Gray-market medicines:

Diphtheria antitoxin and the decay of biomedical infrastructure

Submitted to *The Lancet: Art of Medicine*

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Word count: 1866

Figures: 0

Tables: 0

References: 10

More so than most of its European neighbors, Spain at the turn of the 21st century thought it had successfully relegated diphtheria to the past: the country had not seen a case of diphtheria since 1986.[1] Not, that is, until a 6-year old Catalonian boy was diagnosed with the disease in May 2015. Although diphtheria has been a curable disease since the development of diphtheria antitoxin (DAT) in the 1890s and its widespread manufacture by the early 20th century, scarcely a month after his diagnosis, the child succumbed to the disease known a century earlier as "the strangling angel." Ten months later, a second native-born Western European child—this time in Belgium—perished after contracting diphtheria.

The Spanish and Belgian cases point towards a larger question: what happens to an essential medicine after the epidemic it treats has passed? Diphtheria is a treatable disease, but the window from first symptoms to irreversible damage is short, and delay in treatment can diminish chances of survival. With physicians rarely encountering the disease that today causes less than 5,000 cases annually worldwide,[2] and DAT stocks being low or non-existent, delayed diagnosis and DAT procurement contributed to the death of the two European children. Their case clearly demonstrates that any disruption to immunization can quickly become fatal in countries in which the overall incidence of the disease has become negligible.

Although it is on the World Health Organization's Essential Medicines list, neither Spain nor Belgium had stockpiles of DAT on hand when these cases hit.[3] Both countries had to reach out to EU member states and the WHO to locate supplies of diphtheria antitoxin. Ironically, it was the very successes with diphtheria prevention (especially following >95% vaccination rates with diphtheria toxoid) that had eroded

the market for DAT in Europe and North America—and with it, the availability of treatment.

In Europe, the international concern sparked by the death of the Spanish and Belgian children is reminiscent of an earlier set of outbreaks, at the very end of the Cold War. European states received a stark reminder of the ferocity of diphtheria when, in the early 1990s news of escalating outbreaks started emerging from countries of the former Soviet Union. Political turmoil in these states brought a rise in anti-vaccination sentiments, disruption of health services including immunization programmes and a mass movement of people. Between 1990 and 1998, the 157,000 cases (including 5,000 deaths) in Russia and the Newly Independent States accounted for over 80% of diphtheria cases worldwide.[4]

The epidemic put into motion institutional frameworks in Europe: the foundations of a diphtheria surveillance network, now operating under European Centre for Disease Control (ECDC). Despite the stark contrast between low case fatality rates in Russia, where DAT was readily available, and high ones the Newly Independent States, where it was not, most of the scientific discussion following the outbreak focused on prevention, with little attention paid to maintaining access to the antitoxin. [5][6]

We should not be quick to dismiss the significance of the post-Soviet experience. What had been a country with solid health surveillance and high vaccination rates for decades quickly became a site of a severe epidemic. The outbreak in countries of the former Soviet Union brings to focus the frailty of public health systems in the face of political breakdown, and the force and speed with which long-forgotten diseases can

re-emerge. Concentrating on immunisation alone might not be sufficient in what seems to be a rapidly changing global political structure.

In the rest of Europe incidence of diphtheria remained consistently low and vaccination coverage remained high in the decades since the post-Soviet outbreak. This sustained absence of the disease has had profound effects on industry interest in antitoxin production. While in the early twentieth century a host of national institutions and private companies competed to produce DAT, in the second half of the century sites of production dwindled to a handful of countries. By the mid-2010s pharmaceutical companies and state institutions in Europe ceased DAT production, with Bulgaria remaining the only manufacturer for mostly an internal, national market.[7] Today the continent is left without access to DAT produced in Europe. The global production of diphtheria antitoxin now maps onto countries where the disease is still, or until recently had been endemic: Instituto Butantan in Brazil, a complex of Indian companies, and Mikrogen in Russia.[8]

The American public health system has turned to a quite different approach, which might be instructive for the European challenge of DAT access. The perils of contracting diphtheria after it receded from daily life in North America became acutely visible in the U.S. roughly a decade ago, following the 2003 death of a 63 year old unvaccinated Pennsylvanian man who returned from a week-long churchbuilding trip to Haiti with a sore throat. After receiving DAT nine days into his illness, the patient expired. Just six years earlier, the CDC had announced that Connaught Laboratories--the last remaining supplier of diphtheria antitoxin to the United States market--had ceased production, with the last batch due to expire in

January of 1997.[9] A temporizing solution was arranged with the U.S. Food and Drug Administration (FDA) to make limited quantities of unapproved antitoxin--produced by the French firm Pasteur Merieux—available through a network of U.S. Public Health Service quarantine stations associated with the CDC.

