have poor nutrition and lack access to medical care (Woolhouse and Gowtage-Sequeria, 2005). However, despite the regular appearance of novel infections (Woolhouse *et al.*, 2008), few infections are able to spread effectively within a population. Over the last century, although more than 200 diseases are believed to have emerged, only five novel diseases have swept across the globe—three were novel strains of influenza, another was HIV/AIDS, and more recently we saw the spread of SARS, which emerged in China in November 2002 and spread around the world infecting more than 8,000 people in 32 countries and killing approximately 800 before it was contained (Zhong *et al.*, 2003). Further delays in reporting SARS by China could have resulted in catastrophic consequences worldwide if the pathogen had been more virulent (Heymann and Rodier, 2004).

There is evidence that countries respond to external incentives on whether or not they report infectious disease outbreaks. An outbreak of meningococcal meningitis during the Hajj resulted in more vaccination requirements for travellers coming to Saudi Arabia (Laxminarayan *et al.*, 2014). These requirements, which were introduced in 1988, were associated with reduced reporting of meningitis outbreaks among countries in sub-Saharan Africa, especially among countries with relatively few cases reported between 1966 and 1979. The announcement of a programme in 1996 to assist countries with immediate vaccines conditional on their reporting of outbreaks was associated with an increase in reporting among countries that had previously not reported meningitis outbreaks (Laxminarayan *et al.*, 2014).

Incentives for surveillance and reporting lie at the heart of an effective strategy to respond to avian influenza[1]. Mathematical models have suggested that it may be possible to contain an emerging pandemic of avian influenza if detection and reporting of cases suggestive of increased human transmission occurs within approximately 3 weeks of the initial case (Ferguson *et al.*, 2005; Longini *et al.*, 2005). While the WHO is responsible for coordinating the global response to human cases of avian influenza, decisions on establishing surveillance networks and reporting of outbreaks are the province of national governments.

Incentives to report an outbreak once it has been detected are only one part of the story, since an outbreak must first be detected. Incentives to invest in surveillance to detect an outbreak are likely to be endogenous, and depend on whether or not a country wishes to report an outbreak (Malani and Laxminarayan, 2011). These incentives are driven in part by the 'private' value of early detection to the individual country, but also by the likely consequences of the availability of this information to the rest of the world, either through the act of formal reporting or by informal channels, such as news reports or rumours. The greater the anticipated sanctions, the less likely a country will be to invest in surveillance. Conversely, the higher the perceived benefit of international assistance in preventing or ameliorating the cost of an outbreak, the greater the likely investment in surveillance. Current international mechanisms to encourage better reporting of disease have, by and large, ignored the economic dilemma and strategic behaviour of countries with emergent outbreaks.

Investments in surveillance also depend on the likelihood that the detected outbreak will produce a significant epidemic. The more a country believes a disease will arise and spread, the more significant the incentive to invest in surveillance. However, this investment can be tempered by the likelihood of false positives—the detection of a disease when none exists (Malani and Laxminarayan, 2011). Thus, a trade-off exists between investing in increased surveillance and investing in more accurate surveillance.

A government's decision to report an outbreak can be modelled as a signalling game in which a country has private but imperfect evidence of an outbreak (Malani and Laxminarayan, 2011). An important conclusion is that not all kinds of sanctions may discourage reporting. What does this mean? Let us divide sanctions into two kinds. *Ex ante* sanctions are imposed in the form of reduced trade and travel contact with countries that are perceived to be poor at reporting disease outbreaks promptly. It is for this reason that west Africa is not a favoured tourist destination—even in the absence of

[1] Institute of Medicine Special Public Meeting with Dr David Nabarro, Senior United Nations System Coordinator for Avian and Human Influenza, 11 September 2008.

Ebola, one is never quite sure if the system is able to detect and report this and other diseases. In contrast, an *ex post* sanction is imposed following a disease outbreak. *Ex post* sanctions discourage detection and reporting since they kick in only after an outbreak has been announced. However, *ex ante* sanctions do not deter reporting and if anything they encourage reporting so that countries can signal that they are on top of their disease surveillance programmes. Furthermore, *ex ante* sanctions based on fears of an undetected outbreak can reduce reliance on *ex post* sanctions as ways of controlling outbreaks.

