TIMELINE — TROPICAL INFECTIOUS DISEASES

The life and times of ivermectin — a success story

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Abstract | Since its introduction more than 20 years ago, ivermectin has proved to be one of the most successful therapeutic drugs in veterinary medicine, as well as the basis of one of the most successful public-health programmes of the past century. The drug arose from a unique international collaboration between the public and private sectors. The development process also incorporated the world's first and largest drug-donation programme and involved a unique association between governments, non-governmental organizations and industry. The drug is now being used, free of charge, in two global disease-elimination programmes that are benefiting millions of the world's poorest people.

In 1973, a research partnership was established between the Kitasato Institute in Japan and the Merck, Sharpe and Dohme (MSD) research laboratories in the United States. The outcome of this alliance led to an important advance in animal health products, through the development of an extremely safe drug with a broad spectrum of antiparasitic activity — a drug that has also provided significant benefits to human health for more than 20 years, improving the lives of hundreds of millions of the world's poorest and worst afflicted in the process (TIMELINE).

The partnership

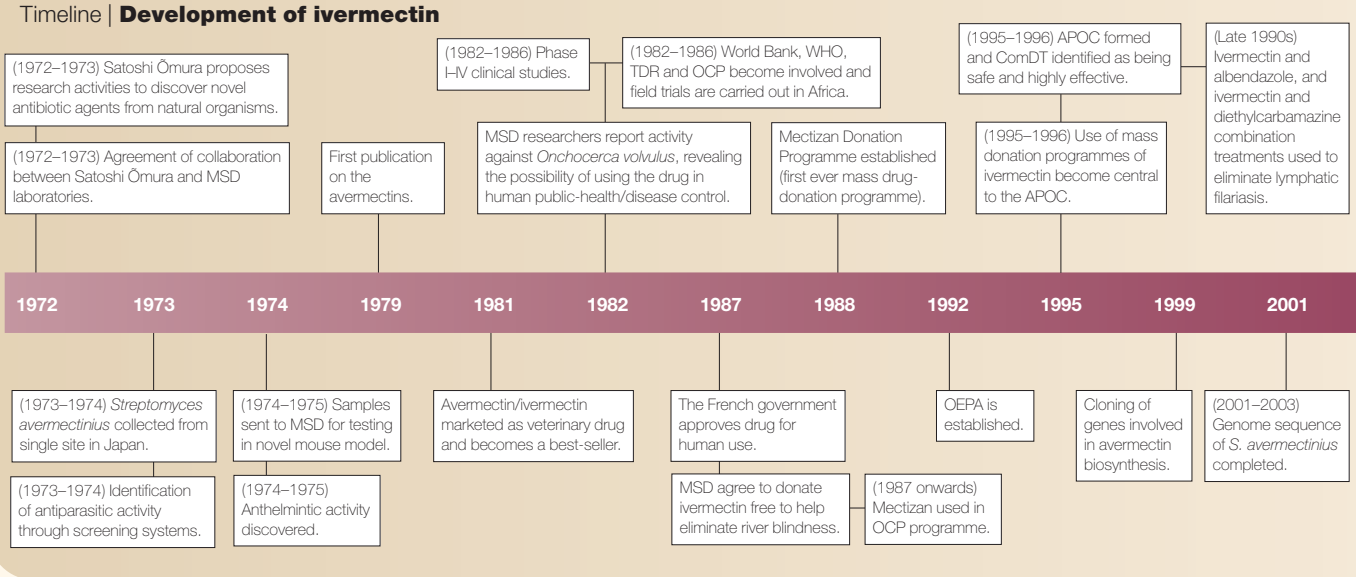
For most of the important breakthroughs in medical research, serendipity has an important role, and so it proved in the case of the drug ivermectin. Researchers at the Kitasato Institute in Tokyo had established a worldwide reputation for their expertise in detecting bioactive compounds produced by microorganisms that are mainly found in the environment. Novel techniques were developed and screening systems were established to increase the chances of accurately detecting minute samples of active compounds[1]. In 1971, one of the authors (S.O.) took a sabbatical from the Kitasato Institute to take up a research post working with Max Tishler, who, after a successful career at MSD, had moved from industry to Wesleyan University in the United States. The Kitasato team were eager to find an industrial partner to participate in a new line of research to discover microorganisms that produce potentially useful compounds with unique chemical structures. Researchers at MSD routinely carried out extensive and innovative *in vivo* work (thereby complementing the *in vitro* work done in Japan) and had the resources to push promising compounds through the drug-development pipeline. By the early 1970s, the testing of synthetic chemicals at the MSD commercial research laboratories was beginning to realize diminishing returns[2], so the company was keen to explore and take advantage of the new research directions that were proposed by the Japanese group. Consequently, the link between Ōmura and Tishler, with his connections to MSD, formed the basis for the new Kitasato–MSD collaboration, which was formally created in 1973.