By 2003, Pasteur Merieux ceased production of diphtheria antitoxin as well, and no other manufacturer had applied for U.S. licensure of a DAT product.[10] In turn, the CDC extended its arrangement with the FDA to include another unapproved version of antitoxin—marketed by the Instituto Butantan in Brazil—as an "Investigational New Drug" which the CDC keeps stockpiled with 24-hour emergency service for release in the case of emergency. Physicians in the U.S. are assured access to DAT when needed, as long as they fill out an FDA form nominally establishing their credentials as a clinical investigator. Since 2003, there have been 33 administrations of DAT in the US and no further known deaths from diphtheria. Yet trouble looms on the horizon, as stockpiles age and the volume of supply from Instituto Butantan has also begun to falter, as the Instituto struggled with licensing and modernizing production in recent years.[11]

It is worth pausing to consider the historical contortions necessary to reframe diphtheria antitoxin—a therapeutic agent developed in the late 19th century and validated on scores of children over the early decades of the 20th century—as an "investigational new drug" in the 21st century. Yet this twist is only one of many ways in which old drugs can become new again, and often newly inaccessible. Recent years have seen many older essential drugs, whose patents long ago expired and whose American markets have dwindled, as with the antiparasitic drugs albendazole and

pyrimethamine re-branded as newly expensive monopoly drugs (under the brand names Albenza and Daraprim, respectively).[12] Although diphtheria antitoxin in the U.S. has not been subject to analogous price-gouging, these cases collectively underscore the hazards of assuming that—after an epidemic recedes—the older effective medicines that helped to keep it at bay will simply remain cheap and available as part of a well-archived clinical and public health armamentarium.

With the increased control of diphtheria on three continents, the success of prevention can paradoxically lead to high costs for those unfortunate individuals who nonetheless still contract it. This is due not only to changes in pharmaceutical markets, but also on the paradoxical effect of successful prevention programs on the practice of diagnosis. In both Belgium and Spain, delay in treatment owed less to the days that it took for the nations to request DAT from EU member states, but in the longer and more plodding process from initial presentation to positive diagnosis of a disease thought long-departed from Europe. While according to the WHO's guidelines, DAT should be administered upon suspicion of diphtheria before laboratory confirmation,[13] these recommendations are unfeasible when DAT is unavailable and where access to limited regional or global stocks needs to follow diplomatic routes.

In the past 50 years, with the exception of a handful of countries,[14] diphtheria like many other, vaccine-preventable diseases moved from being a complex disease with signs and symptoms that most doctors could easily recognize in clinical practice, into an object of the microbiological past—used to make a teaching point and demonstrate biomedical progress and the importance of compulsory vaccination. Reinforced by consistently low incidence rates and high vaccination coverage, this limited

understanding of the disease perpetuates international and national policies that, by the turn of the 21st century focus almost exclusively on epidemic surveillance and immunization. As a result, when cases of diphtheria do occur in Europe or U.S. of the 21st century, they tend to be diagnosed too late for treatment to be effective even if it were available.

The unavailability of older therapeutics further compounds the problem. While the current scarcity of DAT in the global North highlights the problems of states' reliance on private pharmaceutical markets to maintain access to essential medications, it has little to do with the usual problems of pricing and poverty. Rather, conversations today at the ECDC and WHO Euro about DAT availability are eerily similar to those on iron lungs over 60 years ago. As with DAT, the use of this life saving and cutting edge equipment was understood to be time sensitive: lack of access could result in preventable death. In the wake of the polio epidemic, the urgency and unavailability of iron lungs prompted the WHO to begin planning an international solution. After years of debates over determining the overall European stockpile of machines and their locations, it was the Red Cross that was able to put into place an international lending system that reached far beyond the borders of Europe. In contrast, there is no clear data on current European diphtheria antitoxin stockpiles, and plans for international coordination or a common European stockpile have yielded little result. No organization today is playing the part the Red Cross played a half-century ago. The sense of urgency of access to therapeutics might be very similar, but as an overall public health problem, the emergency of an epidemic is entirely missing.

The shifting geography of the disease complicates both our understanding of diphtheria as a disease of the past and the management of the current crisis in diphtheria treatment. The unavailability of DAT in the global North turns many conventional assumptions of global health supply chains on their heads. The elimination of the 'strangling angel' from these geographies has created a newly neglected disease that now resides among the cracks of the most privileged health systems. It is the global North that becomes the locale for scarcity, as European and North American countries look to Brazil and India for crucial public health assistance.

To return to the question we started with: what happens to an essential medicine after the epidemic has passed? With no market in the North to induce pharmaceutical firms to develop newer biotech versions of DAT or to continue older forms of production, the global supply of this lifesaving therapeutic will continue to dwindle. This brief story of diphtheria in the 21st century leaves us with a paradoxical relationship between time and space, historicity and endemicity, in which progress in prevention presents new problems for treatment. Without sustained attention from the World Health Organization and cooperation among its member states, we may well soon face an increasing struggle to keep children from dying from a disease that has been treatable since 1890.

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