Second, improving the quality of surveillance networks to detect outbreaks may not promote the disclosure of an outbreak because the forgone trade from reporting truthfully is that much greater. In sum, obtaining accurate information about potential epidemics is as much about incentives for reporting as it is about the capability and accuracy of surveillance networks.

IV. Disease elimination and eradication

Solving trans-boundary disease problems requires coordinated financing solutions, as has been evident with global eradication programmes. Eradication of a disease means that it is no longer prevalent in any country in the world and requires elimination in every country. Elimination, however, requires only the absence of the disease from a single country.

Global small pox eradication was largely paid for by the United States, even though countries like India stood to gain from the reduction in the number of deaths but were unable to achieve elimination on their own. However, the United States continues to recoup its roughly $150m investment in small pox eradication every 28 days through not having to vaccinate its citizens against the disease. The optimal coverage with a vaccination programme of a disease that can be eradicated is given by $p_c = 1/(1-R_0)$ where R_0 is the reproductive number of the disease—the number of secondary infections generated by a single infected patient entering a completely susceptible population. Note that this critical rate of vaccination coverage depends only on the reproductive number (an epidemiological variable) and not on the costs of vaccination averted or any other economic variables.

Eradication may not be optimal in the case of all diseases, however. For diseases like measles, where the pathogen can be easily engineered through artificial methods and re-introduced into the population, there is no option of stopping vaccination. Indeed, the current cohort of immunized individuals represents a valuable stock that is not easily replaceable in the short term. The optimal level of vaccination coverage of a disease for which vaccination must continue even after the disease has been eliminated can be computed as below. Total costs to society include the costs of the vaccination campaign (vaccination costs), which we assume to increase exponentially with coverage, and costs of infection (infection costs) that we use as an index of the severity of the disease. The assumption that costs are increasing exponentially with coverage is consistent with the idea that reaching the most difficult to access and geographically remote populations involves increasing marginal costs. The total infection costs are proportional to the

total number of the infective individuals in the population. Because there is little evidence for increasing or decreasing marginal costs of infection within a single population (the change in total costs that arises from having one additional infection in the population), we assume constant marginal cost and model the costs of infection as a linear function of the infected. The total cost of the vaccination plus infection is then,

$$\text{Cost} = \begin{cases} c(p) + \mathrm{C}_1 \bar{I}, p < p_c \\ c(p), \quad p \geq p_c, \end{cases} \tag{1}$$

with *per capita* burden C_I. The cost of coverage is $c(p) = ae^{xp}$, where a is the cost of vaccinating the first child (the cost of setting up the programme), and x captures the increase in costs with the increasing coverage p.

When there is no immigration, we can calculate the economic optimum by minimizing Eq. 2 to find the level of coverage that minimizes total costs,

$$p^I = \frac{1}{x} \ln \frac{c_I \mu}{ax(\mu + v)}, \tag{2}$$

which is independent of transmission. If the economic optimum p^I is above the critical elimination threshold, $p_c = 1 - 1/\mathcal{R}_0$, the optimal strategy is to eliminate the infection locally:

$$p^* = \min\left[p_c, p^I\right] \tag{3}$$

(details in Appendix in Klepac *et al.* (2011)). Local elimination can be optimal also in the case of very severe diseases. In fact, for large enough *per capita* burden c_I, i.e.

$$c_I > \frac{ax(\mu + v)}{\mu} \exp\left[x\left(1 - 1/\mathcal{R}_0\right)\right], \tag{4}$$

the economic optimum p_I is always above p_c, and optimal vaccination coverage p^* is reduced to the critical elimination threshold determined by $\mathcal{R}_0$ (Eq. 4). The optimal level of vaccination coverage for a disease that cannot be eradicated is a function of only economic parameters. Indeed, epidemiological parameters play no role at all. Local elimination is optimal only for low $\mathcal{R}_0$ values that result in a critical elimination threshold p_c that is smaller than p_I. Moreover, adding immigration of infection to a single population precludes elimination by local vaccination alone.