When the partnership was founded, only a few of the several thousand active fermentation products that had been isolated had anthelmintic activity. Compounds of significance included anthelmycin, anthelvencin, the antibiotic complex S-15-1, aspiculomycin, the axenomycins, G-418, hygromycin B, the destomycins, myxin, paromomycin and the thiamycins. Only one compound, hygromycin, was considered suitable for further development[3]. To address this shortage, the new, goal-oriented research initiative was focused towards discovering a drug that would be effective against helminth parasites[2].

Discovery and isolation

All of the cultures sent from Japan under the terms of the research partnership were from soil samples that were collected and processed by well-established and sophisticated screening systems. These procedures established the morphological features and physiological properties of organisms and compounds produced in fermentation broths and *in vitro*

Timeline | **Development of ivermectin**



evaluations of the chemical products were carried out. In the second year of the collaboration, the Kitasato team isolated an organism — *Streptomyces avermitilis*, which is a species of actinomycete (FIG. 1) — from soil near a golf course bordering the ocean at Kawana, near Ito City in the Shizuoka region. (In 2002, the Kitasato research group published morphological, physiological, biochemical and phylogenetic evidence arguing for the reclassification of the original microorganism and rename it *Streptomyces avermectinius*[4]). The isolated culture was sent, together with 53 other promising microbial samples, to the MSD laboratories in 1974. MSD researchers screened the samples in a novel mouse model of helminth infection in which mice were infected with the nematode worm *Nematospiroides dubius*. Originally identified as OS-3153, the most promising microbial sample was a *S. avermectinius* strain that was shown to have potent anthelmintic activity with little or no toxicity. The compound responsible for the activity was named avermectin[3] (FIG. 2). Further studies demonstrated that avermectin had biocidal activity against a diverse range of nematodes, insects and arachnids. Moreover, the mode of action of avermectin was both unique and robust, and was 25 times more potent than all currently available anthelmintics. The unique ability of avermectin to kill both ecto- and endoparasites gave rise to the new class of compounds called 'endectocides'. In 1979, the first papers on avermectin and its derivatives were published, describing the molecules as a series of macrocyclic lactone derivatives that lacked antibacterial and antifungal activity but which had powerful anthelmintic properties[5–7].

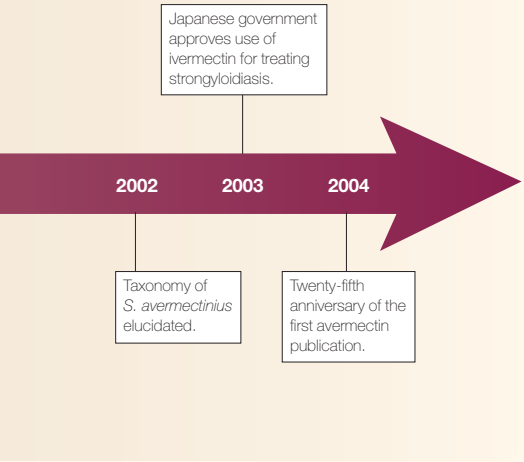


Figure 1 | **Micrograph of *Streptomyces avermectinius*.** *S. avermectinius* is the only organism that has been found to produce the avermectins.