V. Drug resistance

Drug resistance is a global commons problem and covers the full range of infectious disease-causing pathogens from viruses, bacteria, fungi, and parasites through to disease vectors including mosquitoes, blackflies, and sandflies. Resistance can arise in any single country and move globally. In this section, we focus on bacterial resistance and parasite resistance in the context of malaria.

The global burden of resistance is poorly quantified but is likely to be concentrated in three major categories: increasing costs of resistant infections, increasing costs of

antibiotics, and inability to perform procedures that rely on effective antibiotics to prevent infection. A primary burden of resistance is that resistant infections are more expensive to treat, and patients infected with resistant strains of bacteria are more likely to require longer hospitalization and face higher treatment costs than patients infected with drug susceptible strains (Holmberg *et al.*, 1987; The Genesis Report, 1994). An estimated 25,000 people die each year in Europe from antibiotic-resistant bacteria (ECDC/EMEA Joint Technical Report, 2009). In the United States in 2005, an estimated 94,000 invasive methicillin-resistant *Staphylococcus aureus*, or MRSA, infections required hospitalization and were associated with 19,000 deaths (Klevens *et al.*, 2007). These estimates are useful for indicating the order of magnitude, but are imprecise because resistant infections are more common in individuals on long courses of antibiotic treatment: it is difficult to ascertain whether resistance is the cause of death or a correlate of long antibiotic treatment, hospitalization, and underlying sickness.

In low- and middle-income countries, where the ability to pay for second-line drugs is limited, worse health outcomes are common, particularly in newborn children. Even with effective antibiotics, neonatal infections are the major cause of neonatal deaths, which in turn account for more than a third of the global burden of child mortality (Zaidi *et al.*, 2005). Over half of neonates with extended spectrum beta-lactamase (ESBL) sepsis are likely to die (versus a quarter of neonates with non-ESBL infections), and a half of neonates with MRSA die (versus 21 per cent of neonates with methicillin-sensitive *Staphylococcus aureus*) (Kayange *et al.*, 2010). At these rates of mortality, one can estimate roughly 106,514 neonatal deaths attributable to Gram-negative organisms and *S. aureus*, and 58,319 neonatal deaths attributable to ESBL resistance and MRSA in India alone.

A further cost of resistance is that associated with the cost of introducing new, expensive, antimicrobials to replace old ineffective ones (Office of Technology Assessment, 1995). This represents forgone resources that society could deploy elsewhere (Reed *et al.*, 2001). According to one estimate, between 1997 and 1998, increases in drug resistance raised the cost of treating ear infections by about 20 per cent in the United States ($216m) (Howard and Rask, 2002). Resistance can also render broader health system functions such as surgeries, transplantations, and chemotherapy ineffective (Laxminarayan *et al.*, 2007). A recent study estimated that, without effective antibiotics, 30–40 per cent of patients undergoing total hip replacements would have a postoperative infection, with a case-fatality rate of roughly 30 per cent (Smith and Coast, 2013). This category of burden affects both low- and middle-income as well as high-income countries and is likely to be the predominant way in which resistance drives up health care costs.

Take the case of drugs to treat malaria. The use of antimalarials places selection pressure on parasites to evolve resistance to these drugs. Moreover, resistance is bound to arise when these drugs are misused, and could have adverse consequences for all malaria-endemic countries. Efforts to manage resistance across national borders would have to rely on international agreements and regulations (Walker *et al.*, 2009) or on tax or subsidy instruments (Arrow *et al.*, 2004). In the absence of such agreements and regulation, countries are unable to commit themselves to an optimal use of antibiotics, which would be in all countries' interests. At the macroeconomic level, a too intensive use of antibiotics in the health sector results in excessive levels of resistance both for that country and to the rest of the world (Cornes *et al.*, 2001). A supranational

authority would have to consider both the externality benefits of antibiotic use, in terms of reducing infections, and the costs, in terms of resistance (Rudholm, 2002). Whether antibiotic consumption should be taxed or subsidized to reach the first-best outcome then depends on the relative magnitude of the externalities. In practice, the consequences of antibiotic use in sectors such as to make livestock grow faster involve little by way of positive externalities but impose resistance costs on other sectors and should therefore be taxed.