Avermectins are a complex of 16-membered macrocyclic lactones, and fermentation of *S. avermectinius* produces a mixture of eight avermectin compounds (A_{1a}, A_{1b}, A_{2a}, A_{2b}, B_{1a}, B_{1b}, B_{2a} and B_{2b}) (FIG. 2). Compounds of the B-series containing a 5′-hydroxyl group are markedly more active than those of the A-series, which contain a 5′-methoxyl group. The 1-series and 2-series have similar activity against many parasites[8]. An interdisciplinary team at MSD, headed by William Campbell, investigated the eight active compunds, of which avermectins B_{1a} and B_{1b} were found to have the highest activity. Reduction of the C_{22}–C_{23} double bond of B_{1a} and B_{1b} compounds with Wilkinson's catalyst improved both the spectrum of activity and safety (resulting in very low mammalian toxicity), and the resulting 22,23-dihydro B_1 complex (as a mixture of 80% B_{1a} and 20% B_{1b}) was selected for further commercial development under the generic, non-proprietary name, ivermectin[9]. Although structurally similar to macrolide antibiotics and antifungal macrocyclic polyenes, the avermectins have no antibacterial or antifungal activities.

Further analysis revealed that ivermectin was highly efficacious against mite, tick and botfly ectoparasites, which are organisms that cause massive economic losses in the livestock industry. MSD researchers also observed that the compound had remarkable activity against endo- as well as ectoparasites in horses, cattle, pigs and sheep. Ivermectin was also found to be successful in treating larval heartworms, but not adult worms, and could be used to treat mange and other conditions in dogs. However, no activity was found against flatworms, protozoa, bacteria or fungi[10].

In 1999, the Kitasato group reported that 17 genes of *S. avermectinius* encode enzymes that are involved in avermectin biosynthesis. Of these, those encoding four types of I polyketide synthases are concerned with lactone formation, via 12 cycles and 53 steps. The remainder act on pathway-specific regulation, with 12 genes being involved in modification of the lactone ring, biosynthesis of oleandrose and its glycosylation[53].

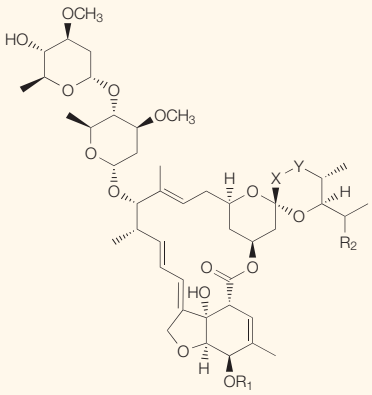
In 2003, the Kitasato team sequenced the *S. avermectinius* genome, which is the largest bacterial genome sequence reported so far[11,12]. Analysis of the genome allowed identification of the gene cluster involved in secondary metabolite production, shedding light on the biology of microbial secondary metabolite synthesis at the genetic level.

Mode of action

Initially, owing to its rapid and specific antiparasitic and anthelmintic action, it was proposed that ivermectin was an agonist for neurotransmitter function. Experimental studies confirmed this proposal when it was shown that inhibition occurred via glutamate-gated chloride ion channels in nerve and muscle cells[13]. Ivermectin interacts with these channels, preventing their closure. Consequently, synapse membranes become increasingly permeable to chloride ions, which leads to hyperpolarization of the neuronal membrane and decreases, or prevents, neuronal transmission. This, in turn, leads to paralysis of the somatic muscles, particularly the pharyngeal pump, causing the death of the parasite[14,15]. γ-aminobutyric acid (GABA)-related chloride ion channels, which are present only in nematodes, insects and ticks, are only inhibited with greater drug concentrations[16–18]. In mammals, GABA receptors and neurons are found in the central nervous system, whereas in arthropods and nematodes they are located in the peripheral nervous system. This, coupled with the relatively low dose concentrations needed, ensures that mammals can ingest ivermectin with a high degree of safety.

Animal health

Ivermectin was introduced to the market in 1981 as a veterinary antiparasitic drug and soon proved to be the most effective, broad-spectrum antiparasitic drug ever developed. It quickly became a remarkable success, rapidly capturing a large portion of the global veterinary antiparasitic market, and became the market leader within two years — the drug has maintained that position ever since, with annual sales of about US$1 billion. Since the introduction of ivermectin, several other



	R_1	R_2	X–Y
Avermectin A_{1a}	Me	Et	CH=CH
Avermectin A_{1b}	Me	Me	CH=CH
Avermectin A_{2a}	Me	Et	$CH_2CH(\alpha OH)$
Avermectin A_{2b}	Me	Me	$CH_2CH(\alpha OH)$
Avermectin B_{1a}	H	Et	CH=CH
Avermectin B_{1b}	H	Me	CH=CH
Avermectin B_{2a}	H	Et	$CH_2CH(\alpha OH)$
Avermectin B_{2b}	H	Me	$CH_2CH(\alpha OH$

Figure 2 | **Structure of the avermectins.** The inclusion of different groups at positions R_1, R_2, X and Y create the eight different avermectin compounds A_{1a}, A_{1b}, A_{2a}, A_{2b}, B_{1a}, B_{1b}, B_{2a} and B_{2b}.

endectocides have appeared but none have replaced ivermectin as the market leader.

Five years after its introduction, ivermectin was registered for use in 46 countries and was being used worldwide to treat approximately 320 million cattle, 151 million sheep, 21 million horses and 5.7 million pigs[19]. Most horses in the United States were treated with the drug to the extent that the horse nematode *Onchocerca cervicalis* has now virtually disappeared.

Public health

At the time the collaboration between the Kitasato Institute and MSD was being set up and becoming operational in the mid-1970s, onchocerciasis (or river blindness) had long been a major global health problem. The disease results from infection with *Onchocerca volvulus*, which is a parasitic worm that lives in the human body. Adult female worms live for up to 14–15 years, producing millions of microscopic larvae (microfilariae) that migrate in the body, causing a variety of symptoms (FIG. 3). The bite of infected blackflies (*Simulium* spp.) transmits immature larval forms of the worms from human to human. Adult worms, which take a year to mature, lodge in nodules under the skin, releasing millions of microfilariae into surrounding tissues, which then migrate through the body, living for 9–18 months. When the microfilariae die, the resulting residue causes visual impairment and blindness, skin rashes, lesions, intense itching and depigmentation of the skin, lymphadenitis and general debilitation. Onchocerciasis is found in 35 countries, including 28 nations in tropical Africa where 99% of infected people live (FIG. 4). Isolated foci also occur in Latin America and Yemen. Each year, approximately 18 million people are infected, with more than 6.5 million people suffering from severe itching, dermatitis and impaired visual acuity, and 270,000 patients suffering from complete blindness. The disease is estimated to be responsible for the loss of 1 million disability-adjusted life years (DALYs) annually. In the early 1970s, the only drugs that were available to treat the disease were suramin, which is a highly toxic molecule that had to be administered in repeated injections over a period of several weeks, and diethylcarbamazine, which also had to be administered over several weeks. Diethylcarbamazine can also cause severe side effects due to the accumulation of dead parasitic tissue, a process that can result in blindness. By the mid-1970s, it was clear that both drugs could actually worsen eye lesions and so the use of chemotherapy for onchocerciasis was stopped[20].