A new class of antimalarial drugs, called artemisinins, requires a different way of thinking about optimal subsidies to manage resistance. When chloroquine, a once-powerful antimalarial drug, became obsolete, the public health world was left with the challenge of optimally deploying the last remaining effective drug class, artemisinins. The WHO has recommended that artemisinins be used in combination with a partner drug that is unrelated to artemisinin's mechanism of action and genetic bases of resistance, so that a single mutation cannot encode resistance to both components (WHO, 2001). Artemisinin combination treatments (ACTs), if used instead of monotherapies of either artemisinin or the partner drug on its own, should slow the emergence of antimalarial resistance. However, the WHO guidelines are routinely flouted because monotherapies are much less expensive than ACTs. In response to this problem, an Institute of Medicine report (Arrow *et al.*, 2004) recommended establishing an international fund to buy ACTs at producer cost and resell them at a small fraction of that cost.

On economic efficiency grounds there is a second-best case for subsidizing ACTs, because the ideal policy—taxing monotherapies and other antimalarials according to the marginal external cost from the elevated risk of the evolution of resistance—is infeasible, given their widespread use in the informal sector. The efficiency argument is further strengthened by the positive externality, to the extent that effective treatment of one individual reduces the risk of infection transmission to other individuals. Laxminarayan *et al.* (2010) show that it is possible to determine the optimal subsidy in a dynamic disease-modelling framework. Bioeconomic analysis has been helpful for determining whether the social benefit from the subsidy, in terms of delayed resistance and saved lives, exceeds the social cost of resistance because of increased use of ACTs (Laxminarayan *et al.*, 2006). It was also instrumental in turning an idea into the Affordable Medicines Facility for malaria (AMFm), a global financing system launched in early 2009.

AMFm was formally evaluated in 2012. In the six pilots where the programme was implemented to a substantial degree, AMFm met or exceeded benchmarks for availability, price, and market share of quality-assured ACTs. In private, for-profit pharmacies, the quality-assured ACT market share at baseline ranged from 2 to 12 per cent (Tougher *et al.*, 2012). A drawback of this evaluation was that it did not attempt to measure the impact on malaria prevalence or artemisinin resistance, both of which would have been difficult to ascribe to the intervention in the timeframe of the evaluation. Nevertheless, the Global Fund to Fight AIDS, Tuberculosis and Malaria made a political decision to discontinue AMFm based on political objections raised by some country delegations (Arrow *et al.*, 2012).

One way to improve the efficiency of AMFm resources was possibly to target children, though it would avert significantly fewer deaths. However, the benefits of a child-targeted subsidy (i.e. deaths averted) are eroded as leakage increases (i.e. older individuals taking young child-targeted doses), with few of the benefits (i.e. reductions in overall prevalence)

of a universal subsidy (Klein *et al.*, 2015). Although potentially more cost-effective, a child-targeted subsidy must contain measures to reduce the possibility of leakage.

VI. Conclusion—towards global policies for global health

Most global health problems are 'commons problems'. Therefore, it is often essential to have cooperative financing mechanisms for global health interventions, whether to eradicate disease, encourage appropriate levels of disease surveillance and reporting, or to reduce the likelihood of drug resistance. Innovative financing that takes into account cross-country spillovers can play a critical role in arriving at globally optimal outcomes. For instance, in the case of the AMFm subsidy, a high-level financing mechanism that lowers the cost of quality ACTs to all countries, including those that were at highest risk of using monotherapies, both enabled access to effective treatment and also reduced the threat of resistance. No bilateral financing solution could have achieved the same impact because of potential leakage to other countries, as discussed earlier.

A global mechanism that is able to provide resources that incentivize surveillance and reporting of disease outbreaks can successfully counter the disincentives faced by countries for prompt reporting. Again, bilateral assistance that simply focuses on subsidizing surveillance but does not pay attention to the lack of incentives for reporting cannot solve the problem. The three exemplars of trans-boundary problems that we have discussed can be applied to other global health problems with a public goods nature.

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