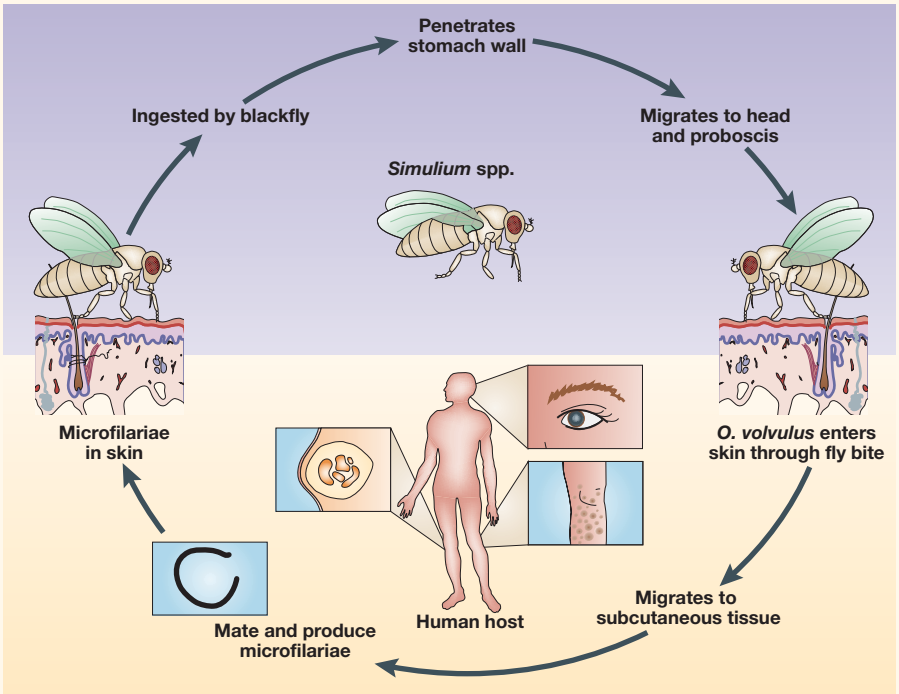


Figure 3 | **Schematic representation of the life cycle of *Onchocerca volvulus*.** When a parasitized female blackfly (*Simulium* spp.) takes a blood meal, infective *Onchocerca* larvae pass into the host through the fly-bite wound. Larvae enter subcutaneous tissue, where they migrate, aggregate in nodules, mature into adult worms and mate. After mating, eggs in female worms develop into immature larvae (microfilariae), each worm is capable of producing 1,000 microfilariae per day. Many thousands of microfilariae are released to migrate in subcutaneous tissue. When they die, they cause skin rashes, lesions, intense itching and skin depigmentation. Microfilariae also migrate to the eye and can cause visual impairment and blindness. When the infected host is bitten by another female fly, microfilariae pass into the blackfly, where they develop into infective larvae, and the life cycle continues.

There was hope, however, for a new and effective treatment. The MSD research in horses had demonstrated that ivermectin killed *Onchocerca cervicalis*, which are nematodes that are closely related to *Onchocerca volvulus*, so work began to investigate the possible use of ivermectin in humans. MSD joined forces with the World Health Organization (WHO), the Special Programme for Research and Training in Tropical Diseases (TDR) and the Onchocerciasis Control Programme in West Africa (OCP) to carry out an extensive collaborative research programme in humans. This proved to be an early example of the so-called public–private partnerships (PPPs) that are now being created in increasing numbers to coordinate the production and distribution of effective therapies for diseases for which there is little likelihood of a financial return on investment.

In 1981, clinical trials of ivermectin, which was produced under the brand name 'Mectizan', began in Senegal[21,22]. Over the next

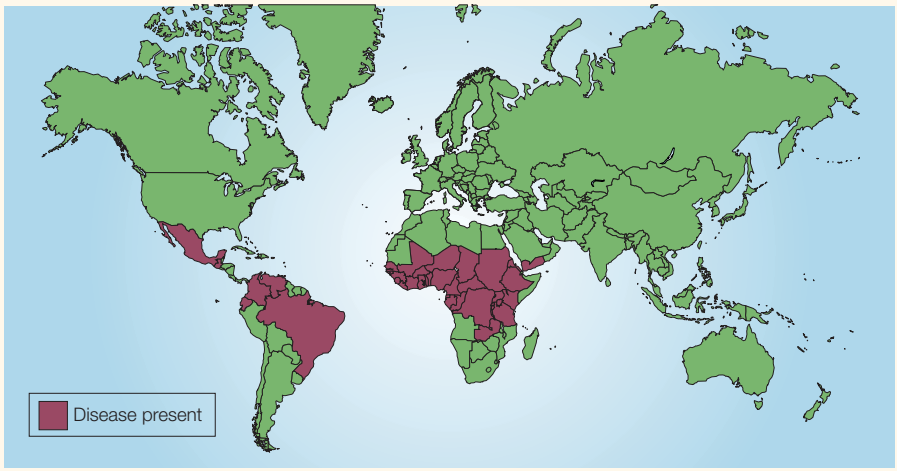


Figure 4 | **Global distribution of onchocerciasis.** Data obtained from the WHO.

four years, large-scale field trials involving hundreds of thousands of individuals were undertaken in Ghana, Guatemala, Cote d'Ivoire, Liberia, Mali, Senegal and Togo. Phase II studies reported that local inflammatory responses in ocular tissue were less severe with ivermectin than with diethylcarbamazine, thereby avoiding the unwanted Mazzotti reaction — by which the accumulation of dead parasitic material can induce blindness. Results showed that a single annual dose of 200 μg per kg of body weight eradicated microfilarial worms from the eye and skin after one month, and patients remained worm-free for up to 12 months after treatment[23–25]. Later, large-scale community trials in various epidemiological conditions, including hyper- and meso-endemic areas, found that ivermectin reduced the levels of skin microfilaria by 96–99% within the first few months of therapy[26]. It has been repeatedly shown that ivermectin has little impact on adult worms and that multiple doses do not have much impact on oogenesis[27]. Adult worms can continue to reproduce, so ivermectin is suppressive rather than curative; however, treatment leads to a marked reduction in the number of immature worms and reduces microfilarial loads after each course of treatment[21,28]. Several follow-up studies have shown that the marked reduction in both prevalence and intensity of microfilaridermia is maintained, even after five years of treatment[29–31]. Ivermectin has the added benefits of allowing the body to repair minor eye lesions and reduces the severity of itching and the prevalence of skin lesions[32]. Some researchers argue that ivermectin alters the mechanisms by which adult worms locate each other and that this explains why fewer males are found in nodules after multiple treatments[33]. More frequent administration of ivermectin, for example bi-annually rather than annually, could have a sterilizing effect on adult female worms and reduce their lifespan[34]. Nevertheless, taking the drug over the lifespan of the adult worms effectively prevents patients from developing the disease.

Following the work of a truly international partnership involving the public and private sectors, governments of disease-endemic countries and affected communities, the human formulation of ivermectin was registered for use by French regulators in 1987 with mass drug administrations commencing in 1988.

The use of ivermectin can cause adverse side effects, the most common being oedema, fever, pruritus and pain[35,36]. They are generally mild and transient, however, and can be easily treated by primary healthcare workers or trained lay members of the community. Indeed, the incidence of adverse reactions in follow-up studies on distribution programmes has actually been less than that observed during clinical trials[37]. Ivermectin can also have serious effects on individuals heavily infected with *Loa loa*, which causes severe encephalopathy that can prove fatal[38]. Consequently, it is essential to take appropriate safety measures to exclude any such people from mass drug-administration programmes. A comprehensive review of serious adverse events following Mectizan treatment carried out in 1989–2001 found 207 cases from a reported 165 million treatments, representing an incidence ratio of 1 per 800,000 treatments[39].

Drug donation

During the latter stages of human trials, discussions took place between the public and private sectors to determine a suitable price for the drug, bearing in mind that the end-users of the product would be poor and marginalized communities. In 1987, after receipt of consent from the Kitasato Institute, which agreed to forego royalties, P. Roy Vagelos, the then chief executive of MSD, announced that ivermectin (under the brand name Mectizan) would be provided free of charge for the treatment of river blindness for "as long as it is needed", a pledge that has been honoured ever since. The advent of this drug donation has transformed the treatment of onchocerciasis to a point where elimination of the disease has become an achievable goal.

Community-directed treatment

Also in 1987, the TDR began to fund pioneering research on the concept of 'community-based treatment' using ivermectin. The rationale behind this concept was that the drug was so safe and easy to use that affected communities should be able to organize their own drug distribution and treatment. In the field, community-directed treatment proved to be remarkably successful and, in 1989, the WHO announced that ivermectin could be administered "with minimal supervision". It was subsequently noted that ivermectin coverage was greatest when affected communities were allowed to design and implement their own drug-distribution programme[40]. The TDR went on to develop the community-directed treatment with ivermectin (ComDT) procedure, which became the operational basis of the African Programme for Onchocerciasis Control (APOC). Established in 1995, the aim of APOC is to create sustainable community-directed distribution systems using mass distribution of ivermectin to all those eligible by 2007, ultimately covering 59 million people in African countries where the disease remains a serious public-health problem and where 15 million people are heavily infected. The goal is to eliminate the disease in the 17 African nations where it still persists after the successful control of the disease in the 11 west-African nations covered by the OCP. Meanwhile, the Onchocerciasis Elimination Programme in the Americas (OEPA), which was launched in 1992, is based on the premise that mass administration of Mectizan tablets can rid the region of the disease relatively quickly, as the vector blackflies in this region transmit the parasite with reduced efficiency. The programme is expected to achieve its goal of eliminating the disease from the region by 2007 (REF. 20). Community-directed treatment is producing excellent results in the fight against onchocerciasis. Affected villages collect Mectizan tablets, deliver them to all those eligible and report back to health authorities — and meet all the costs involved themselves

(the drug being provided free to district health posts). The correct dosage can be calculated simply by measuring the height of the recipient. In 2003, approximately 56 million Africans were taking a single annual dose of ivermectin[41]. The overall goal of these programmes is to eliminate onchocerciasis as a public-health problem globally by 2010.

Economic aspects

Mectizan is viewed by some as one of the finest public-health success stories of the past century, and a model for all future public and private sector partnerships. However, analysis of the economics indicates that success depends on financial commitment from both sectors. Cost-effective analyses of the mass distribution of ivermectin have identified a cost of US$14–30 per DALY that is prevented[42]. This compares reasonably well with other control programmes for priority diseases, but the benefit ratio in this case is only possible due to the huge financial commitment from Merck & Co., which pays the production costs of Mectizan, the costs of transport from the manufacturing facility in France to the recipient countries and the related customs and other handling costs. In total, more than 250 million doses of ivermectin have been administered since the start of the Mectizan donation programme. In 2000, APOC devoted 63% of its total annual budget of US$9.4 million to ivermectin distribution programmes. Using the US$1.50 figure claimed by the Mectizan Donation Programme as being the cost of a single tablet, the value of the ivermectin contributed by Merck & Co. in 2001 is estimated to be US$143.6 million for APOC countries alone. This can be compared with the total 15-year costs of the APOC programme, which are estimated to be US$182.5 million[43].

APOC and others are working towards reducing the actual costs of 'free drug' donation programmes, with APOC focusing on a target distribution cost of US$0.20 per treatment[43]. A study of two villages in Nigeria found that 92–93% of inhabitants were willing to pay US$0.30 and US$0.28, respectively, to meet their ivermectin distribution needs. The actual costs of treatment in the two villages were calculated as US$0.13 and US$0.17, respectively[44,45], which bodes well for maintaining sustainable, long-term mass distribution programmes for the period of time that is needed to achieve disease elimination. The continuing, concerted and long-term commitment of donors (led by the World Bank), non-governmental organizations, governments, health services and affected communities will be essential if the elimination goal is to be achieved.

Lymphatic filariasis

The success of ivermectin does not stop with the potential elimination of onchocerciasis as a public-health threat. Combinations of ivermectin and albendazole or ivermectin and diethylcarbamazine have been adopted as the basis of mass treatment in the Global Alliance to Eliminate Lymphatic Filariasis, which was initiated by the WHO in 1997. The efficacy of the ivermectin and albendazole combination therapy for bancroftian filariasis was first reported in 1997 (REF. 46). Lymphatic filariasis is one of the most prevalent tropical diseases, with an estimated 120 million people being infected annually. The disease is responsible for 5 million DALYs lost each year, ranking it third among tropical diseases in terms of DALYs, after malaria and tuberculosis. Almost 1 in 5 of the world population are at risk of infection and the disease remains a major impediment to socio-economic development in endemic areas — India loses an estimated US$1 billion annually as a result of lymphatic filariasis. In an effort to curb this disease, Merck & Co. confirmed that they would donate Mectizan free of charge to the elimination programmes in regions where onchocerciasis and lymphatic filariasis coexist. GlaxoSmithKline, the manufacturers of albendazole, also announced that they would donate this drug for lymphatic filariasis control programmes, which are working towards the goal of eliminating the disease by 2020.

New uses for ivermectin continue to be found. For example, in 2003, ivermectin was registered for the treatment of strongyloidiasis, an intestinal parasitic disease that is widely distributed in the tropics and subtropics and which is prevalent in south-east Asia and southern Japanese islands. More than 10 million people are infected with the causative microorganism.

Future use

A microorganism from a single site in Japan has provided a drug that has proved to be one of the most successful tools in human and animal health, and one that has been the mainstay of several of the most successful disease-control programmes in the history of public health. Moreover, the benefits continue to accrue. It is common knowledge that malnutrition and undernutrition are major causes of ill health in Africa and throughout the developing world, particularly among young children. Ivermectin is known to be particularly effective against infection with *Ascaris* worms and reasonably effective against hookworm and *Trichuris*[47,48]. Furthermore, the prevalence of head lice is markedly reduced in children taking ivermectin tablets[49]. In Japan, ivermectin may soon be routinely used in special circumstances, such as in homes for the elderly to help control the incidence of scabies.

Perhaps of greater significance, ivermectin became available at a time when resistance to other similar drugs, such as benzimidazole and levamisole, was common. Very few cases of resistance to ivermectin have been reported and any future development of widespread resistance is thought to be unlikely[16]. Parasites that are resistant to the avermectins are also resistant to the milbemycins and it is likely that P-glycoproteins (plasma-membrane-associated drug efflux transporters) are involved in the resistance mechanism[50]. It is also postulated that resistance could be mediated by mutations in the gene encoding the α-subunit of glutamate-gated chloride channels; However, the exact resistance mechanism is still a matter of conjecture[51].

The discovery, development and deployment of ivermectin through the efforts of Merck & Co. and the Kitasato Institute, aided by a group of international partners from a range of disciplines, has been hailed by some commentators as one of the greatest medical achievements of the twentieth century[52]. Vigilance is now needed to ensure that the progress that has been made against several devastating diseases is maintained. The strain of *Streptomyces* found in Japan remains the only microorganism that produces avermectin. The Kitasato Institute, and similar organizations, remain dedicated to the search for further microbiological treasures for use in public health from among the myriad of substances produced by the world's reservoir of environmental microorganisms.

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Competing interests statement
The authors declare no competing financial interests.

Online links

FURTHER INFORMATION
WHO: http://www.who.int/en/
TDR: http://www.who.int/tdr/
Onchocerciasis control programme: http://www.who.int/pbd/blindness/onchocerciasis/ocp/en/
African programme for onchocerciasis control: http://www.who.int/pbd/blindness/onchocerciasis/apoc/en/
Global alliance to eliminate lympatic filariasis: http://www.filariasis.org/index.pl
CDC onchocerciasis fact sheet: http://www.cdc.gov/ncidod/diseases/submenus/sub_river_blindness.htm
CDC lymphatic filariasis fact sheet: http://www.cdc.gov/ncidod/diseases/submenus/sub_filariasis.htm
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OPINION — ANTI-INFECTIVES

Antibiotic resistance: a view from the prescriber

Roger G. Finch

Abstract | Antibiotic resistance is increasingly affecting the management of infectious diseases. The prescribing clinician is not only important to the development of the problem but also central to its solution. This article addresses the current weaknesses in the information systems and the evidence base that support prescribing. Remedies necessary for improvements in prudent prescribing include better guidance in managing specific diseases where resistance is of prognostic significance and also increasing diagnostic precision.

The increasing prevalence of antibiotic-resistant microorganisms is now an issue of major public concern. Newspaper headlines and media reports regularly feature details of their impact on individuals as well as raising the spectre of widespread and untreatable drug-resistant infections. The breadth and significance of antibiotic-resistant micro-organisms is becoming increasingly apparent. Examples include outbreaks of multiply antibiotic-resistant pathogens in intensive care or neonatal units; the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in hospitals and, more recently, nursing homes; the global occurrence of drug-resistant malaria in tropical and sub-tropical regions; and drug-resistant tuberculosis, with its links to poverty, HIV and social exclusion.

Reports on antibiotic resistance and concerns raised by infection specialists over the past fifty years were largely unheeded until the mid-1990s when the significance of the problem achieved political recognition. In 1995, the American Society for Microbiology[1], and in 1998, a House of Lords Select Committee in the United Kingdom[2], issued reports that have been influential in establishing national strategies. In the United States, a task force was established[3]. The European Union also published its strategy[4] and addressed the problem through a series of conferences on antibiotic resistance, such